The Significance of Microsaccades for Perception and Oculomotor Control

by

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ABSTRACT

During attempted fixation, the eyes are not still but continue to produce so called "fixational eye movements", which include microsaccades, drift, and tremor. Microsaccades are thought to help prevent and restore vision loss during fixation, and to correct fixation errors, but how they contribute to these functions remains a matter of debate. This dissertation presents the results of four experiments conducted to address current controversies concerning the role of microsaccades in visibility and oculomotor control.

The first two experiments set out to correlate microsaccade production with the visibility of foveal and peripheral targets of varied spatial frequencies, during attempted fixation. The results indicate that microsaccades restore the visibility of both peripheral targets and targets presented entirely within the fovea, as a function of their spatial frequency characteristics.

The last two experiments set out to determine the role of microsaccades and drifts on the correction of gaze-position errors due to blinks in human and non-human primates, and to characterize microsaccades forming square-wave jerks (SWJs) in non-human primates. The results showed that microsaccades, but not drifts, correct gaze-position errors due to blinks, and that SWJ production and dynamic properties are equivalent in human and non-human primates.

These combined findings suggest that microsaccades, like saccades, serve multiple and non-exclusive functional roles in vision and oculomotor control, as opposed to having a single specialized function.

DEDICATION

This work is dedicated to my loving family. My hard-working parents, Francisco and Amelia, have made innumerable sacrifices in order to help me add a few letters to the end of my name. They have always provided me with unconditional love and care. My brother Álvaro also deserves my deepest appreciation for his kindness and determination. Without my family's love and support, this would not have been possible.

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Introduction

The human eye is one of the most complex organs in our body. It carries out the difficult task of transducing light into neural signals, and then transmitting these signals to the brain's visual system. Vision (sight) is the perception of objects in the environment by means of the light that they emit or reflect. *Light* is visible electromagnetic radiation, which has wave bands between 400 to 700 nm in wavelength.

The eyeball is a sphere about 24 mm in diameter with three principal components: (1) three layers (tunics) that form the wall of the eyeball; (2) optical components that admit and focus light; and (3) neural components, the retina and optic nerve.

Six extrinsic eye muscles (four rectus muscles and two obliques) attach to the walls of the orbit and to the external surface of the eyeball. They move the eye up, down, medially, and laterally. The three tunics of the eyeball are as follows: The outer layer is made up of the *sclera* and the *cornea*. The middle layer is composed of the *choroids*, the *ciliary body*, and the *iris*. The inner layer is made of the *retina* (See **Figure 1**).

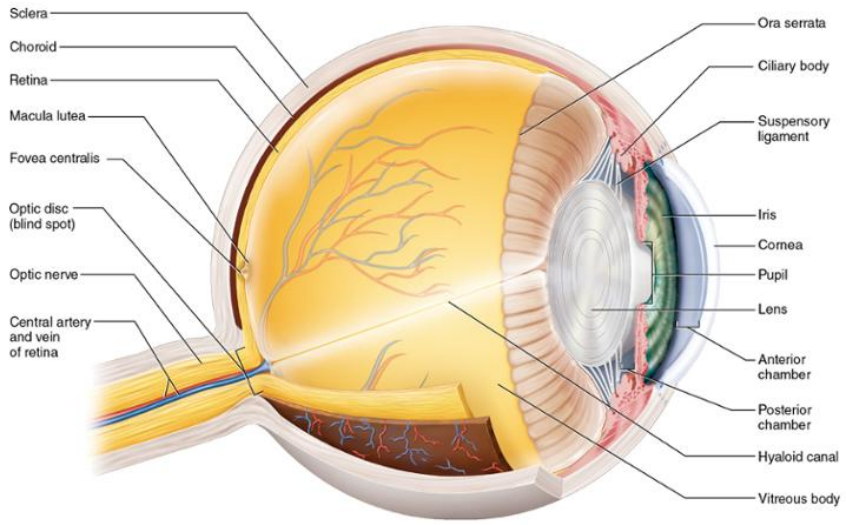


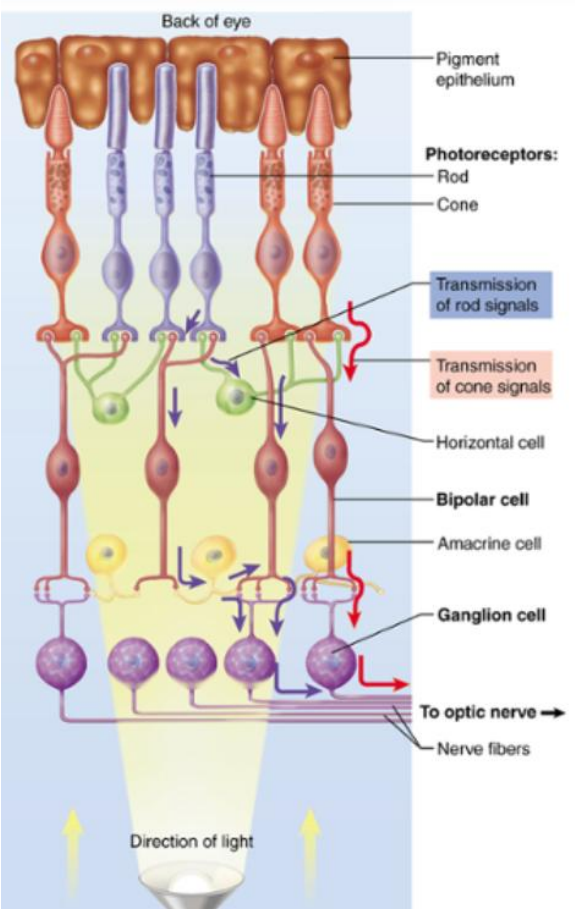
Figure 1. Sagittal section of the eye (from Saladin, 2012).

The optical components of the eye are transparent elements that admit light rays, bend (refract) them, and focus images on the retina. They include the *cornea,* and two spaces that are filled with fluid in the eye. The fluid between the cornea and the lens is called the *aqueous humor,* and the fluid filling the rest of the eyeball is called the *vitreous humor*.

Image formation depends on refraction, the bending of light rays. There are two ways to focus light coming into the eye. The *cornea,* the external focusing apparatus, is not as important as the *lens,* the internal focusing element. The lens creates images by bending light towards its thickest part. The lens's *ciliary bodies* contract or relax to change the lens's shape.

The neural components of the eye are the *retina* and the *optic nerve*. The *fovea centralis* is the spot on the retina directly behind the lens where light focuses perfectly. The conversion of light energy into action potentials occurs in the retina. The neural components of the retina consist of three principal cell layers: *photoreceptor cells, bipolar cells,* and *ganglion cells* (**Figure 2**).

- The photoreceptors are cells that absorb light and generate a chemical or electrical signal. There are two main kinds: *rods* and *cones*. Rod cells are responsible for night (scotopic) vision and produce images only in shades of gray (monochromatic vision). Cones are responsible for day (photopic) vision and produce images in color (trichromatic vision).



- Bipolar cells. Rods and cones synapse with the dendrites of bipolar cells, which in turn synapse with the ganglion cells.

- Ganglion cells. Ganglion cells are the largest neurons of the retina, arranged in a single layer close to the vitreous body.

Figure 2. Schematic of the layers and synaptic connections of the inner layer of the eye (from Saladin, 2012).

The retina processes inputs from 100 million rods and 4 million cones, contacting 1 million ganglion cells (Breedlove, 2013). The axons of retinal ganglion cells exit the retina via the optic nerves. The region where the optic nerves exit the eye is called the *optic disk*, aka the blind spot because there are no receptors in this region. The optic nerves leave each orbit through the optic canal and then converge to form an X, the *optic chiasm*, inferior to the hypothalamus and anterior to the pituitary gland. Beyond this, the fibers continue as a pair of optic tracts that terminate in the lateral geniculate *nucleus* (the visual part of the thalamus), which in turn relays this information to the primary visual cortex of the occipital lobe (see **Figure 3**).

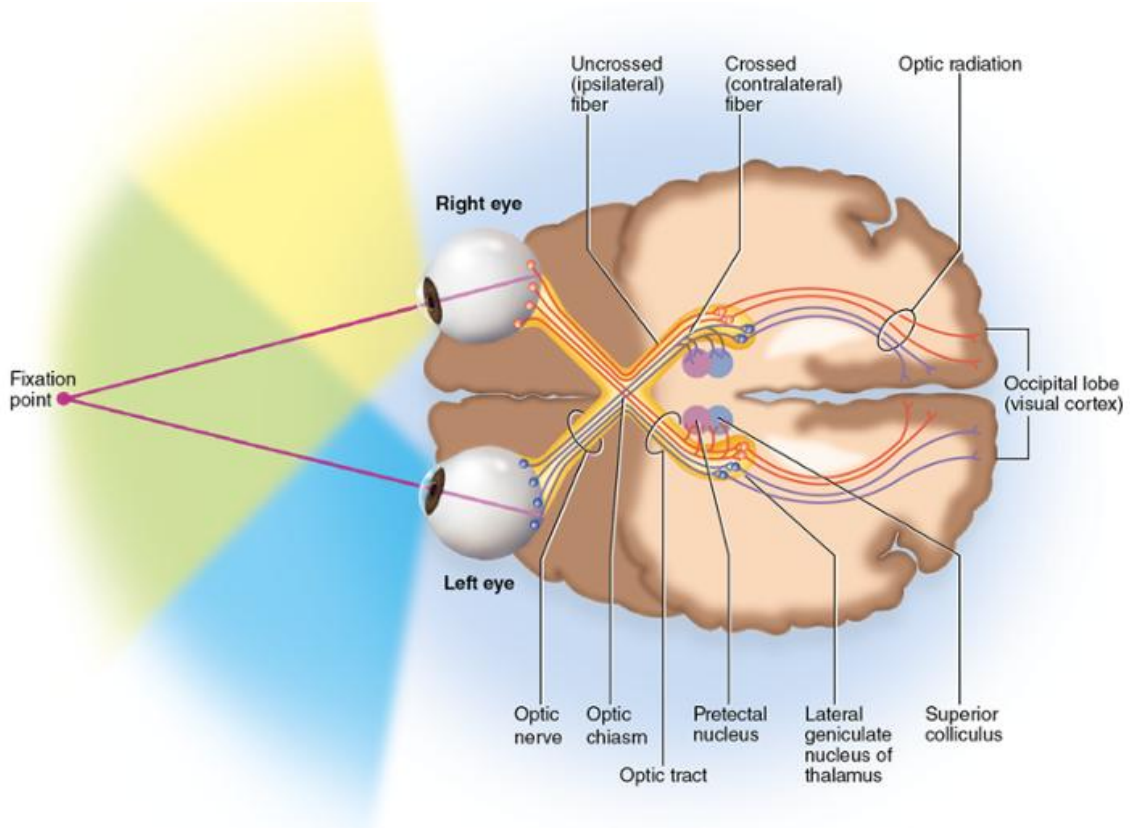


Figure 3. The visual projection pathway. Blue and yellow indicate the receptive fields of the left and right eyes; green indicates the area of overlap and stereoscopic vision (from Saladin, 2012)

Human visual perception relies upon constantly changing input. Steady state stimuli create uniform stimulation of retinal receptors and thus lead to neuronal adaptation. The perceptual fading of stationary objects during fixation is known as Troxler fading (Troxler, 1804). This phenomenon consists on the visual disappearance on an unchanging stimulus upon steady fixation (See **Figure 4**). When the eyes are stabilized in the laboratory, stationary objects fade from perception quickly due to the lack of eye movements (Riggs and Ratliff, 1951; Ditchburn and Ginsborg, 1953; Yarbus, 1957). Perfectly stabilized images disappear in as little as 80 msec, indicating that normal visual processing entails a rapid mechanism for image creation and erasure (Coppola and

Purves, 1996). When the eyes are no longer stabilized, or if the stabilized image changes, visual perception is restored (Krauskopf, 1957; Ditchburn et al., 1959; Gerrits and Vendrik, 1970; Sharpe, 1972 p.19; Drysdale, 1975).

Figure 4. Troxler fading effect. When one fixates on the red dot above for even a short period of time, the unchanging peripheral ring fades away and disappears. Taken from Martinez-Conde et al. (2004).

Our visual system can detect stationary objects because the images projected onto our retinas are never stationary for long. Our eyes are constantly moving, even when we try to fixate on an object. These microscopic movements are called *fixational eye movements* (Yarbus, 1967).

There are three main types of fixational eye movements in the primate: *tremor*, *drift* and *microsaccades* (Yarbus, 1967; Carpenter, 1977)(see **Figure 5**). Microsaccades

are small, spontaneous jerk-like rapid shifts of the eye that occur at a rate of 1-2 per second. They are the fastest and largest of the three types of fixational eye movements, which makes them easiest to characterize objectively and automatically. Drift is a slow and erratic curvy motion that occurs in between microsaccades. Not many studies have focused on drift, due to its persistent nature, so little is known about its perceptual consequences. Tremor is the smallest of the fixational eye movements (~1 photoreceptor width), an irregular motion superimposed on the drift movements. Tremor's high frequency (~60-100 Hz) and small amplitude pose an important challenge to its accurate detection and measurement.

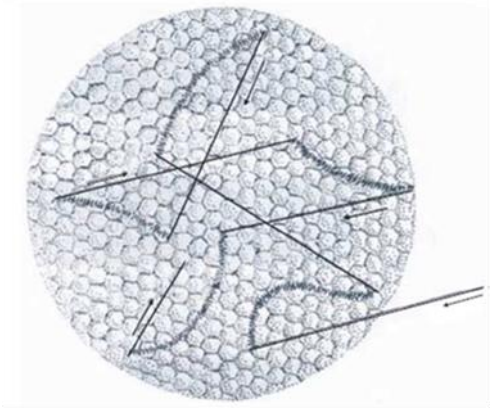


Figure 5. Fixational eye movements carry the image across the retinal photoreceptors. High frequency tremor is superimposed on slow drifts (curved lines). Microsaccades are fast jerk-like movements, (straight lines). The diameter of the patch of the fovea shown here is 0.05 mm. From Pritchard (1961).

Although they are related to many aspects of visual perception, attention, and cognition (Martinez-Conde *et al.* 2009), the specific roles of each fixational eye movement type remain controversial (McCamy, *et al.*, 2012).

Saccades are conjugated binocular high-velocity movements with a clear correlation of magnitude and peak velocity. Microsaccades share these characteristics

(Ditchburn and Ginsborg, 1953; Zuber et al., 1965; Engbert and Kliegl, 2003; Rolfs et al., 2006, 2008a, 2008b; Otero-Millan et al., 2008), and recent findings indicate that a common generator underlies both saccade and microsaccade production (Otero-Millan *et al* 2008; Rolfs *et al.* 2008a; Hafed *et al.* 2009; Martinez-Conde *et al*. 2009; Otero-Millan *et al* 2011). In recent years, interest in the role of microsaccades in visual and oculomotor function has risen (Collewijn and Kowler, 2008; Poletti and Rucci, 2010; Kowler, 2011), despite controversies that have limited progress in the field (Martinez-Conde et al 2004; Martinez-Conde et al 2009; Rolfs 2009).

Microsaccades and visibility

Recent studies have set to determine the correlation between microsaccade production and visibility (Engbert and Mergenthaler, 2006; Martinez-Conde et al., 2006; Troncoso et al., 2008a; Hsieh and Tse, 2009; McCamy et al., 2012).

Martinez-Conde et al (2006) asked human subjects to fixate a small spot, and simultaneously report the visibility of a target, via button press. Increased microsaccade production resulted in enhanced visibility of peripheral (6 and 9 degrees of eccentricity) and parafoveal (3 degrees eccentricity) visual targets. Decreased microsaccade rate preceded target fading. These results indicated a potentially causal relationship between microsaccades and target visibility during fixation.

Microsaccade production has also been investigated during the filling-in of artificial scotomas (Troncoso et al., 2008a), and in connection to perceptual transitions in binocular rivalry (van Dam and van Ee, 2006), motion-induced blindness (Hsieh and Tse, 2009) and illusory motion (Laubrock et al., 2008; Otero-Millan et al., 2008; Troncoso et

al., 2008a). All of these studies found an influence of microsaccades on perception. Other researchers however argued that microsaccades are only effective within a narrow range of peripheral and low-contrast targets (Collewijn and Kowler, 2008; Kowler and Collewijn, 2010; Kowler, 2011). Collewijn and Kowler (2008) stated that microsaccades cannot be essential for foveal visibility because foveated images do not fade.

The fovea is defined as the highest-resolution, rod-free region of the retina, subtending approx. 1.25 degrees of visual angle (Curcio et al., 1990). There is discrepancy in the literature about the existence of foveal fading. Some studies have concluded that it is weak or nonexistent (Troxler, 1804; Clarke, 1960; Gerrits, 1978), but others disagree (Krauskopf, 1963; Pessoa and De Weerd, 2003; Simons et al., 2006). McCamy et al. (2012) found recently that microsaccades are the most important eye movement contributor to restoring the visibility of faded targets during fixation, both in the visual periphery and in the fovea. The edges of these targets extended beyond the limits of the fovea, however, and the only target contrast tested was 40% (**Figure 6**).

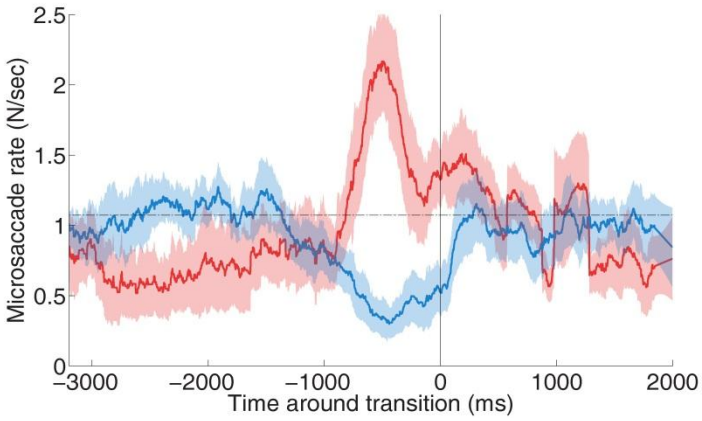


Figure 6. Microsaccades counteract visual fading of 40% contrast stimuli.

Microsaccade rates before transitions towards visibility (red) vs. fading (blue). The horizontal line indicates the average rate of microsaccades during the session. Shaded areas indicate SEM between subjects. From McCamy et al (2012).

No previous studies have examined the ability of microsaccades to restore the visibility of peripheral vs. foveally-contained faded stimuli. In addition, no research to date has investigated the impact of microsaccades on visibility as a function of stimuli parameters, such as contrast and spatial frequency content.

Our ***FIRST HYPOTHESIS*** is that microsaccades will restore the perception of faded stimuli in the center of vision. Our ***SECOND HYPOTHESIS*** is that microsaccades will enhance the perception (i.e. they will counteract fading and restore the visibility) of any and all stimuli that do fade during fixation. We conduct two human psychophysical experiments to test these hypotheses. Our aim is to determine the ability of microsaccades to restore the visibility of foveally contained targets, and to counteract visual fading as a function of target characteristics, such as spatial frequency content.

Experiment #1 determines the effect of microsaccades on the visibility of central targets with varying contrast levels.

Experiment #2 determines the effect of microsaccades on the visibility of peripheral targets of varied spatial frequencies.

Microsaccades and oculomotor control

The potential role of microsaccades in fixation correction has been controversial for more than fifty years (Martinez-Conde et al., 2004, 2009, 2013; Rolfs, 2009). Cornsweet originally hypothesized that microsaccades return the eyes to a fixated target, correcting gaze displacements produced by intersaccadic drifts (Ditchburn and Ginsborg 1953; Cornsweet 1956; Yarbus 1967). This proposal was later challenged, however, and by the end of 1970's most of the field agreed that drifts, rather than microsaccades, were essential for the control of fixation position. This conclusion was based on the limited accuracy of potentially corrective microsaccades and the occurrence of non-corrective microsaccades (Ratliff and Riggs, 1950; Fiorentini and Ercoles, 1966). Yet, other studies showed that correction by drift was not as effective as correction by the subset of microsaccades that did play that role (St.Cyr and Fender, 1969; Schulz, 1984). Other research concluded that both microsaccades and drift may be error-correcting and error-producing (Nachmias, 1961; Steinman et al., 1973).

de Bie and van den Brink (1984) compared the behavior of fixational eye movements produced in response to different target shifts and also during the view of a stationary target. They found that both drifts and microsaccades reduced fixation errors by an amount proportional to the displacement from the fixation target previous to the correction, and concluded that both eye movement types are beneficial to fixation stability.

Engbert and Kliegl (Engbert and Kliegl, 2004) performed new analyses indicating that microsaccades counteract neural adaptation on a short timescale and correct fixation errors on a longer timescale. Otero-Millan et al. (2011) analyzed the role of corrective microsaccades within SWJs in humans. SWJs are the most common type of saccadic intrusions, each consisting of a small, conjugate saccade that moves the eye away from the fixation target, followed after a short interval by a corrective saccade that will bring the fovea back to the target, leading to "square wave coupling" (**Figure 7**). SWJs are present in most human subjects, but are prominent by their increased frequency and size in certain parkinsonian disorders and in recessive, hereditary spinocerebellar ataxias. SWJs have been also documented in monkeys with tectal and cerebellar etiologies, but to date there is no study confirming the existence of square wave jerks in healthy non-human primates.

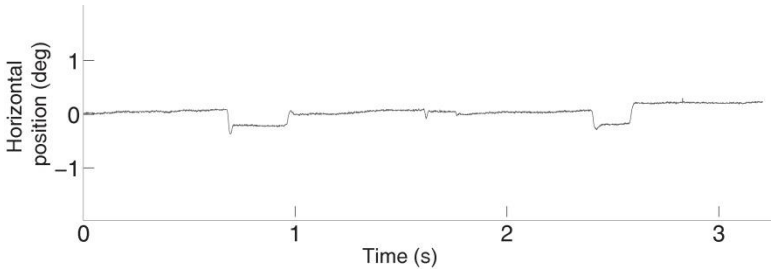


Figure 7. Fixation correction, in the form of SWJ coupling. Fixation correction occurs for large but not small microsaccades. A 3 s horizontal eye position trace from one human subject is illustrated.

Both neural noise and fixation error appear to play a role in microsaccade generation. If the distance between the gaze position and the fixation goal exceeds a certain threshold, a corrective microsaccade is generated. Conversely, if the fixation error is insignificant, neural noise might trigger microsaccade production instead (Cornsweet 1956; Otero-Millan et al. 2011b).

The eye moves involuntarily during blinking in a downward and nasalward trajectory (Ginsborg, 1952; Evinger et al., 1984; Collewijn et al., 1985; Riggs et al., 1987; Porter et al., 1993) that can lead to fixation errors. There is evidence showing that saccades following blinks correct such blink-induced errors in humans (Collewijn et al., 1985; Takagi et al., 1992) and non-human primates (Goossens and Van Opstal, 2000).

Here we set out to determine whether fixational microsaccades play a more general role in error correction during fixation than previously thought, by determining their potential role in the correction of fixation errors due to blinks in humans and monkey, as compared to drifts.

Our ***FIRST HYPOTHESIS*** is that microsaccades correct blink-induced gaze position errors. Our ***SECOND HYPOTHESIS*** is that SWJs occur in healthy non-human primates and that they share the corrective characteristics found in human SWJs.

Experiment #3 examines and compares the roles of microsaccades and drift in the correction of blink-induced fixation errors in non-human primates and human subjects.

Experiment #4 examines whether square wave jerks occur in healthy non-human primates and investigates their characteristics as compared to those of human SWJs.

These four experiments seek to establish that microsaccades serve multiple non-exclusive roles (similar to those served by large saccades). This proposal focuses on the roles of microsaccades in vision (i.e. the effects of microsaccades on visibility as a function of stimulus contrast, spatial frequency content, and retinal eccentricity) and oculomotor control (i.e. fixation correction).

Experiment 1 (Microsaccades restore the visibility of minute foveal targets)

During attempted fixation, the eyes are not still but continue to produce so called "fixational eye movements", which include microsaccades, drift and tremor (Martinez-Conde et al., 2004). In the 1950s, several groups demonstrated that visual perception of stationary objects faded in the absence of eye movements (Ditchburn and Ginsborg, 1952; Riggs and Ratliff, 1952; Yarbus, 1957). Thus, fixational eye movements were linked to the prevention of visual fading and restoration of visibility during fixation, although the specific roles of each fixational eye movement type remained controversial (McCamy, et al., 2012). Microsaccades, the largest and fastest fixational eye movement, have been linked to the visual restoration of faded targets (Martinez-Conde et al., 2006; McCamy et al., 2012), but their role in peripheral versus central vision has been less clear.

Recent research (McCamy, et al., 2012) reported microsaccades to be the most important eye movement contributor to restoring faded targets, both in the visual periphery and in the fovea (the highest-resolution, rod-free region of the retina, subtending approx. 1.25 degrees of visual angle (Curcio et al., 1990). The target size tested extended beyond the limits of the fovea, however, and so the ability of microsaccades to restore minute targets contained within the fovea continues to be in question.

Here, human subjects reported on the visibility of a target that was centered on the fovea and was smaller than the area of the fovea, during attempted visual fixation. The target did not change physically, but its visibility decreased and increased intermittently during fixation, in an illusory fashion (a perceptual phenomenon known as Troxler fading

(Troxler, 1804)). Microsaccade rates increased significantly before the target became visible, and decreased significantly before the target faded, for a variety of target contrasts. These results support previous research linking microsaccade onsets to the visual restoration of peripheral and foveal targets (Martinez-Conde, et al., 2006; McCamy, et al., 2012), and extend the former conclusions to small-size targets that are contained within the fovea.

Method

Subjects

Eight subjects (7 males, 1 female) with normal or corrected-to-normal vision participated in the experiments. Six subjects were naive and were paid $15/session. Experiments were carried out under the guidelines of the Barrow Neurological Institute's Institutional Review Board (protocol number 04BN039). Written informed consent was obtained from each subject.

Experimental design

Subjects rested their forehead and chin on the EyeLink 1000 head/chin support, ~57 cm away from a linearized video monitor (Barco Reference Calibrator V, 75 Hz refresh rate). The experiment consisted of 4 sessions of ~1 hour, each including 50 randomly interleaved 30-second trials. The first session was counted as a training session and not included in the analyses.

While fixating a small red spot (0.03º diameter) on the center of the screen, subjects continuously reported whether a stimulus was faded/fading (button press) or

intensified/intensifying (button release) (Martinez-Conde, et al., 2006; McCamy, et al., 2012, McCamy et al., 2013a). To start the trial, subjects pressed a key and the stimulus appeared on the screen. Subjects were instructed to release the button as soon as they saw the stimulus. The stimulus was a two-lobe Gabor patch with a peak-to-trough width of 0.5º (Gaussian standard deviations of x = 0.2º and y = 0.2º; sine wave period of 1º; sine wave phase of 0). The Gabor was presented at the center of the screen and contained within the fovea, with contrast levels of 5%, 10%, 20%, and 40% from peak-to-trough and the same average luminance (50%) as the background. The orientation of the Gabor varied randomly between 0º and 360º in each trial, to control for orientation adaptation effects (Martinez-Conde, et al., 2006; McCamy, et al., 2012). After 30 seconds, the stimuli disappeared and the trial ended.

Eye movement analyses

Eye position was acquired noninvasively with a fast video-based eye tracker at 500 Hz (EyeLink 1000, SR Research). We recorded eye movements simultaneously in both eyes (instrument noise 0.01º RMS). We identified and removed blink periods as portions of the raw data where pupil information was missing. We also removed portions of data where very fast decreases and increases in pupil area occurred (> 50 units/sample, such periods are probably semi-blinks where the pupil is never fully occluded) (Troncoso et al., 2008a). We added 200 ms before and after each blink/semi-blink to eliminate the initial and final parts where the pupil was still partially occluded (Troncoso et al., 2008a). Saccades were identified with a modified version of the algorithm developed by Engbert & Kliegl (Engbert and Kliegl, 2003; Laubrock et al., 2005; Engbert, 2006; Engbert and

Mergenthaler, 2006; Rolfs et al., 2006) with λ = 4 (used to obtain the velocity threshold) and a minimum saccadic duration of 6 ms. To reduce the amount of potential noise, we considered only binocular saccades, that is, saccades with a minimum overlap of one data sample in both eyes (Laubrock et al., 2005; Engbert, 2006; Engbert and Mergenthaler, 2006; Rolfs et al., 2006). Additionally, we imposed a minimum intersaccadic interval of 20 ms so that potential overshoot corrections might not be categorized as new saccades (Møller et al., 2002). Microsaccades were defined as saccades with magnitude < 1º in both eyes (Martinez-Conde et al., 2009, 2013) . To calculate microsaccade properties such as magnitude and peak velocity we averaged the values for the right and left eyes. **Figure 8A-B** shows the magnitude distribution (**Figure 8A**) and peak velocity-magnitude relationship (**Figure 8B**) for both microsaccades (<1°) and saccades (≥1°). All subsequent analyses (**Figures 3-5**) concern microsaccades only, that is, saccades with magnitude <1°.

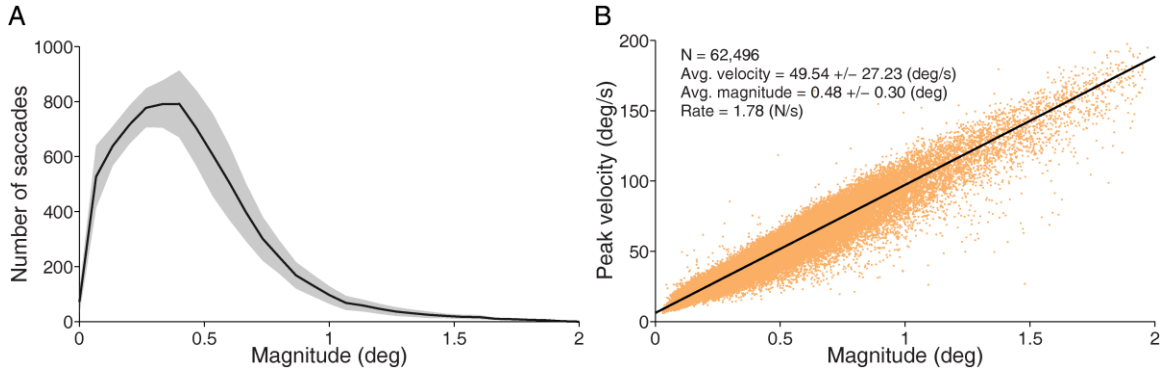


Figure 8. Descriptive statistics for microsaccades (<1°) and saccades (≥1°) A) Microsaccadic and saccadic magnitude distribution for all subjects combined (n = 8). B) Microsaccadic and saccadic peak velocity–magnitude relationship for all subjects combined. Each orange dot represents a microsaccade or a saccade with peak velocity indicated on the y-axis and magnitude indicated on the x-axis. The inset legend shows the microsaccade descriptive statistics. Error bars and shadows indicate the SEM across subjects.

Microsaccade correlations with reported transitions

Let X_M, X_S, X_B, and X_R be the stochastic processes representing the onsets of microsaccade, and intensification report (R). For example, if $s_1, s_2, \cdots, s_k$ are the start times of all the microsaccades for a given subject, then X_M for that subject will be given by $X_M(t) = 1$ if $t = s_i$ for some $1 \le i \le k$, and $X_M(t) = 0$ otherwise; similarly for intensification reports.

We obtained correlations of microsaccades with reports of intensification for each subject, using $\xi_{MR}(t) = \sum_{n=-\infty}^{n=\infty} X_M(n+t) X_R(n)$ and then converting it to a rate (similarly for transitions to fading) (McCamy, et al., 2012). For each subject, correlations were smoothed using a Savitzky-Golay filter of order 1 and a window size of 151 ms (Martinez-Conde, et al., 2006). Average correlations are the average of the smoothed correlations (**Figures 10-11)**.

ROC analyses

We used a sliding receiver operating characteristic (ROC) analysis (Green and Swets, 1966; Britten et al., 1992; Hernández et al., 2002; Romo et al., 2002, 2004; Feierstein et al., 2006; Troncoso et al., 2008a) to quantify how well microsaccade rate may predict the type of perceptual transition (towards intensification versus fading) reported by the subjects, for the different foveal target contrasts. The area under an ROC curve provides a measure of the discriminability of two signals and is directly related to the overlap of the two distributions of responses that are compared (Feierstein et al.,

2006). In our case, the area under the ROC curve can be interpreted as the probability with which an ideal observer, given the microsaccade rate during a window of time around a particular transition, can correctly determine the type of transition (towards fading or intensification). An ROC area of 0.5 corresponds to completely overlapping distributions (the ideal observer cannot discriminate between the two types of transitions); an area of 1 corresponds to transitions that can be perfectly discriminated based on microsaccade rate. This analysis makes no assumptions about the underlying distributions (Feierstein, et al., 2006). For a given point in time, we compared the microsaccade rate distributions for transitions to intensification (true-positive rate) and transitions to fading (false-positive rate) for each subject. To obtain the ROC curve at that time, we plotted the probability of true positives as a function of the probability of false positives for all possible criterion response levels. We performed a sliding ROC analysis (kernel width 500 ms, slid in 2-ms increments) to calculate each subject's area under the ROC curve at each time point around the transition. To determine the time point at which the ideal observer became better than chance, we calculated significance using a permutation procedure (Siegel and Castellan, 1988 p.199; Hernández et al., 2002; Romo et al., 2002, 2004; Feierstein et al., 2006; Troncoso et al., 2008a) with n = 1,000 shuffles for each subject and a criterion p-value < 0.01.

Statistical methods

To analyze the effect of target contrast on time faded per trial and rate of fading onsets (**Figure 9A-B**), we conducted separate single-factor repeated measures ANOVAs with the different contrast levels tested as the within-subjects factor. All post-hoc

comparisons were done using Tukey's HSD method. To assess whether microsaccade rates before transitions to intensification were significantly higher than those before transitions to fading, we performed one-tailed paired *t*-tests in each bin (bin size = 20 ms), using Bonferroni correction to account for multiple comparisons (**Figures 10-11**). Significance levels were set to $\alpha = 0.01$ throughout.

Results

Subjects fixated a small spot on the center of a computer screen and continuously reported, via button press/release, whether an unchanging visual target (a 2-lobe Gabor patch with 5%, 10%, 20%, or 40% contrast), presented within the fovea, was faded (or in the process of fading) versus intensified (or intensifying) (Martinez-Conde, et al., 2006; McCamy, et al., 2012). Fading prevalence decreased as the target's contrast increased (**Figure 9A**), and the 10% contrast target generated the largest number of perceptual transitions, as indicated by subjects' reports (**Figure 9B**). As expected, lower-contrast targets were faded for longer time periods than higher contrast targets; thus the 5% contrast target resulted in the longest fading periods and the 40% contrast target in the longest intensification periods, whereas the 10% contrast target produced fading and intensification periods of comparable length (**Figure 9C-F**).

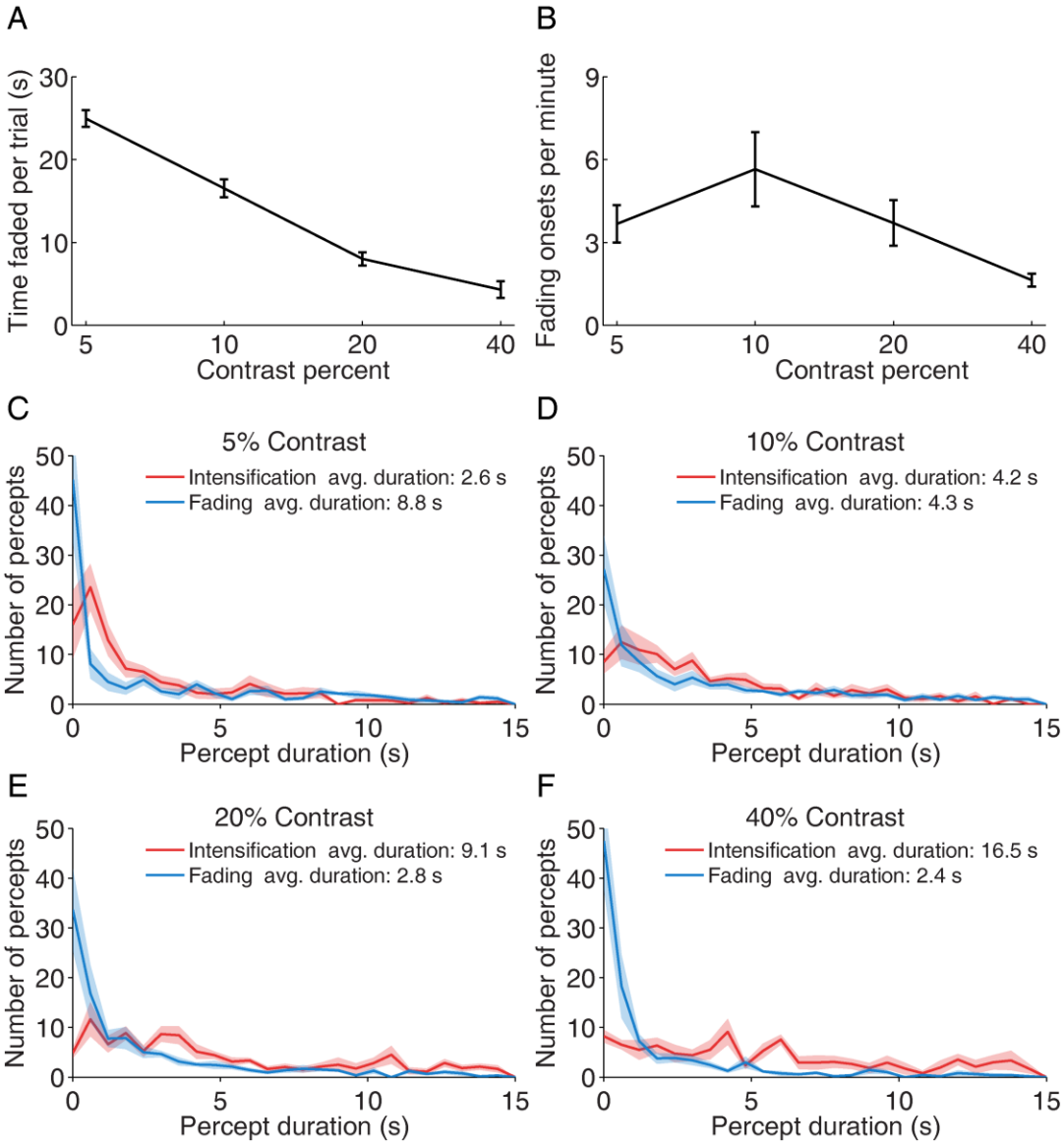


Figure 9. Perceptual reports A) Average time faded per trial for each target contrast. The time faded per trial decreased linearly with target contrast ($F(3, 21) = 88.48$, $p < 0.001$; linear trend $F(1, 7) = 112.36$, $p < 0.0001$). B) Fading onset rate for each target contrast. The effect of contrast was significant ($F(3, 21) = 8.58$, $p = 0.0065$). A Tukey HSD posthoc comparison showed a significant difference only between the 10% and 40% contrast target ($p < 0.01$). C-F) Distribution of the durations of intensification and fading periods for each target contrast. Error bars and red and blue shadows indicate the SEM across subjects ($n = 8$).

Microsaccade rates increased before transitions to intensification and decreased before transitions to fading, with the intermediate-contrast targets (10% and 20%) showing the strongest correlations between microsaccade rate increases and intensification reports (**Figure 10**).

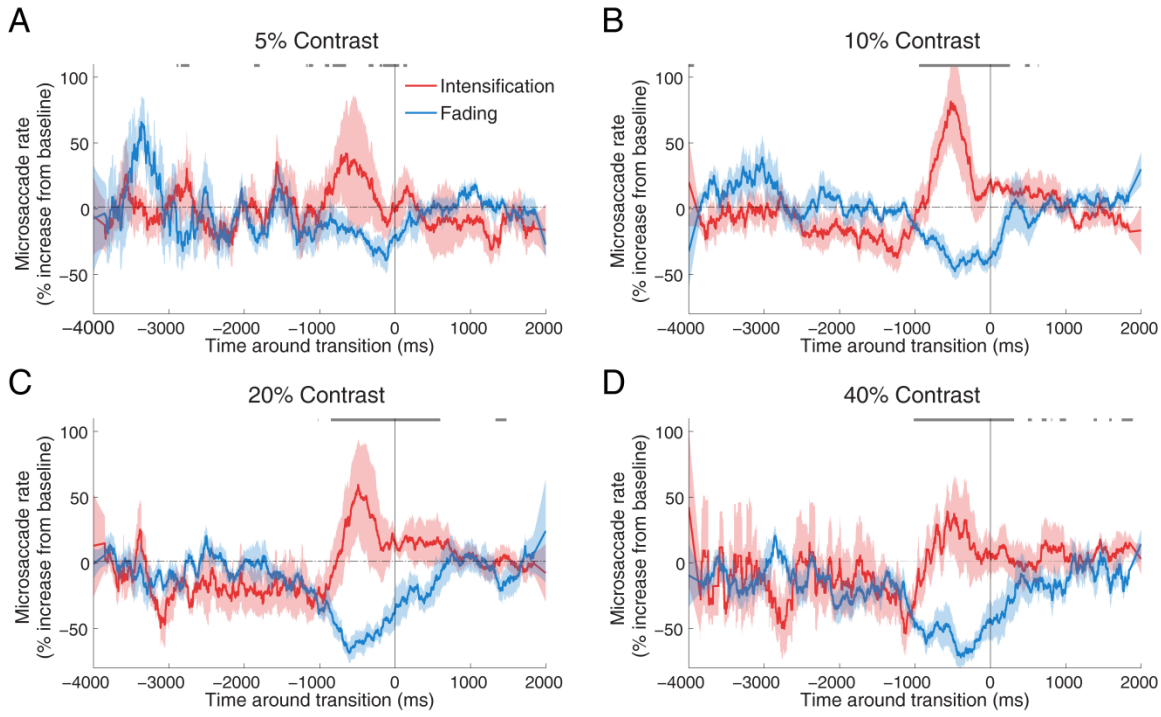


Figure 10. Microsaccade correlations with reported transitions. A-D) Percent increase in microsaccade rate over baseline (i.e. relative to the average microsaccade rate (dashed horizontal line) for a given target contrast) around reported transitions toward intensification versus fading, for each target contrast. The solid vertical line indicates the reported transitions (t = 0). Target contrast is indicated at the top of each panel. The gray lines at the top indicate the bins where microsaccade rates before transitions to intensification were significantly higher than microsaccade rates before transitions to fading (see Methods for details). Red and blue shadows indicate the SEM across subjects (n = 8).

Microsaccade magnitude

We analyzed the effects of microsaccade size on perceptual transitions to intensification and fading. To do this, we separated all microsaccades in 4 different

categories according to size (0-15 arcmin, 15-30 arcmin, 30-45 arcmin, and 45-60 arcmin) and correlated them to the perceptual intensification and fading reports for each target contrast (**Figure 11**). The smallest microsaccades failed to restore target visibility, especially for those targets with the lowest levels of contrast (not shown). This result is consistent with the previous finding that larger microsaccades are more efficacious than smaller ones, possibly due to their increased ability to bring the neuronal receptive fields to uncorrelated stimulus regions (McCamy, et al., 2012). As microsaccades grew in size, their correlation with perceptual transitions became stronger, also consistent with previous research (McCamy, et al., 2012)).

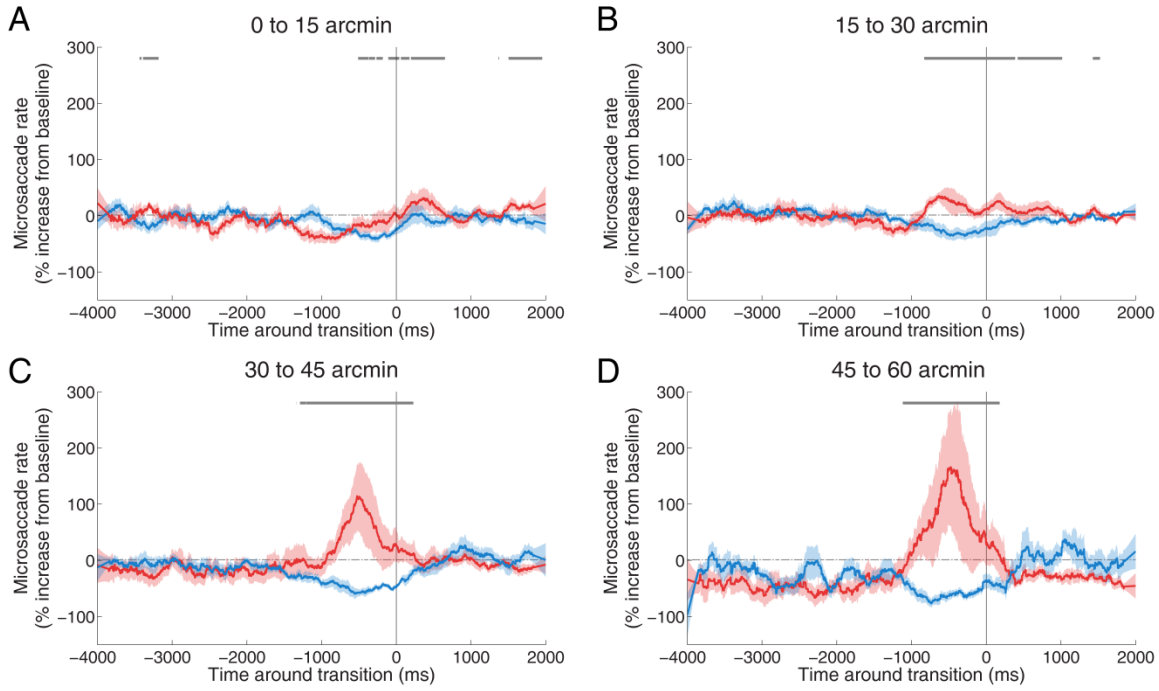


Figure 11. Correlations between microsaccades of different sizes and reported transitions. Microsaccade sizes (0-15 arcmin; 15-30 arcmin; 30-45 arcmin; 45-60 arcmin) are indicated at the top of each panel and we have collapsed across target contrasts. All other details as in Figure 3.

ROC analysis

To further quantify our conclusions, we conducted a sliding ROC analysis to calculate the ability of an ideal observer to predict the type of perceptual transition (towards intensification or fading) based on microsaccade rates. **Figure 12** shows that the ideal observer becomes significantly better than chance (determined by permutation analysis; see Methods for details) ≈ 800 ms before the reported transitions, for targets of 10%, 20%, and 40% contrast.

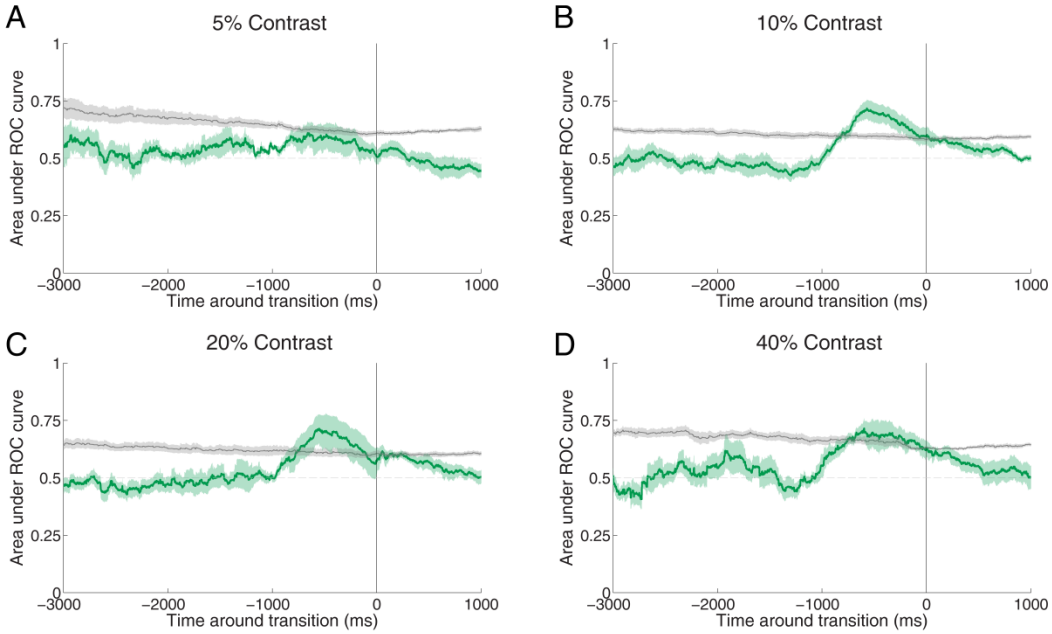


Figure 12. ROC analysis. A-C) The ideal observer can predict the type of illusory transitions (intensification vs. fading) based on microsaccade rate. The green line is the area under the ROC curve at any given time. The solid horizontal gray line indicates the significance level (i.e. the level at which the ideal observer performs above chance (horizontal dashed line; see Methods for details). Target contrast is indicated at the top of each panel. Significance is reached whenever the green line is above the grey line. The ideal observer's prediction (green line) becomes significantly better than chance ≈800 ms before the reported transitions, for target contrasts of 10%, 20% and 40%. The shaded green area indicates the SEM across subjects (n = 8).

Discussion

In 1804, Troxler described the perceptual fading of stationary objects during fixation, a perceptual phenomenon that came to be known as Troxler fading (Troxler, 1804). Despite Troxler's report that not only peripheral, but also centrally fixated targets were susceptible to fading, Troxler fading became equated with peripheral fading in subsequent decades (see (Wade and Tatler, 2005) for a historical review). Yet, foveal fading has been reported by numerous researchers in a number of experimental conditions (Darwin, 1795 p.197; Troxler, 1804 p.18; Krauskopf, 1963; Pessoa and De Weerd, 2003; Simons et al., 2006; McCamy et al., 2012). A recent study found that microsaccades counteracted the perceptual (i.e. Troxler) fading of peripherally and foveally presented Gabor patches with peak-to-trough widths of 2.5º (McCamy, et al., 2012). Because the edges of such centrally presented targets extended beyond the foveal limits, here we asked whether smaller size targets, constrained to the area of the fovea, might similarly fade from perception, and if so, whether microsaccades could restore their visibility as well.

Subjects reported the visibility of centrally presented 2-lobe Gabor patches with peak-to-trough widths of 0.5º (that is, 5 times smaller than in (McCamy, et al., 2012)), of varying contrasts (5%, 10%, 20%, 40%). As with previous fading experiments (Spillmann and Kurtenbach, 1992; Martinez-Conde et al., 2006; Troncoso et al., 2008a; McCamy et al., 2012), subjects reported that the perceptual state of the (foveally contained) targets appeared to oscillate between the faded/fading state and the visible/intensifying state. Thus, minute targets constrained to the fovea are subject to perceptual fading during fixation, in much the same manner as larger, foveally centered

targets, and peripherally presented targets are (Martinez-Conde, et al., 2006; McCamy, et al., 2012). Microsaccade rates increased before transitions to visibility and decreased before transitions to invisibility, also in agreement with previous reports (Martinez-Conde, et al., 2006; McCamy, et al., 2012; Troncoso et al., 2008). These findings indicate that microsaccades have comparable effects in visual target restoration across the retina, for a variety of target sizes and contrasts.

Target contrast and foveal fading

As expected, lower-contrast targets faded more often and for longer amounts of time than higher-contrast targets (**Figure 9**). Perhaps more surprisingly, targets of moderate contrast levels (i.e. 20% and 40%) also faded, albeit less often, and microsaccades restored them perceptually at such times (**Figures 9-10**, **12**). The correlation between microsaccade production and visual restoration of faded targets was most obvious for the intermediate contrast targets (i.e. 10% and 20%), although still present for lower and higher contrasts (i.e. 5% and 40%) (Figures 3 and 5). Why did microsaccades restore the visibility of low-contrast (i.e. 5%) targets less effectively than that of intermediate-contrast targets? It seems likely that, when target visibility is highly degraded (for instance, due to minimum contrast levels), shifting of the retinal image due to microsaccades or other eye movements may not produce enough photoreceptor stimulation to generate a perceptual experience in a reliable way. Conversely, when intermediate or moderate contrast targets fade from perception, their visibility may be degraded just enough that microsaccades are able to restore them with high efficiency.

The current results are consistent with previous evidence that stimuli do fade at all retinal eccentricities (Wade & Tatler, 2005), despite the concerted actions of the three types of fixational eye movements (i.e. microsaccades, drift and tremor), and that microsaccades can successfully bring back such faded stimuli (McCamy, et al., 2012).

Are microsaccades relevant to foveal visibility?

The present results show that microsaccades can restore the visibility of small, foveally contained targets of moderate-to-low (i.e. ranging from approximately 40% to 10%) contrasts. Very low contrast targets (i.e. 5% contrast) were visible for a small amount of the time only, and microsaccades did not significantly restore their visibility (although there was a trend between microsaccade production and target intensification (**Figures 10-12**), especially for the larger microsaccade sizes (not shown)). High-contrast targets (i.e. higher than 40% contrast) were not tested in this study, but the current data suggest that they would have faded too briefly and rarely for microsaccades to restore their visibility in a substantial manner.

In light of these combined results, what is the value of microsaccades to foveal perception? We posit that—despite assumptions that only high-contrast stimuli are pertinent to foveal vision—most visible stimuli are relevant to perception by definition, regardless of their contrast. That is, fading of any stimulus (i.e. irrespective of contrast) is a visual degradation that microsaccades often supersede. Indeed, there are many small-sized, low-contrast objects that one might want to see optimally with central vision. A diamond earring on a white carpet, or small features in medical and research images, are two of many examples. Thus, the fovea has the capacity to inspect stimuli of all contrasts

and spatial frequencies, and microsaccades can restore the visibility of a range of such foveal stimuli, after fading sets in. Therefore, microsaccades are relevant to human perception of foveal stimuli.

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On the visibility of fixation targets

One frequent argument against the value of microsaccades to foveal vision is that fixation targets, which are presented centrally, never fade, even in the absence of microsaccades. We note that the sizes, colors and shapes of fixation targets used in vision studies vary widely (McCamy et al., 2013b; Thaler et al., 2013), but their contrasts (and high spatial frequency content) are almost universally maximized. The present results suggest that fixation targets remain perpetually visible by virtue of their high contrast (and possibly high spatial frequency), rather than their small size and/or foveal presentation. Further, our results show that it is possible for one foveal stimulus to fade from perception (i.e. the low-to-moderate contrast Gabor patches presented here) and for another foveal stimulus to remain visible (i.e. the fixation target) at the same time.

Complete fading versus partial loss of visibility during fixation

Troxler fading, the perceptual experience at the heart of the present study, is a gradual, rather than an instantaneous process. Often, an object becomes less and less visible until it eventually disappears (and then reappears, typically when microsaccades bring it back, as shown here). Other times, an object's visibility decreases at first, and then it is restored (again, usually in connection with microsaccade production) before

complete fading has occurred. The current research set out to quantify the *precise timing* of the interactions between microsaccades and perceptual experience (similarly to Martinez-Conde et al., 2006; McCamy et al., 2012). Thus, experimental subjects indicated when the target was faded/fading versus intensified/intensifying, rather than reported merely when the target was completely faded versus fully visible. Had we considered only "total fading" and disregarded "partial fading" events, we would have achieved an incomplete picture of the role of microsaccades in visual restoration, rather than the full, dynamic picture of the interactions between microsaccade production and the ongoing perceptual experience that characterizes natural vision. Future research may investigate how microsaccades and other fixational eye movements impact the perception of gradations in fading/visibility (i.e. by obtaining a continuous measure of the subject's perceptual experience, as in (Simons et al., 2006), rather than focus on the perceptual transitions to increased or decreased visibility (i.e. as in the present paradigm).

Fading prevention versus visibility restoration

Fixational eye movements are thought to overcome loss of vision by thwarting the neural adaptation (and thus the visual fading) ensuing from stable stimulation of the retinal receptors (Martinez-Conde et al., 2004). A fruitful discussion of the perceptual effects of microsaccades—in central vision and at other retinal eccentricities—must separately address their impact on counteracting (that is, reversing) fading versus preventing the fading from occurring in the first place (Martinez-Conde, et al., 2013). Here we set out to address the ability of microsaccades to counteract (i.e. reverse) fading; that is, to restore the visibility of already faded objects. Future research should establish

the ability of the different types of fixational eye movements to *prevent* rather than counteract fading (i.e. to prevent vision loss versus restore faded vision), as well as the physiological mechanisms by which fixational eye movements prevent and counteract neural adaptation.

Previous studies found that drift does not contribute strongly to reversing fading (Martinez-Conde, et al., 2006; McCamy, et al., 2012). Whereas microsaccades counteract fading once it has occurred, it is possible that both microsaccades and drift work together to prevent fading *before* it happens. Future research should also investigate this hypothesis.

In sum, fixational eye movements serve to prevent fading in the fovea and elsewhere, but not perfectly. Microsaccades have the ability to bring stimuli back to perception, when peripheral *and* foveal fading do occur.

Experiment 2 (The effect of microsaccades in the visibility of spatial frequency)

Previous studies have shown that microsaccades restore the visibility of faded visual targets at various retinal eccentricities: peripheral (6 and 9 degrees of eccentricity) and parafoveal (3 degrees eccentricity) (Martinez-Conde et al., 2006; McCamy et al., 2012). No research to date has investigated how microsaccade production may affect visibility as a function of the spatial frequency content of the visual target, however. Experiment #2 set out to determine the impact of microsaccades on the visibility of targets of varied spatial frequencies (0.375 cpd, 0.75 cpd, 1.5 cpd, 3 cpd and 6 cpd), presented peripherally.

Method

Subjects

Fifteen subjects (7 males, 8 females) with normal or corrected-to-normal vision participated in the experiments. Thirteen subjects were naive and were paid $15/session. Experiments were carried out under the guidelines of the Barrow Neurological Institute's Institutional Review Board (protocol number 04BN039). Written informed consent was obtained from each subject.

Experimental design

Subjects rested their forehead and chin on the EyeLink 1000 head/chin support, ~57 cm away from a linearized video monitor (Barco Reference Calibrator V, 75 Hz refresh rate). The experiment consisted of four sessions of ~ 1 hour, each including 50

randomly interleaved 30-second trials. The first session was counted as a training session and not included in the analyses.

While fixating a small red spot (0.5º diameter) on the center of the screen, subjects continuously reported whether a stimulus was faded/fading (button press) or intensified/intensifying (button release) (Martinez-Conde, et al., 2006; McCamy, et al., 2012;). The stimulus was a Gabor patch with a peak-to-trough width of 2.5º (Gaussian standard deviations of x = 1.5º and y = 1º; sine wave period of 5º; sine wave phase of 0). The Gabor was presented at the periphery at a eccentricity of 6º, and five possible spatial frequency levels (0.375 cpd, 0.75 cpd, 1.5 cpd, 3 cpd, and 6 cpd), sustaining a maximum contrast of 40% from peak-to-trough and the same average luminance (50%) as the background. The position of the Gabor varied randomly across trials at one of the eight points of the compass to control for possible contrast adaption effects across trials. The orientation of the Gabor also varied randomly between 0º and 360º in each trial, to control for orientation adaptation effects (Martinez-Conde, et al., 2006; McCamy, et al., 2012). To start the trial, subjects pressed a key and the stimulus appeared on the screen. Subjects were instructed to release the button as soon as they saw the stimulus. After 30 seconds, the stimuli disappeared and the trial ended.

Eye movement analyses

Eye position was acquired noninvasively in both eyes at 500 Hz (EyeLink 1000, SR Research). Saccades were identified with a modified version of the algorithm developed by Engbert & Kliegl (Engbert, 2006; Engbert & Kliegl, 2003; Engbert &

Mergenthaler, 2006; Laubrock, Engbert, & Kliegl, 2005; Rolfs, Laubrock, & Kliegl, 2006) as in Costela et al., 2013. Microsaccades were defined as saccades with magnitude < 1º in both eyes (Martinez-Conde et al., 2009, 2013). To calculate microsaccade properties such as magnitude and peak velocity we averaged the values for the right and left eyes. **Figure 13A-B** shows the magnitude distribution (**Figure 13A**) and peak velocity-magnitude relationship (**Figure 13B**) for both microsaccades (<1°) and saccades (≥1°). All subsequent analyses (**Figures 16-18**) concern microsaccades only, that is, saccades with magnitude <1°.

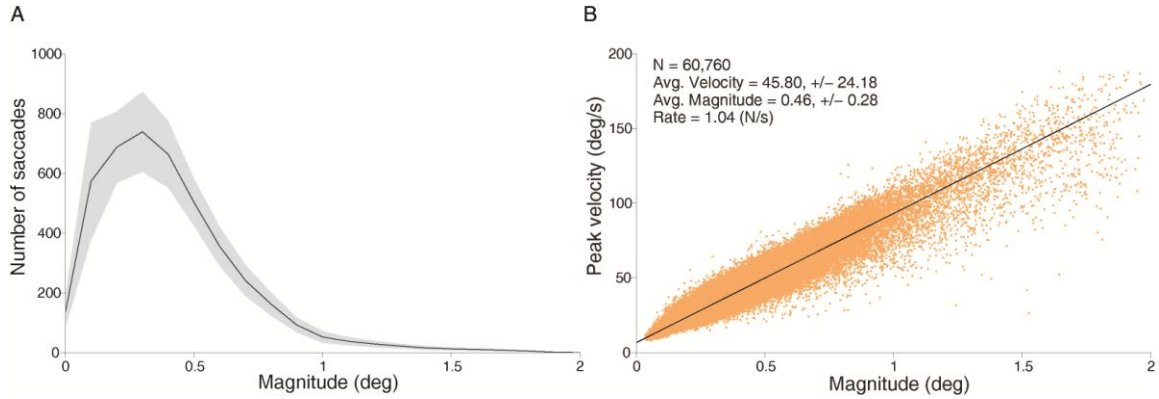

Figure 13. Descriptive statistics for microsaccades (<1°) and saccades (≥1°). A) Microsaccadic and saccadic magnitude distribution for all subjects combined (n = 15). B) Microsaccadic and saccadic peak velocity–magnitude relationship for all subjects combined. Each orange dot represents a microsaccade or a saccade with peak velocity indicated on the y-axis and magnitude indicated on the x-axis. The inset legend shows the microsaccade descriptive statistics. Error bars and shadows indicate the SEM across subjects.

Microsaccade correlations with reported transitions

We obtained correlations of microsaccades with reports of intensification for each subject following similar methods as in Experiment #1. Average correlations are the average of the smoothed correlations (**Figures 16-18**).

ROC Analysis

We used a sliding receiver operating characteristic (ROC) analysis (Britten et al., 1992; Feierstein et al., 2006; Green & Swets, 1966; Hernandez, Zainos, & Romo, 2002; Romo, Hernandez, & Zainos, 2004; Romo et al., 2002; Troncoso et al., 2008) to quantify how well microsaccade rate may predict the type of perceptual transition (towards intensification versus fading) reported by the subjects, for the different foveal target contrasts. ROC analysis details as in Troncoso et al., 2008.

Statistical methods

To analyze the effect of target contrast on time faded per trial and rate of fading onsets (**Figure 14A-B**), we conducted separate single-factor repeated measures ANOVAs with the different contrast levels tested as the within-subjects factor. All post-hoc comparisons were done using Tukey's HSD method. To assess whether microsaccade rates before transitions to intensification were significantly higher than those before transitions to fading, we performed one-tailed paired *t*-tests in each bin (bin size = 20 ms), using Bonferroni correction to account for multiple comparisons (**Figures 16-18**). Significance levels were set to $\alpha = 0.01$ throughout.

Results

Subjects fixated a small spot on the center of a computer screen and continuously reported, via button press/release, whether an unchanging visual target (a Gabor patch with 0.375 cpd, 0.75 cpd, 1.5 cpd, 3 cpd and 6 cpd frequency), presented at an eccentricity of 6º, was faded/fading or intensified/ intensifying (Martinez-Conde, et al., 2006; McCamy, et al., 2012). Fading prevalence was lower for the intermediate frequency levels (0.75 cpd, 1.5 cpd, and 3 cpd) (**Figure 14A**). The 0.375 cpd frequency target generated the largest number of perceptual transitions, as indicated by subjects' reports (**Figure 14B**).

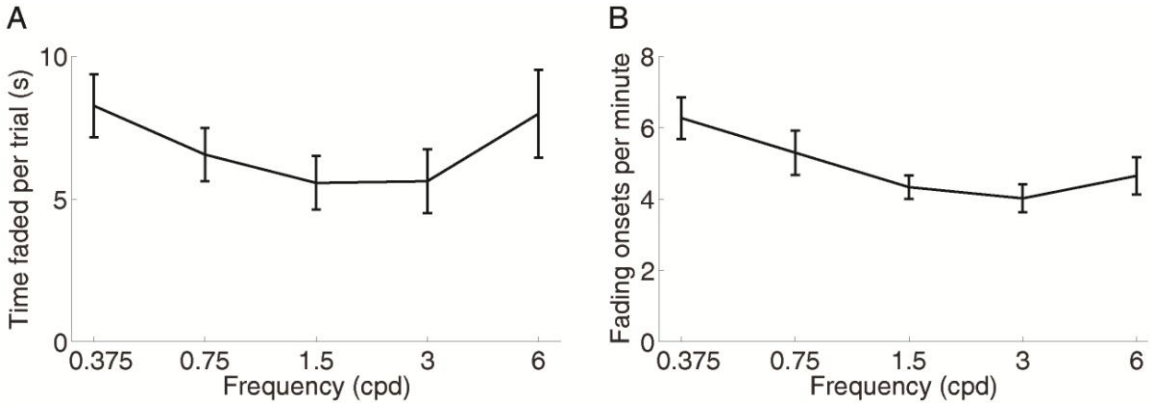

Figure 14. Psychometric measures of perceptual reports. A) Average time faded per trial for each target frequency. The effect of frequency was significant ($F(4, 56) = 6.153$, $p = 0.00035$). A Tukey HSD posthoc comparison showed a significant difference between both third and fourth levels (1.5 cpd and 3 cpd) in respect to the first and fifth level (0.375 cpd, 6 cpd) ($p < 0.05$). B) Fading onset rate for each target frequency. The effect of frequency was significant ($F(4, 56) = 8.51$, $p = 0.00002$). A Tukey HSD posthoc comparison showed a significant difference between the 0.375 cpd frequency and the highest 3 frequency levels, and between the 0.75 cpd frequency and the 3 cpd frequency level ($p < 0.05$). Error bars indicate the SEM across subjects ($n = 15$).

The length and number of fading and intensification periods depended on the targets' spatial frequencies. The 3 cpd frequency target resulted in the longest intensification period, and the 0.375 cpd frequency target produced the smallest difference between the length of fading and intensification periods (**Figure 15**).

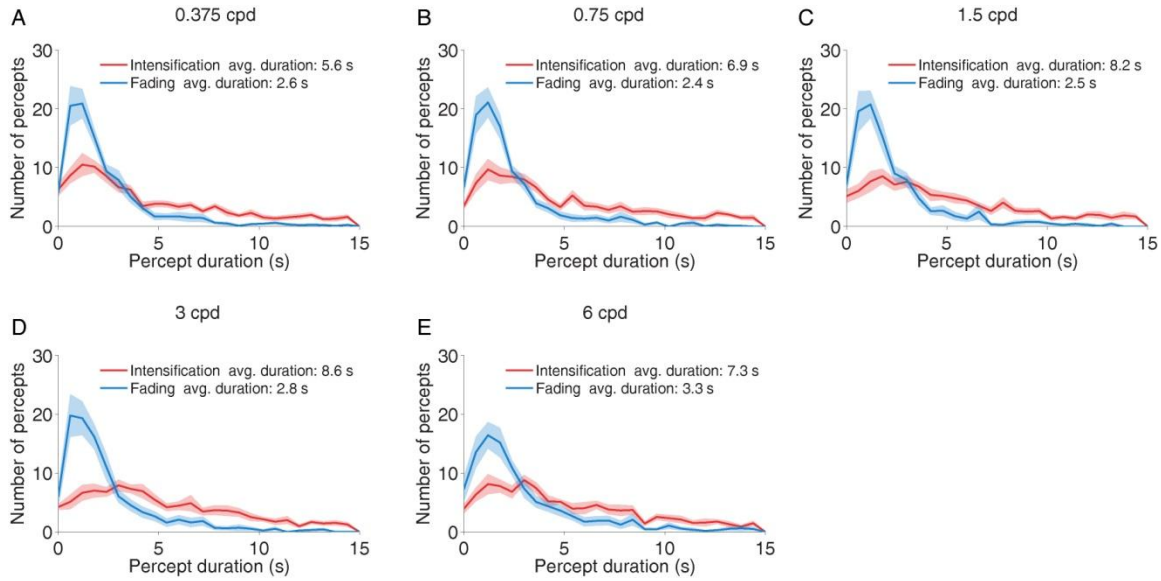

Figure 15. Number of perceptual reports. C-F) Distribution of the durations of intensification and fading periods for each target frequency. Red and blue shadows indicate the SEM across subjects (n = 15).

Microsaccade rates increased before transitions to intensification and decreased before transitions to fading, with the lowest frequency targets (0.375 cpd and 0.75 cpd) showing the clearest correlations between microsaccade rate increases and intensification reports. The highest frequency (6 cpd) showed the weakest correlation between microsaccade rate and both intensification and fading reports (**Figure 16**).

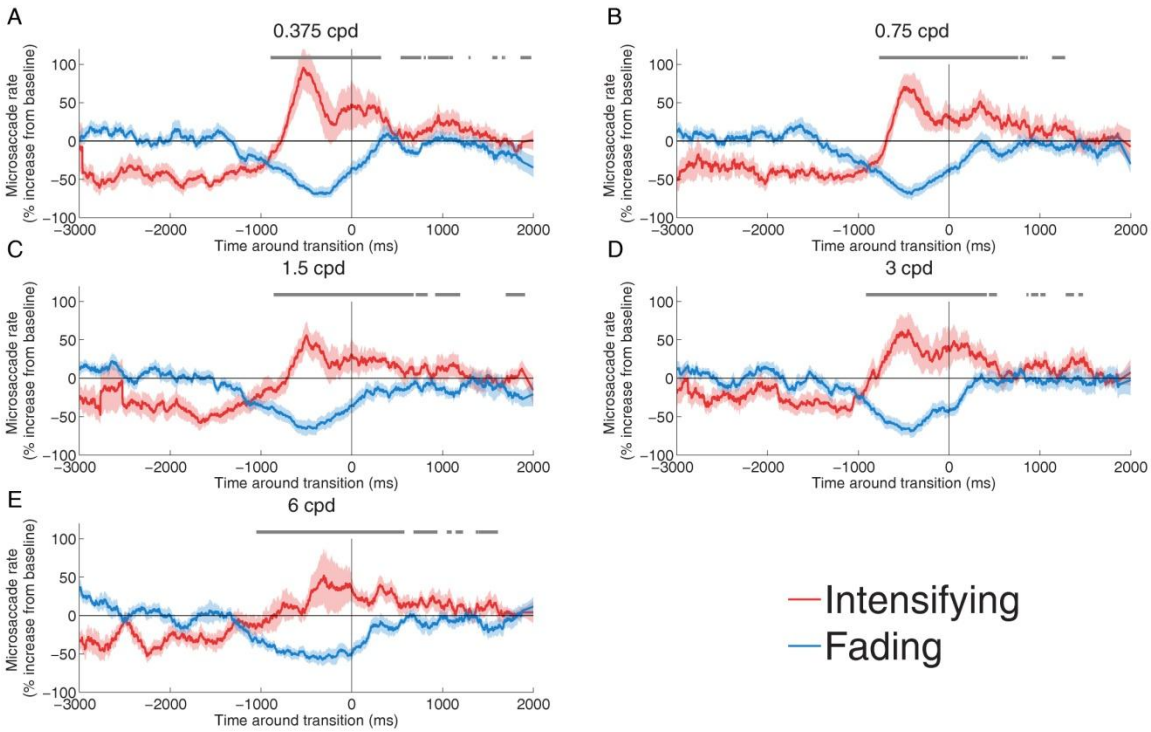

Figure 16. Microsaccade correlations with reported transitions. A-E) Percent increase in microsaccade rate over baseline (i.e. relative to the average microsaccade rate (dashed horizontal line) for a given target frequency) around reported transitions toward intensification versus fading, for each target frequency. The solid vertical line indicates the reported transitions (t = 0). Target frequency is indicated at the top of each panel. The gray lines at the top indicate the bins where microsaccade rates before transitions to intensification were significantly higher than microsaccade rates before transitions to fading (see Methods for details). Red and blue shadows indicate the SEM across subjects (n = 15).

Microsaccade magnitude

We analyzed the effects of microsaccade size on perceptual transitions to intensification and fading. To do this, we binned microsaccades according to their sizes (0-15 arcmin, 15-30 arcmin, 30-45 arcmin, and 45-60 arcmin) and correlated them to the perceptual intensification and fading reports for each target spatial frequency (**Figure 17**). The smallest microsaccades failed to restore target visibility, especially for those targets with the highest spatial frequencies (not shown). This result is consistent with the

previous finding that larger microsaccades are more efficacious than smaller ones, possibly due to their increased ability to bring the neuronal receptive fields to uncorrelated stimulus regions (McCamy, et al., 2012). As microsaccades grew in size, their correlation with perceptual transitions became stronger, also consistent with previous research (McCamy, et al., 2012).

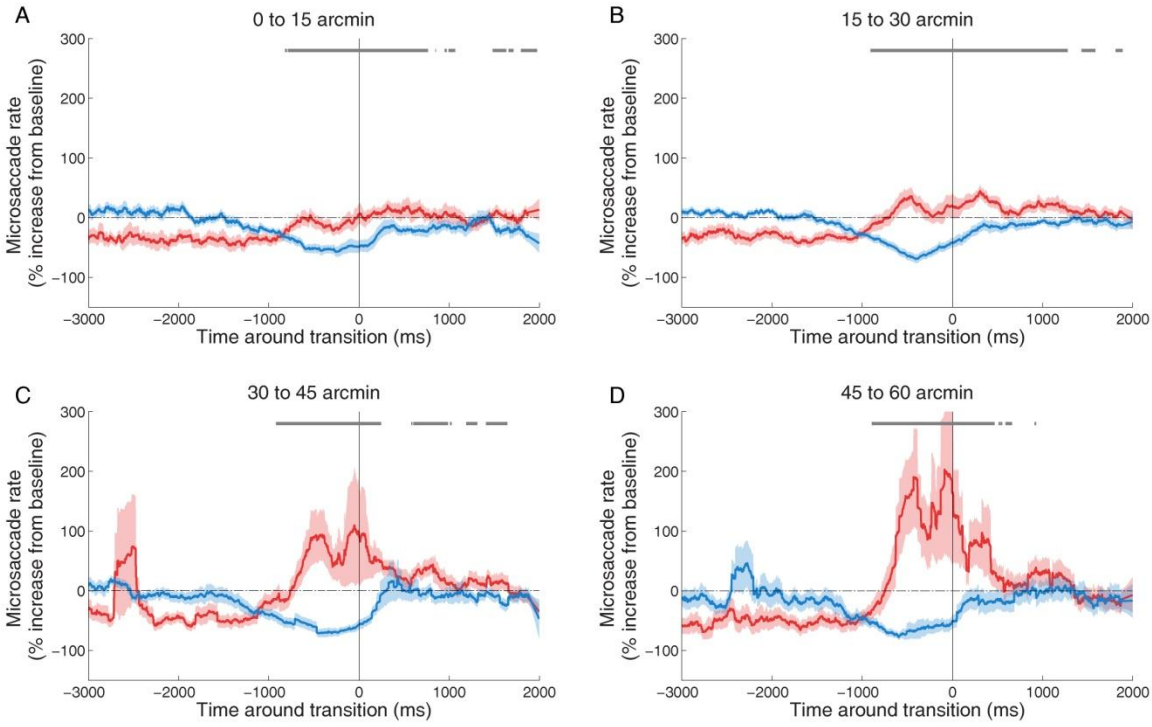

Figure 17. Correlations between microsaccades of different sizes and reported transitions. Microsaccade sizes (0-15 arcmin; 15-30 arcmin; 30-45 arcmin; 45-60 arcmin) are indicated at the top of each panel and we have collapsed across target frequencies. All other details as in Figure 4.

ROC Analysis

To further quantify our conclusions, we conducted a sliding ROC analysis to calculate the ability of an ideal observer to predict the type of perceptual transition (towards intensification or fading) based on microsaccade rates. **Figure 18** shows that the ideal observer becomes significantly better than chance (determined by permutation analysis; see Methods for details) ≈ 750 ms before the reported transitions, for all target spatial frequencies except for 6 cpd (the highest spatial frequency tested).

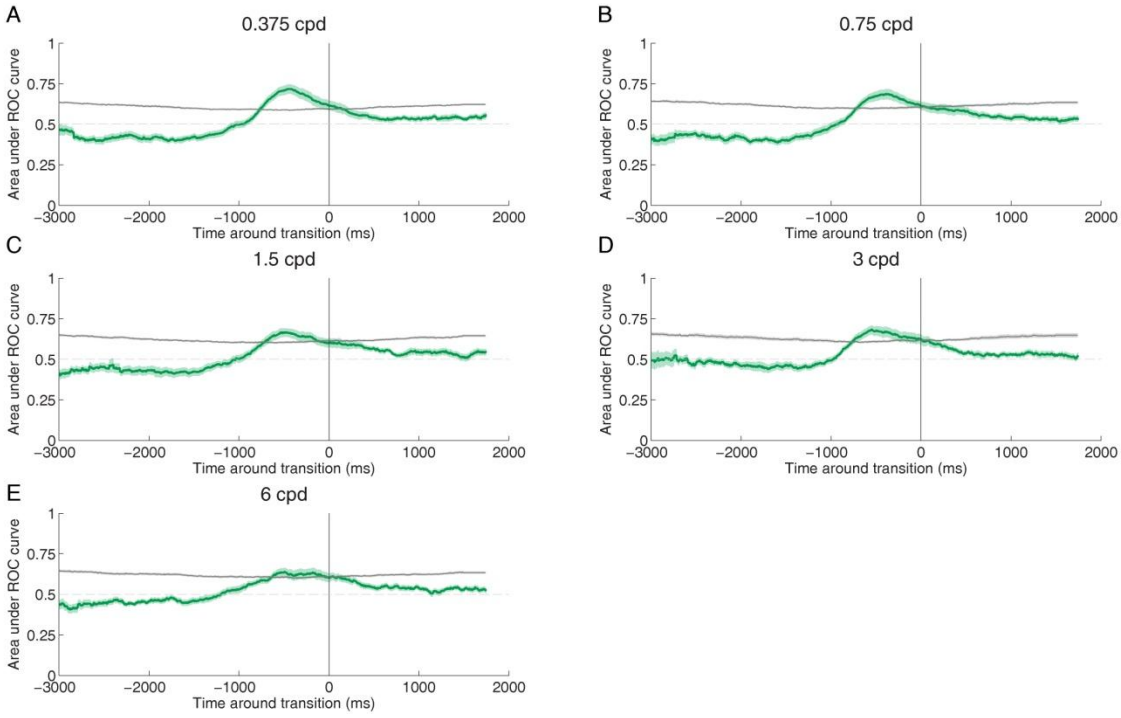

Figure 18. ROC analysis. A-E) The ideal observer can predict the type of illusory transitions (intensification vs. fading) based on microsaccade rate. The green line is the area under the ROC curve at any given time. The solid horizontal gray line indicates the significance level (i.e. the level at which the ideal observer performs above chance (horizontal dashed line; see Methods for details). Target frequency is indicated at the top of each panel. Significance is reached whenever the green line is above the grey line. The ideal observer's prediction (green line) becomes significantly better than chance ≈750 ms before the reported transitions, for target frequencies of 0.375, 0.75, 1.5, and 3 cpd. The shaded green area indicates the SEM across subjects (n = 15).

Discussion

Subjects reported the visibility of peripherally presented Gabor patches of various spatial frequencies (0.375 cpd, 0.75 cpd, 1.5 cpd, 3 cpd and 6 cpd). As with previous fading experiments (Spillmann and Kurtenbach, 1992; Martinez-Conde et al., 2006; Troncoso et al., 2008a; McCamy et al., 2012), subjects reported that the perceptual state of the targets appeared to oscillate between the faded/fading state and the visible/intensifying state. The 3 cpd frequency target resulted in the longest intensification periods, consistent with previous psychophysical findings.

Microsaccade rates increased before transitions to visibility and decreased before transitions to fading, also in agreement with previous reports (Martinez-Conde, et al., 2006; McCamy, et al., 2012; Troncoso et al., 2008). Whereas the lowest frequency targets (0.375 cpd and 0.75 cpd) showed the strongest correlations between microsaccade rate increases and intensification reports, the highest frequency targets (6 cpd) showed the weakest correlation between microsaccade rate and both intensification and fading reports.

Experiment 3 (Microsaccades correct blink-induced gaze position errors)

The role of microsaccades in the control and correction of fixation position has been controversial for over 50 years (Martinez-Conde et al., 2004, 2009, 2013; Rolfs, 2009). Cornsweet originally proposed that microsaccades serve to re-foveate the target after intersaccadic drifts (Cornsweet, 1956), but was subsequently challenged. By the end of the 1970s, most of the field agreed that microsaccades were not necessary for the control of fixation position, whereas drift (also called slow control) served that purpose (see (Rolfs, 2009) for a historical review). This conclusion remained uncontested until the early 2000s, when new analyses indicated that microsaccades introduce fixation errors on a short timescale, and correct fixation errors on a longer timescale (Engbert and Kliegl, 2004).

Research into the mechanisms of microsaccade generation has helped to clarify the role of microsaccades in fixation correction. Current findings support a combined role of neural noise and fixation error in triggering microsaccades during attempted fixation, with the contribution of each signal depending on the magnitude of the gaze position error (Otero-Millan et al., 2011a). For example, if a subject's gaze deviates from the target by ~0.5° or more, corrective microsaccades might rectify the error (Cornsweet, 1956; Otero-Millan et al., 2011b), whereas if the fixation error is small or insignificant, neural noise might trigger subsequent microsaccades instead (Otero-Millan et al., 2011a).

Otero-Millan et al previously showed a corrective role for microsaccades in the form of SWJ pairing (Otero-Millan et al., 2011b, 2013b), but it is not known whether microsaccades play a more general role in error correction during fixation. Indeed, the role of microsaccades in improving fixation stability remains in question (Collewijn and

Kowler, 2008), as do the comparative roles of drift and microsaccades in oculomotor control (Rolfs, 2009).

Here we set out to a) characterize the fixation errors due to gaze position changes caused by spontaneous blinks, and b) probe the comparative significance of microsaccades and drift for the correction of blink-induced gaze errors. Our results indicate that blinks contribute to gaze instability during fixation (i.e. eye motion during blinks results in sizable fixation errors at the end of the blinks) and that microsaccades correct blink-induced fixation errors better than drifts.

Method

Subjects

Non-human primates

Eye position was recorded monocularly at 1000 Hz with a scleral search coil (Robinson, 1963; Martinez-Conde et al., 2000, 2002). Recordings included data from five awake adult rhesus macaques (*Macaca mulatta*). Three monkeys were studied at Harvard Medical School (Eye-tracking equipment by Remmel Labs, Inc) and two monkeys were studied at the Barrow Neurological Institute (Eye-tracking equipment by Riverbend Instruments, Inc). Standard sterile surgical techniques, recording procedures and animal care methods were approved by the Harvard Medical School Standing Committee on Animals and the Institutional Animal Care and Use Committee at the Barrow Neurological Institute. Monkeys sat in a custom primate chair with their heads restrained, and fixated their gaze on a small fixation target on a video monitor (Reference Calibrator

V, 60-120 Hz refresh rate; Barco) placed at a distance of 57 cm. Fruit juice rewards were provided for every ~1.5-2 seconds of fixation. Eye movements exceeding a 2 x 2 deg fixation window were recorded but not rewarded. Three monkeys were tested during previously reported studies that addressed different experimental questions (Martinez-Conde et al., 2000, 2002).

The animals were bred in captivity and housed individually in non-human primate cages (group 4; dimensions 89 cm width, 147 cm height, 125 cm depth, including perch) for the duration of the experiment. Monkeys were provided with several kinds of environmental enrichment, including a television, various fruits and vegetables, food puzzles, perches, Kong toys, mirrors, and other enrichment tools as available, along with visual and auditory contact with several other monkeys that were also housed individually in the same room, and positive daily human contact. The room had a 12 hour light/dark cycle. Regular veterinary care and monitoring, balanced nutrition, and sensory and social environmental enrichment were provided in accordance to the National Institutes of Health Guide for the Care and Use of Laboratory Animals, to maximize physical and psychological well-being. Monkeys had abundant access to food (i.e. feed biscuits were provided twice a day (approximately 12 biscuits/monkey), Purina Lab Diet Monkey Diet, Product# 0001333). Daily fluid intake was controlled and monitored during the experiments. Monkeys typically earned over 80% of their daily fluid allotment during the testing sessions, and received water and/or fruit supplements after the experiments. Whenever the animals were not actively participating in testing or training

sessions (i.e. weekends, analysis and manuscript writing periods, etc), they had free access to water in the vivarium.

Cranial head-post and scleral search-coil implantation surgeries were conducted previous to the eye movement recordings, under general anesthesia using aseptic techniques, and with full post-operative analgesia and antibiotic therapy. No animals were sacrificed at the end of the experiments.

Humans

We recorded the eye movements of sixteen naive adult subjects (12 males, 5 females) with normal or corrected-to-normal vision, over 4 experimental sessions of ~30 min each, as part of a previously reported study (McCamy et al., 2013b). Experiments were carried out under the guidelines and ethical approval of the Barrow Neurological Institute's Institutional Review Board (protocol number 04BN039). Written informed consent was obtained from each subject, and each subject received $15/session. Subjects rested their forehead and chin on the EyeLink 1000 (SR Research) head/chin support 57 cm away from a linearized video monitor (Barco Reference Calibrator V, 75 Hz refresh rate). Subjects were instructed to look at a central circular target, or at the center of a 50% gray screen (see (McCamy et al., 2013b) for details). Trials were 30 s long, and subjects took short (~2–5 min) breaks after each eleventh trial. Each subjects' eye position was calibrated at the beginning of the experimental session, and re-calibrated after each break. We used custom code and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) to display visual stimuli. Six subjects were discarded

because they made fewer than 100 blinks. The present analyses do not overlap with analyses previously reported.

Blink detection

Non-human primates

We identified eye movements during blinks as epochs with sustained motion faster than typical drifts. Specifically, we classified an eye movement sample as part of a blink if 70% of the samples in the 200 msec around it had velocities above a threshold of 3 deg/s plus twice the median velocity of the recording. We added an extra 50 msec before and after each blink to account for the slow start and end of some blinks. To calculate the eye velocity associated with blinks, we low-pass filtered the eye position (50 Hz Butterworth filter of order 20), and then calculated the polar velocity and filtered it with a 21 msec boxcar filter. We defined the magnitude of an eye movement during a blink as the maximum excursion of gaze direction from the initial gaze position at the start of the blink to the final gaze position at the end of the blink (microsaccade and drift magnitudes were calculated similarly). We analyzed eye movements of all magnitudes during blinks. Blinks and microsaccades followed different magnitude/peak velocity relationships (i.e. microsaccades had higher peak velocities than blinks), suggesting that our detection algorithm distinguished blinks from microsaccades successfully (**Figure 19**). The blink magnitude/peak velocity relationship found here is moreover in agreement with that previously reported by (Goossens and Van Opstal, 2000).

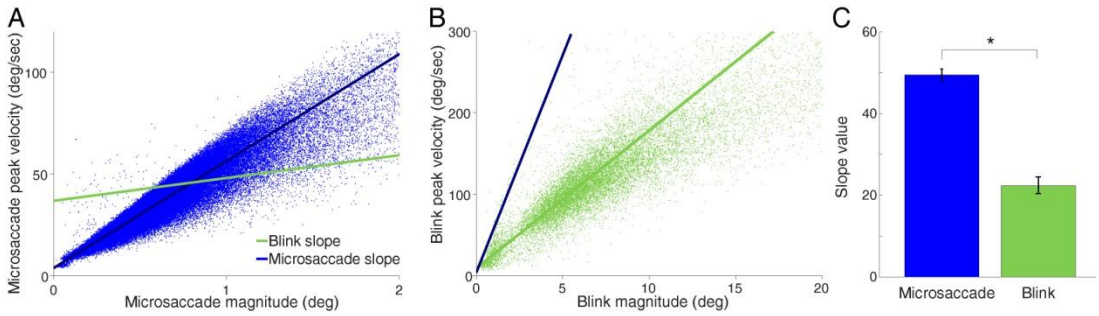

Figure 19. Microsaccadic magnitude/peak velocity relationships. (A) and blink magnitude/peak velocity relationship (B) for one experimental subject (monkey Y). Each dot represents one microsaccade or blink. The lines are the linear fits to the data. Microsaccadic peak velocity was greater than blink peak velocity. (C) Average slope for microsaccades and blinks. Error bars indicate the SEM across subjects. Asterisk indicates statistical significance (two-tailed paired *t*-test, $p < 0.05$) ($n = 5$ monkeys).

Humans

We identified blink periods as the portions of the EyeLink 1000 recorded data where the pupil information was missing. We added 100 ms before and after each period to further include the initial and final parts of the blink, where the pupil is partially occluded. We moreover removed those portions of the data corresponding to very fast decreases and increases in pupil area (>50 units per sample) plus the 100 ms before and after. Such periods are probably due to partial blinks, where the pupil is never fully occluded (thus failing to be identified as a blink by the EyeLink 1000 software) (Troncoso et al., 2008a).

Microsaccade detection

We identified saccades with a modified version of the algorithm developed by Engbert & Kliegl (Engbert and Kliegl, 2003; Laubrock et al., 2005; Engbert, 2006; Engbert and Mergenthaler, 2006; Rolfs et al., 2006) with $\lambda = 8$ (used to obtain the velocity threshold) and a minimum saccadic duration of 8 msec, in both humans and non-

human primates. Additionally, we imposed a minimum intersaccadic interval of 20 msec so that potential overshoot corrections might not be categorized as new saccades. We defined microsaccades as saccades with magnitude < 2º (Betta and Turatto, 2006; McCamy et al., 2013a, 2013b; Siegenthaler et al., 2014).

Drift detection

We only conducted drift analyses for the search coil-recorded non-human primate data. We defined drifts as the data between (micro)saccades, overshoots, and blinks, occurring in periods of at least 100 msec. To calculate the properties of each drift period, we low-pass filtered the eye position (60 Hz, Butterworth filter of order 13) and removed 10 msec at the beginning and the end to reduce edge effects due to the filter. We defined drift direction and magnitude as the direction and magnitude of the vector between the start and end of each drift.

Fixation error and correction ratio

We defined fixation error as the distance between the current eye position and the position of the fixation target. To quantify how well microsaccades and drift corrected fixation errors due to blinks, we defined the correction ratio (CR) as follows. For each blink and subsequent microsaccade/drift pair (that is, for the first microsaccade and drift that occurred immediately after the end of each blink), we calculated two quantities: BE, the blink error, which is the distance between the fixation point and the eye position at the end of the blink (the distance between point 1 and point 2 in **Figure 20B**, and the distance between point 2 and the black cross in **Figure 20C**), and D, the distance between

the fixation point and the eye position at the end of the first microsaccade/drift following the blink (the distance between point 4 and the black cross for microsaccades, and the distance between point 3 and the black cross for drifts, in **Figure 20C**). We defined the correction ratio as: $CR = \frac{\mathrm{BE}-\mathrm{D}}{\mathrm{BE}+\mathrm{D}}$. CR is always between -1 and 1, with positive values indicating corrective eye movements (microsaccades/drifts that decrease blink error), and negative values corresponding to non-corrective eye movements (microsaccades/drifts that increase blink error). If the microsaccade/drift brings the eye position to the exact original position then D = 0 and CR = 1.

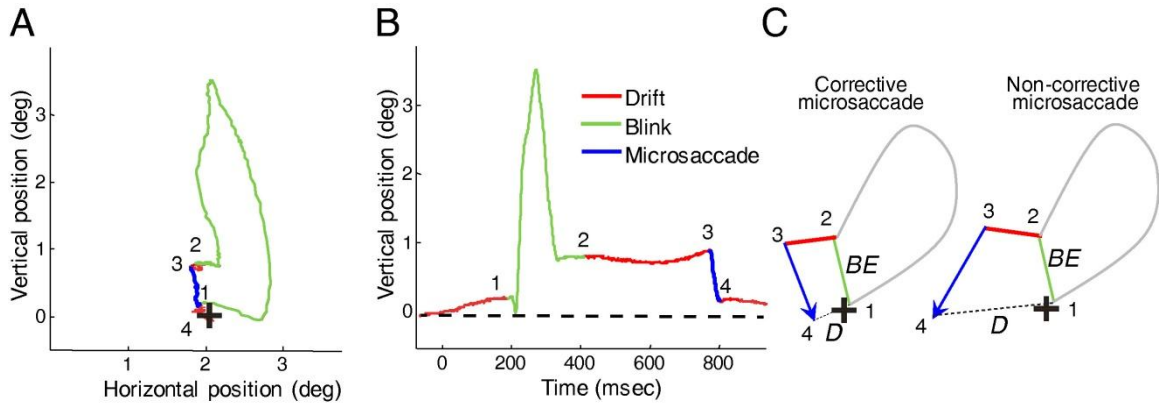

Figure 20. Blink-induced fixation errors. (A) Eye position trace showing an example of a blink (green) followed by drift (red) and then a microsaccade (blue). The black cross represents the fixation target. The eye position at the end of the blink (2) does not match the fixation target (black cross). A microsaccade corrects the error by bringing the eye from position (3) to (4), closer to the fixation target. (B) Vertical eye position for the same trace. The dashed line represents the fixation target. (C) Cartoons of corrective and non-corrective microsaccades. BE (dashed line) indicates the blink-induced fixation error and D (dotted line) the distance between the eye position at the end of the microsaccade and the fixation target. Left: the microsaccade reduces the blink-induced eye position error (D is shorter than BE). Right: the microsaccade increases the eye position error (D is longer than BE).

Permutation analyses

To test the significance of the CR values, we used a permutation analysis to calculate the correction ratio expected by chance. For each blink-induced error we measured CR by replacing the post-blink microsaccade with a randomly selected microsaccade (from all the post-blink microsaccades). That is, we replaced the microsaccade (from point 3 to point 4 in **Figure 20A**) with the new random microsaccade (effectively changing the position of point 4 in **Figure 20A**). Likewise, we replaced each post-blink drift with another random drift. We repeated the permutation method 1000 times and averaged the resulting CR values.

Results

Blink-induced fixation errors

Awake rhesus macaques fixated a small target while we recorded their eye movements with the scleral search coil technique (Robinson, 1963). During the fixation task, eye movements consisted primarily of microsaccades and drifts, in addition to occasional larger saccades and spontaneous blinks. Spontaneous blinks resulted in fixation errors of moderate size (0.88 +/- 0.45 deg on average)(See **Table 1**), where the eye position at the end of a blink did not match the position of the fixation target (**Figure 20**).

Table 1. Characteristics of non-human primate blinks.

Non-human primate	#Blinks	% blinks increasing fixation error	Blink rate (blinks/sec)	Average magnitude of blink-induced error (deg)	Median post-blink microsaccade latency (msec)
Y	22,686	75.71%	0.28	0.79	408
H	16,404	85.55%	0.23	0.83	345
C	9,797	72.92%	0.28	0.75	215
J	1,928	59.62%	0.19	1.28	202
F	43,700	58.74%	0.39	0.72	154

Fixation errors after blinks were generally larger than fixation errors previous to blinks (0.33 +/- 0.17 deg on average). (See **Table 2** for the average magnitude of fixation errors associated with different types of ocular events).

Table 2. Average magnitude of fixation errors induced by different types of ocular events. Fixation errors associated with blinks tended to be larger than those associated with (all) microsaccades or drifts, but not significantly so.

	Blinks	Microsaccades	Drifts
Non-human primates	0.88 +/- 0.45 deg	0.44 +/- 0.15 deg	0.76 +/- 0.18 deg
Humans	0.95 +/- 0.38 deg	0.68 +/- 0.16 deg	-

We set out to determine whether fixational eye movements (i.e. microsaccades and/or drift) produced after blinks might correct or reduce blink-induced fixation errors. We limited our analyses to those cases where the fixation error increased from pre-blink to post-blink. This occurred for the 70.50% of the non-human primate blinks.

The magnitudes of post-blink microsaccades were significantly correlated to those of blink-induced fixation errors ($p < 10^{-13}$; $r^2 = 0.075$) (**Figure 21A**). Moreover, the

direction of post-blink microsaccades was counter to that of blink-induced fixation errors (**Figure 21B**), supporting a potential corrective role for post-blink microsaccades. Microsaccade production was highest (74.12% of all post-blink microsaccades) in the first ~400 msec after the blink, and asymptoted subsequently (**Figure 21C**). Accordingly, post-blink fixation errors were largest immediately after the blink, and decreased gradually for the first several hundred msec, stabilizing at ~400 msec after the end of the blink (**Figure 21D**).

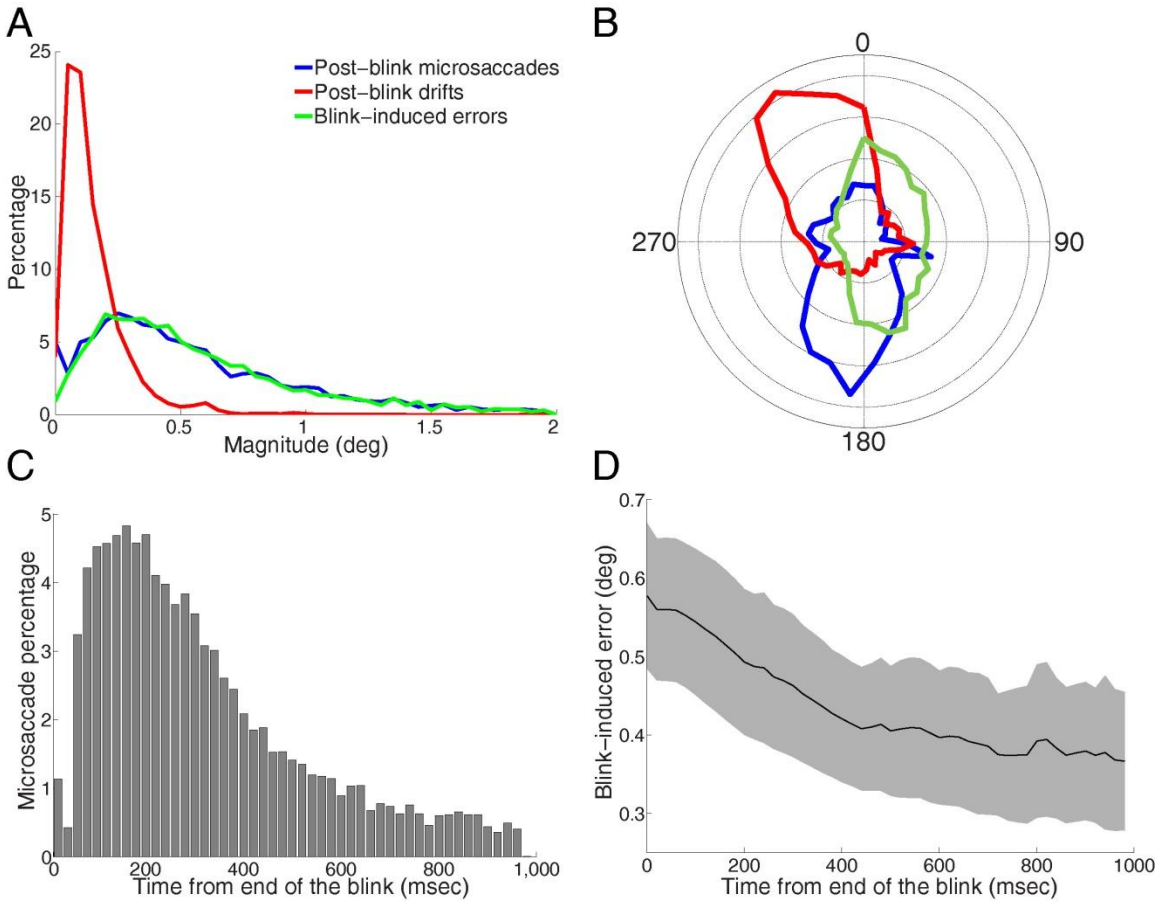

Figure 21. Blink-induced error and microsaccade properties. (A) Normalized magnitude distributions of blink-induced fixation errors, post-blink microsaccades, and post-blink drifts across non-human primates. The distribution of post-blink microsaccade magnitudes matches closely that of blink-induced fixation errors. (B) Polar histogram of the directions of blink-induced fixation errors, post-blink microsaccades, and post-blink drifts. Blink-induced fixation errors are more likely directed upward. Post-blink microsaccades tend to move the eye downward, thus counteracting the error introduced

by the blink. (C) Latency distribution for post-blink microsaccades (all monkeys combined): 74.12% of post-blink microsaccade onsets occurred in the initial 400 msec after the end of the blink. (D) Blink-induced error as a function of time, from the end of the blink onward. We calculated the blink-induced error at every point in time, whether there were concurrent microsaccades or drifts. The blink-induced error declines gradually, showing the largest decrease in the initial 400 msec interval, simultaneous to the highest production of post-blink microsaccades. Shaded area indicates the SEM across monkeys (n = 5 monkeys).

We conducted the same analyses for human fixational eye movements recorded with a high-speed video-tracker (EyeLink 1000, SR Research; see Methods for further details), and also limited the analyses to those cases where the fixation error increased from pre-blink (0.41 +/- 0.19 deg on average) to post-blink (0.95+/- 0.38 deg on average). This occurred for 61.23% of the blinks in the human data. The results were comparable to those found in non-human primates (**Figure 25**). Microsaccade production was highest (61.32% of all post-blink microsaccades) in the first ~200 msec after the blink (**Figure 25A**). Correspondingly, blink-induced fixation errors greatly decreased during this period, stabilizing at ~400 msec after the end of the blink (**Figure 25B**).

Corrective role of microsaccades and drift

To further establish whether fixational eye movements might correct post-blink gaze position errors, we calculated the correction ratio for microsaccades and drifts (CR; i.e. how much microsaccades and drifts reduced (positive CR) or increased (negative CR) such errors; see *Methods*). 76.65% of all post-blink microsaccades and 47.82% of all post-blink drifts reduced blink-induced error (positive CR). To establish significance, we compared those values to a chance level determined by random permutations (see

Methods), and found that microsaccades, but not drifts, significantly corrected blink-induced errors in primates (**Figure 22**).

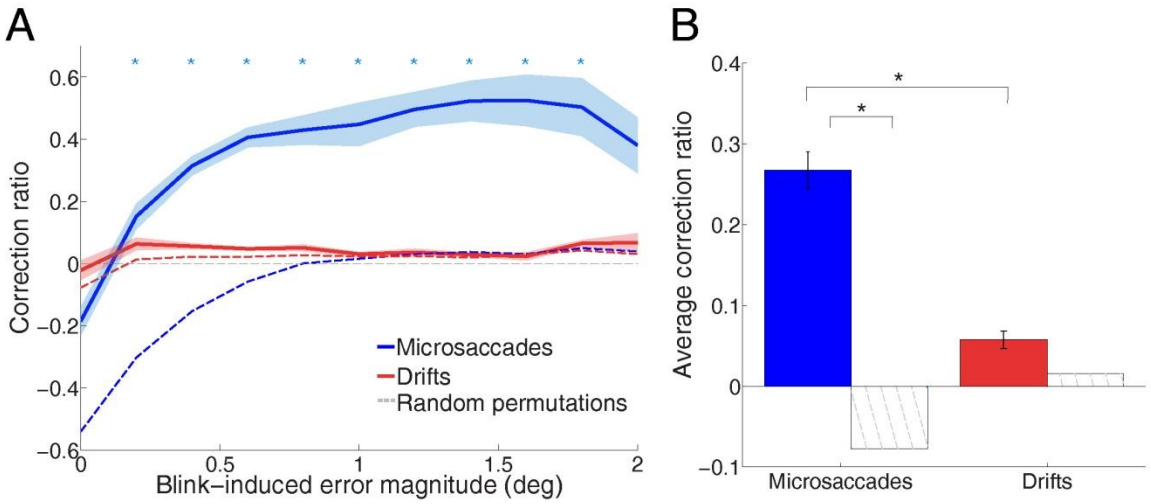

Figure 22. Blink-induced error correction by fixational eye movements. (A) Correction ratio for microsaccades and drifts (solid lines) versus random permutations (dotted lines) as a function of error magnitude. Asterisks indicate statistical significance (two-tailed paired *t*-test between microsaccade or drifts and permutations, Bonferroni corrected $p < 0.01$). Microsaccades correct blink-induced fixation errors better than chance (i.e. random permutations; see *Methods* for details). Drifts are not significantly different than permutation. Microsaccades corrected large blink-induced errors (>0.2 degrees) better than small blink-induced errors. Error bars and shaded areas indicate the SEM across monkeys ($n = 5$). **(B)** Average correction ratio for microsaccades and drifts (filled bars) compared to chance (striped bars). Asterisks indicate statistical significance (two-tailed paired *t*-test, $p < 0.01$) ($n = 5$ monkeys).

In humans, 82.39% of all post-blink microsaccades reduced blink-induced error. Also consistent with the primate results, human microsaccades corrected blink-induced errors significantly better than chance (**Figure 26**). We did not perform drift analyses on the human eye movement data (see *Methods*).

Large blink-induced errors (>0.2 deg) were more effectively corrected than smaller ones in the primate (**Figure 22A**). We note that the chance level for the CR is

negative (rather than zero) for small blink-induced fixation errors. In the presence of very small errors, microsaccades will tend to be error-increasing rather than error-correcting, owing to being larger than the error. **Figure 23** illustrates blink-induced error magnitude as a major determinant of microsaccade triggering: large or moderate fixation errors resulted in corrective microsaccades (**Figure 23A**), whereas smaller errors led to microsaccades of random directions (**Figure 23B**). In the latter case, microsaccades overshot the zero position typically, even if they traveled in the adequate direction to correct the error (**Figure 23B**).

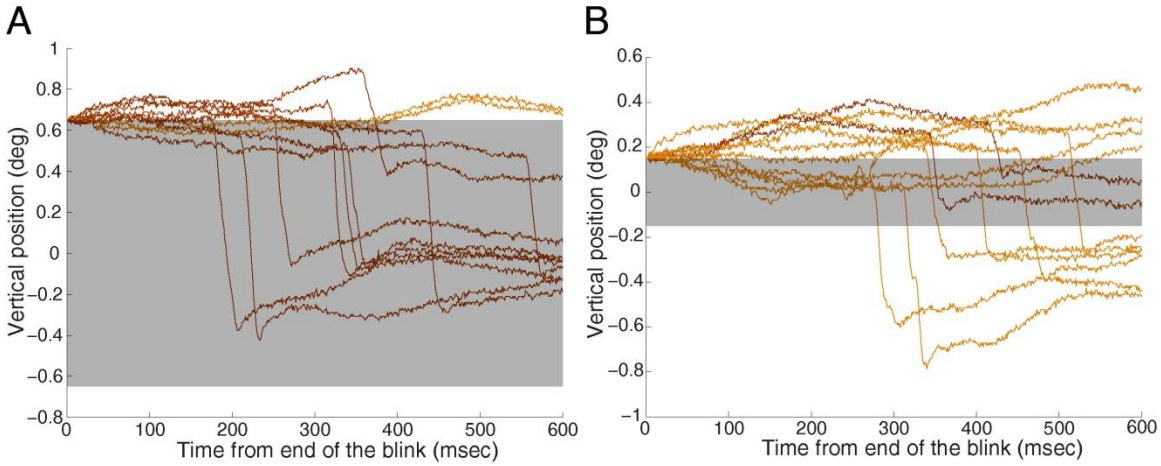

Figure 23. Microsaccades decrease large and increase small blink-induced fixation errors. (A) Vertical eye-position traces after 11 randomly-selected blinks that led to large vertical errors ([0.64-0.66 deg], monkey Y). (B) Vertical eye-position traces after 11 randomly-selected blinks that led to small vertical errors ([0.14-0.16 deg], monkey Y). (A, B) Grey band: range of final eye positions resulting in a positive CR. Brown traces: microsaccades decreased the blink-induced error. Orange traces: microsaccades increased the error. [We note that, although we considered all blinks in our analyses, blinks that took the eye below the fixation point were relatively infrequent (~18%). Thus, this figure illustrates the more typical situation where blinks induced errors above the fixation point].

If gaze position errors due to blinks trigger corrective microsaccades, then microsaccades occurring shortly after blinks should be more corrective than

microsaccades produced later on. Correspondingly, the primate data show that the most corrective post-blink microsaccades had the shortest latencies (**Figure 24A**). Further, microsaccade latencies after blinks were inversely related to the magnitude of the blink-induced errors (**Figure 24B**). That is, microsaccades occurred earlier after large than small fixation errors due to blinks, and those microsaccades produced quickly after blinks corrected gaze position errors better than microsaccades that occurred later in time.

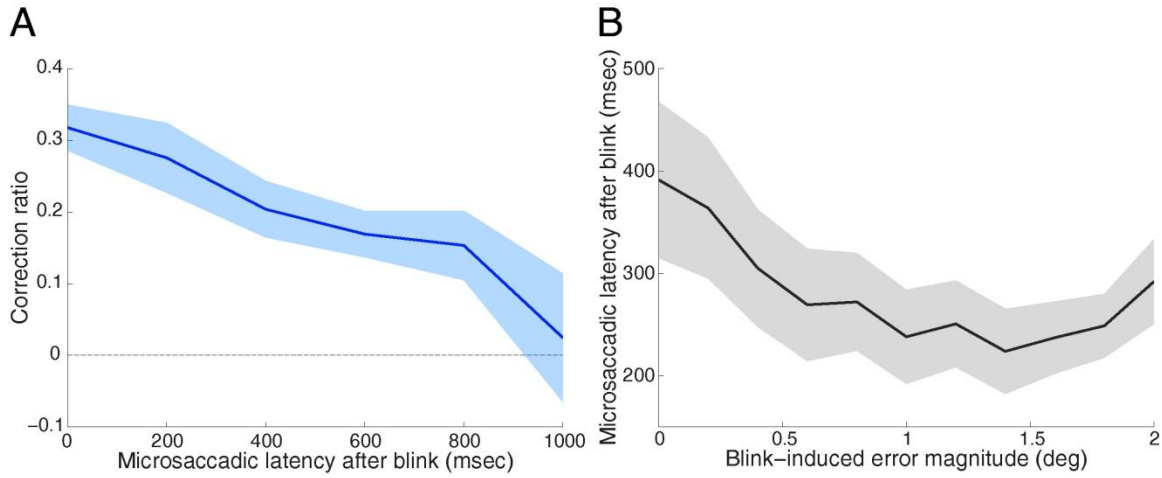

Figure 24. Latency of microsaccades after blinks. (A) Relationship between post-blink microsaccadic latency and correction ratio. Microsaccades occurring shortly after blinks were more corrective than microsaccades occurring later in time. (B) Relationship between blink-induced error magnitude and post-blink microsaccadic latency. Microsaccade latencies were shorter after large than small errors. Shaded areas indicate the SEM across monkeys (n = 5).

Equivalent analyses of the human eye movement data showed comparable results (**Figure 27**).

Our combined results indicate that blinks contribute to the instability of gaze during fixation, and that microsaccades help to correct the fixation errors introduced by blinks.

Discussion

Many microsaccade functions have been proposed, such as keeping the fixated region centered on the optimal locus (Cornsweet, 1956 p.19; Nachmias, 1961; Boyce, 1967; St.Cyr and Fender, 1969; Engbert and Kliegl, 2004; Putnam et al., 2005; McCamy et al., 2013b), counteracting and preventing perceptual fading (Martinez-Conde et al., 2006; Troncoso et al., 2008a; McCamy et al., 2012, 2013a, 2014a; Costela et al., 2013), enhancing fine spatial detail/improving visual acuity (Donner and Hemilä, 2007; Rucci et al., 2007), scanning small visual regions (Haddad and Steinman, 1973; Otero-Millan et al., 2013a), and sampling the informative regions of a scene (McCamy et al., 2014b). In addition, microsaccades have been linked to the perception of illusory motion in certain static repetitive patterns (Troncoso et al., 2008b; Otero-Millan et al., 2012) (presumably in combination with cortical activation of motion-selective neurons, see (Gori et al., 2006; Kuriki et al., 2008; Ashida et al., 2010; Ruzzoli et al., 2011)**)**. These various roles need not be mutually exclusive but may overlap considerably.

Here we examined the characteristics of gaze position errors induced by spontaneous blinks in fixating primates and humans, and set out to assess how subsequent fixational eye movements, including microsaccades and drift, might correct them. To our knowledge, no previous studies have determined the comparative contributions of post-blink microsaccades and drifts to the correction of blink-induced errors.

Blink-induced fixation errors

Blinking dynamics have been described in humans and in non-human species (Ginsborg, 1952; Ginsborg and Maurice, 1959 p.19; Evinger et al., 1984; Porter et al., 1993; Gruart et al., 1995). In the alert cat, spontaneous blinks consist of a fast, large downward lid movement followed by a slower up phase (Gruart et al., 1995). In humans, transient downward and nasalward movements of both eyes, with amplitudes ranging from one to several degrees, tend to accompany voluntary and reflex blinks (Collewijn et al., 1985; Riggs et al., 1987). Blink-induced gaze position errors and subsequent corrective saccades have been reported in humans (Collewijn et al., 1985; Takagi et al., 1992) and primates (Goossens and Van Opstal, 2000). (Interestingly, strong eye retraction in fish --an early precursor of the eyelid blinks of terrestrial animals-- also elicits the return of both eyes to a central position in the orbit (Pastor et al., 1991)). Our present results extend this research by indicating that a) Eye motion during spontaneous blinks results in sizable gaze-position errors in fixating primates and humans, and b) The magnitude of these blink-induced fixation errors (0.88 +/- 0.45 deg on average in primates and 0.95 +/- 0.38 deg on average in humans; **Figures 20A-B**, **21D**, **Figure 26, Table 1**) is such that microsaccades work to reduce them, and to return the eye to the fixation position.

Corrective role of microsaccades and drift

Having determined that eye movements during blinks result in sizable gaze position errors (**Figures 20A-B**, **21D**, **Table 1**), we set out to measure the comparative contributions of subsequent microsaccades and drift to their correction. Our results show

that primate microsaccades work to correct blink-induced gaze position errors during fixation, whereas drifts do not correct better than chance. Our results also indicate that primate and human microsaccades are similarly corrective.

Microsaccades corrected large blink-induced errors better than small blink-induced errors, consistent with the report that large fixation errors (due to error-inducing microsaccades) act to trigger subsequent corrective microsaccades of similar magnitude and opposite direction, resulting in SWJs (Otero-Millan et al., 2011b). Our results are also compatible with the proposal that microsaccades are error-inducing on a short timescale and error-correcting on a longer timescale (Engbert and Kliegl, 2004), and indicate that microsaccades play a more general role in error correction during fixation than thought previously.

In sum, our data indicate that 1) blinks contribute to the instability of gaze during fixation in the primate, 2) microsaccades but not drifts correct fixation errors introduced by blinks better than chance, 3) large fixation errors are better corrected than small errors, and 4) that primate and human microsaccades are similarly corrective. These findings provide new insights about eye position control during fixation.

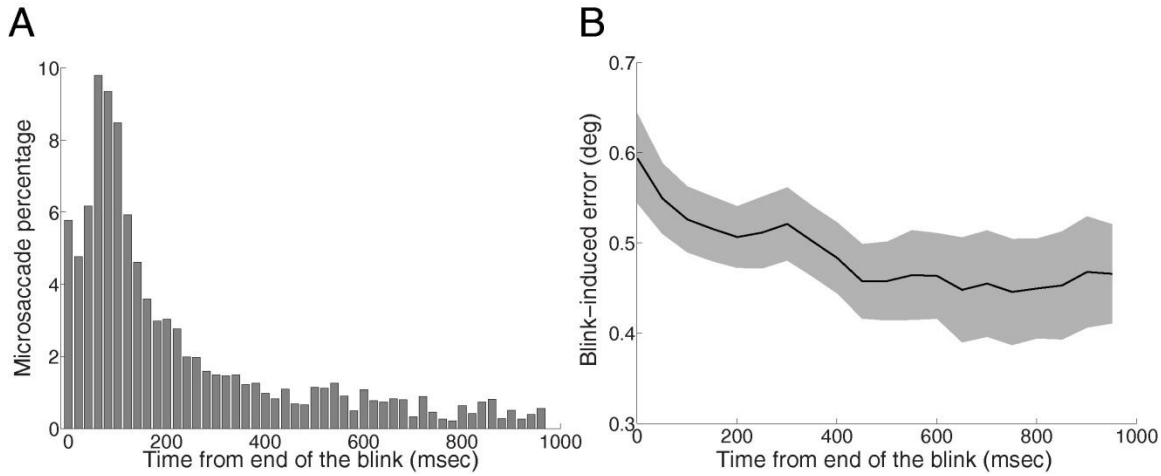

Figure 25. Blink-induced error and microsaccade properties in human subjects. (A) Latency distribution for post-blink microsaccades (all human subjects combined): 61.32% of post-blink microsaccade onsets occurred in the initial 200 msec after the end of the blink. (B) Blink-induced error as a function of time, from the end of the blink onward. We calculated the blink-induced error at every point in time, whether there were concurrent microsaccades or drifts. The blink-induced error declines gradually, showing the largest decrease in the initial 400 msec interval, simultaneous to the highest production of post-blink microsaccades. Shaded area indicates the SEM across human subjects (n = 11).

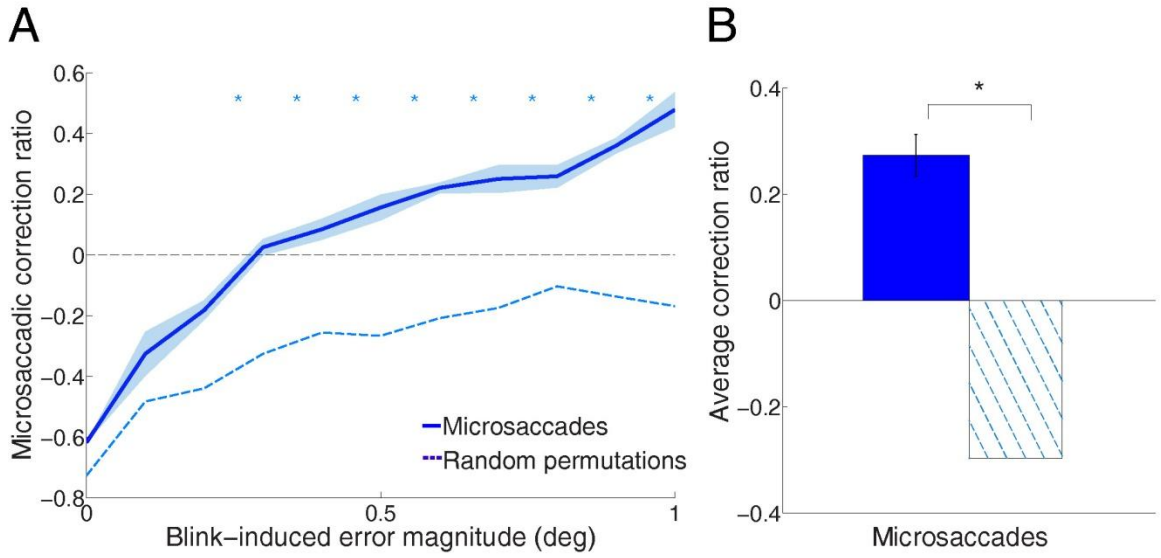

Figure 26. Blink-induced error correction by microsaccades in human subjects. (A) Correction ratio for microsaccades (solid lines) versus random permutations (dotted lines) as a function of error magnitude. Asterisks indicate statistical significance (two-tailed paired t-test between microsaccade and permutations, Bonferroni corrected $p < 0.01$). Microsaccades correct blink-induced fixation errors better than chance (i.e. random permutations; see *Methods* for details). Microsaccades corrected large blink-induced errors (>0.2 degrees) better than small blink-induced errors (see Figure 4). (A,B) Error bars and shaded areas indicate the SEM across humans (n = 11). (B) Average correction

ratio for microsaccades (filled bars) compared to chance (striped bars). Asterisks indicate statistical significance (two-tailed paired *t*-test, $p < 0.01$) ($n = 11$ subjects).

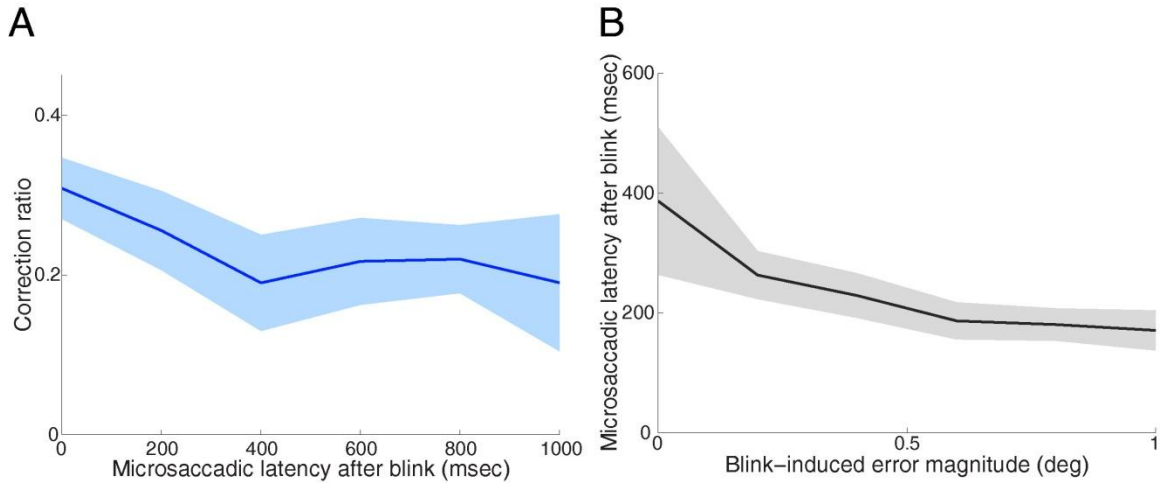

Figure 27. Latency of microsaccades after blinks in human subjects. (A) Relationship between post-blink microsaccadic latency and correction ratio. Microsaccades occurring shortly after blinks were more corrective than microsaccades occurring later in time. (B) Relationship between blink-induced error magnitude and post-blink microsaccadic latency. Microsaccade latencies were shorter after large than small errors. Shaded areas indicate the SEM across humans ($n = 11$ subjects).

Experiment 4 (Characteristics of SWJs in the primate)

Attempted visual fixation of a target is repetitively interrupted by saccadic intrusions (SIs) and fixational eye movements. SWJs (SWJs), the most frequent type of saccadic intrusion (SI), consist of an initial saccade away from the fixation target, followed by a return saccade that brings the eye back onto target (Abadi and Gowen, 2004).

SWJs are present in most human subjects, but occur with increased frequency in patients with progressive supranuclear palsy (PSP), Parkinson's disease, and recessive, hereditary spinocerebellar ataxia (Rascol et al., 1991; Abadi and Gowen, 2004; Fahey et al., 2008; Otero-Millan et al., 2011b, 2013b; McCamy et al., 2013b).

Fixational eye movements include tremor, drift, and microsaccades (i.e. small-magnitude saccadic eye movements, also called fixational saccades) (Martinez-Conde et al., 2004, 2013; Rolfs, 2009) and can be observed in human and nonhuman primates, as well as in other foveate species (Martinez-Conde and Macknik, 2008).

Recent research has shown that SWJs and microsaccades share similar features in both healthy human subjects and in patients with a variety of neurological disorders (Otero-Millan et al., 2011b, 2013b), and suggests that SIs (including SWJs) and microsaccades are part of a continuum of fixational instabilities (Gowen et al., 2007), generated by a common neural circuit (Martinez-Conde et al., 2013).

Previous studies have moreover reported irrepressible saccades and SWJs in monkeys with tectal and cerebellar lesions (Weber et al., 1989; Carasig et al., 2006; Gnadt et al., 2013). It is not known, however, if SWJs are also present in healthy nonhuman primates. This question is interesting, not only because of the importance of the macaque monkey brain to oculomotor neurophysiology studies, but also because, unlike human microsaccades and saccadic intrusions, which are predominantly horizontal, microsaccades in monkeys do not typically display a horizontal preference (Cui et al., 2009). Here we set out to determine the characteristics of SWJs in healthy rhesus macaques during attempted fixation of a small visual target.

From here on, for simplicity, we will refer to all (micro)saccades made during attempted fixation as fixational saccades or, simply, saccades, regardless of size.

Method

Animals

Eye position was recorded monocularly at 1000 Hz with a scleral search coil (Robinson, 1963; Martinez-Conde et al., 2000, 2002). Recordings included data from five awake rhesus macaques (*Macaca mulatta*). See Animal description from Experiment #3 for details.

Saccade detection

We identified all saccadic eye movements automatically with a modified version of the algorithm developed by Engbert & Kliegl (Engbert and Kliegl, 2003; Laubrock et al., 2005; Engbert, 2006; Engbert and Mergenthaler, 2006; Rolfs et al., 2006). This method detects saccades in the two-dimensional velocity space using a threshold that adapts to the level of noise of each recording. We set $\lambda = 8$ (used to obtain the velocity threshold) and established a minimum saccadic duration of 8 msec. Some saccades are followed by a fast and small saccadic eye movement in the opposite direction, called dynamic overshoot, which is often more prominent in the eye that moves in the abducting direction (Kapoula et al., 1986). Unlike the return saccade in a SWJ, a dynamic overshoot follows a saccade without latency between the two movements. We identified dynamic overshoots as saccades that occurred less than 20 ms after a preceding saccade (Møller et al., 2002; Troncoso et al., 2005, 2008a, 2008b), and considered them part of the preceding saccade (i.e. we did not regard them as new saccades). That is, we discarded the second saccade and modified the end point of the first saccade to include the overshoot. **Figure 29** shows the peak velocity-magnitude relationship (main sequence) for fixational saccades with magnitudes < 2 degrees of visual angle [deg] (Betta and Turatto, 2006; Martinez-Conde et al., 2006, 2009; McCamy et al., 2013a, 2013b; Siegenthaler et al., 2014), and the corresponding saccade magnitude and peak velocity distributions.

SWJ detection

We defined a SWJ as the combination of one small saccade that moves the eye away from the fixation target, followed after a short period by a second corrective saccade directed back towards the target (Abadi and Gowen, 2004; Leigh and Zee, 2006; Martinez-Conde, 2006; Otero-Millan et al., 2011b) (**Figure 28**).To characterize SWJs in an objective manner, we first identified all individual saccades up to 5 deg (Otero-Millan et al., 2011). We chose this 5-deg upper magnitude threshold to include the range of SWJ magnitudes reported previously in healthy human subjects (0.1–4.1 deg; (Abadi and Gowen, 2004)), as well as in neurological patients (Otero-Millan et al., 2011b).

We identified SWJs by measuring how similar a given saccade pair (that is, a pair of consecutive saccades) was to an ideal SWJ. In an "ideal SWJ" the two saccades are separated by a short interval (usually around 200 ms), have the same magnitudes, and their directions are exactly opposite (Otero-Millan et al., 2011b, 2013b; McCamy et al., 2013b). We calculated a SWJ index based on these three defining SWJ characteristics: (a) the direction dissimilarity of first and second saccade, (b) the magnitude similarity of first and second saccade, and (c) the temporal proximity of first and second saccade. The SWJ index provides a single, continuous variable between zero and one for each saccade pair. Values closer to one indicate more similarity to an ideal SWJ. If a saccade pair's SWJ index was larger than a given threshold (Otero-Millan et al., 2011b), we classified the pair as a SWJ. By "SWJ saccades", we refer to the two saccades that define a complete SWJ. By "non-SWJ saccades", we refer to any other saccades that are not part of SWJs, including fixational saccades. We defined SWJ magnitude as the average magnitude of

the two saccades defining the SWJ. We defined likelihood of being part of a SWJ as the percentage of saccades from the pool that were considered as part of SWJ, detected by our algorithm.

Statistical methods

To compare the characteristics of saccades inside and outside SWJs, we performed separate Wilcoxon's signed-rank tests for each dependent variable (saccadic magnitude, peak velocity, slope of the peak velocity/magnitude relationship, direction, vertical component, and polar asymmetry). To calculate the vertical component of saccades of different magnitudes, we first normalized the magnitudes of all saccades to 1 deg. Polar asymmetry was defined as $A = \sqrt{\sum_{\theta}^{\frac{\pi}{2}}(H(\theta) - H\left(\theta + \frac{\pi}{2}\right))^2}$, where A is the Euclidean distance between a given point in the polar histogram and its symmetric counterpart. To assess the relationship between saccadic magnitude and the likelihood of being part of a SWJ, we performed separate Friedman's tests for the saccadic vertical component, likelihood of being part of a SWJ, and intra-SWJ inter-saccadic interval [ISI]. Saccadic magnitude was the within subjects factor variable (10 bins of 0.2 deg each). We also considered the distance to fixation target as a within subjects factor (10 bins of 0.2 deg each) for the likelihood of being part of a SWJ and intra-SWJ ISI. Finally, we ran logistic regressions between a saccade's likelihood of being part of a SWJ, and the saccadic magnitude and post-saccadic distance to the fixation target, considering the saccade pool from all monkeys. Significance levels were set at $p < 0.05$ throughout.

Results

SWJs are the most common type of SI in human subjects. Here we set out to determine the characteristics of spontaneous SWJs in five healthy rhesus macaques during attempted visual fixation of a small target. Eye movements recorded during the fixation task consisted primarily of fixational saccades (i.e. microsaccades) and drifts, in addition to occasional larger saccades and spontaneous blinks.

Characteristics of SWJ saccades and non-SWJ saccades

All five primates produced spontaneous SWJs. The average likelihood for any given saccade to be part of a SWJ was 30.62% (SD +/-22%) (**Figure 28**). This value is in line with previous findings for healthy human subjects (Otero-Millan et al., 2011b; McCamy et al., 2013b).

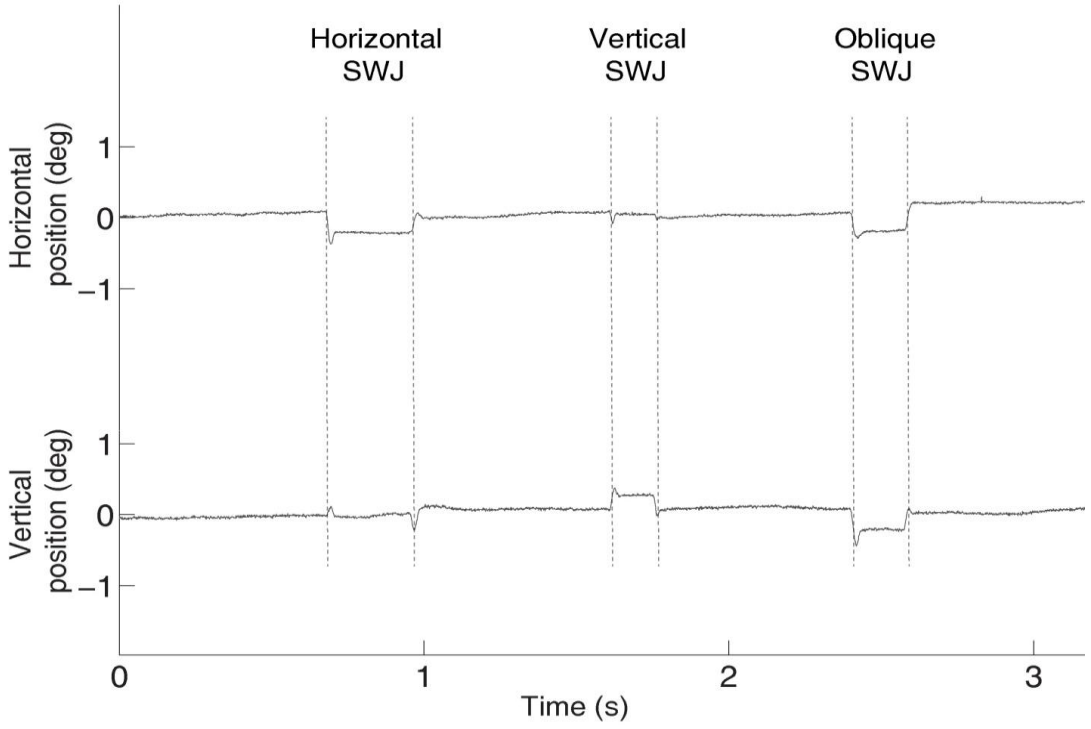

Figure 28. Examples of primate SWJs. Each trace represents 3 seconds of horizontal (top) and vertical (bottom) eye position recordings containing SWJs. Primarily horizontal (left), vertical (middle), and oblique (right) SWJs are displayed. All time scales are as in the bottom trace.

Also consistent with prior human studies (Otero-Millan et al., 2011b; McCamy et al., 2013b), the magnitude and peak velocity of the saccades being part of SWJs (heretofore SWJ saccades) were greater than for those saccades not being part of SWJs (heretofore non-SWJ saccades). The peak velocity-magnitude relationships and their corresponding linear fit slopes were comparable in SWJ saccades and non-SWJ saccades (**Figure 29, Table 1**).

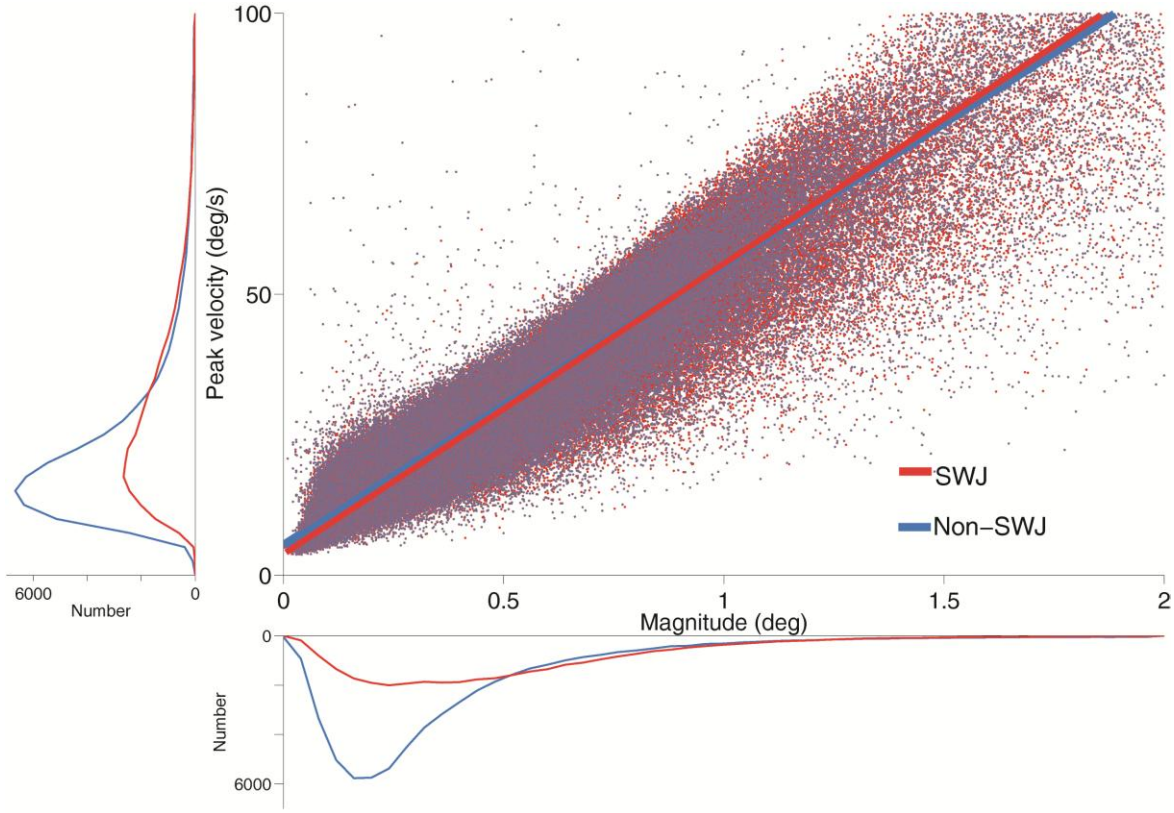

Figure 29. Peak velocity-magnitude relationship for SWJ saccades and non-SWJ saccades. Main panel: Each dot represents a saccade with the peak velocity indicated on the y-axis and the magnitude on the x-axis. Color determines whether the saccade was part of a SWJ (red) or not (blue). Bottom panel: Average saccade magnitude distribution across monkeys (n = 5). Left panel: Average peak velocity distribution across monkeys (n = 5). Saccade magnitude and peakvelocity were greater for SWJ saccades than for non-SWJ saccades (Z-values = 2.02; p-values = 0.04). The slopes of the peak velocity-magnitude relationships for SWJ saccades and non-SWJ did not differ statistically (Z-value = 1.75; p = 0.08).

Human SWJs are typically composed of horizontal saccades, both in neurological patients and in healthy individuals (Abadi and Gowen, 2004; Otero-Millan et al., 2011b, 2013b). Here we found that such horizontal preference does not extend to SWJs in the macaque monkey, as both SWJ saccades and non-SWJ saccades had a strong vertical component (**Figure 30A**). Polar asymmetry was larger for non-SWJ saccades than for SWJ saccades, however, consistent with the square-wave coupling that characterizes

SWJs, where the second (i.e. return) saccade has roughly opposite direction to that of the first saccade (**Figure 30A, Table 3**).

In human subjects, the fixational saccadic preference for horizontal direction decreases moderately with saccade magnitude (Otero-Millan et al., 2011b). In contrast, the primate fixational saccadic preference for vertical direction (Cui et al., 2009) was unrelated to saccade magnitude, either for SWJ saccades or non-SWJ saccades (**Figure 30B, Table 3**).

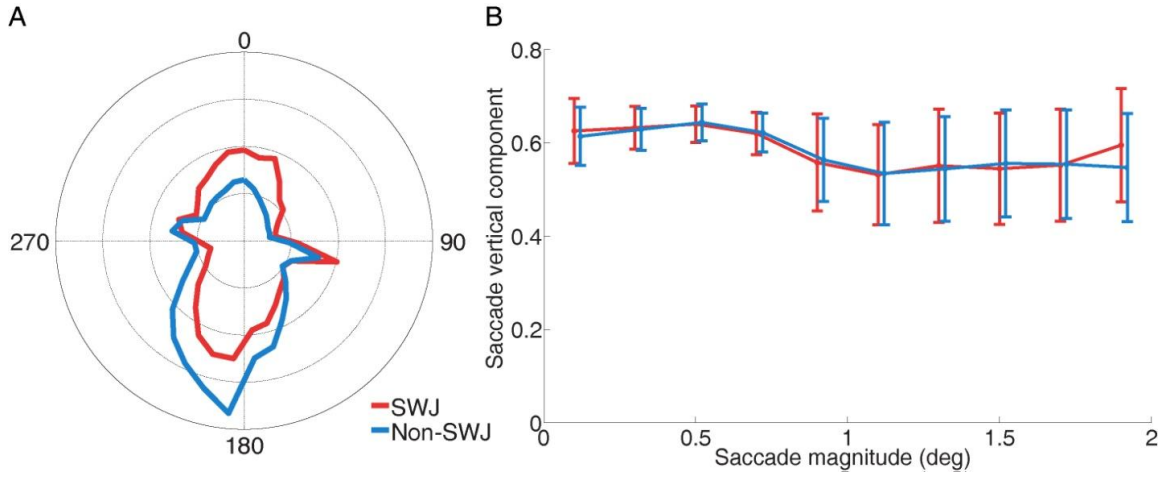

Figure 30. Direction of SWJ saccades and non-SWJ saccades. A) Polar histogram of saccade directions for SWJ saccades and non-SWJ saccades. We show the average saccade direction distribution across monkeys (n = 5). Both SWJ saccades and non-SWJ saccades are biased vertically. Whereas downward-directed component is prominent for both SWJ saccades and non-SWJ saccades, the upward-directed component is more pronounced for SWJ saccades than non-SWJ saccades. Median Euclidean distance values were significantly lower for SWJ saccades than for non-SWJ saccades, indicating higher symmetry (Z-value = 2.02; p = 0.04; see Methods). B) Saccade magnitude and vertical component. The vertical component remained constant across saccadic magnitudes for both SWJ saccades (*Friedman's test* (5, 9) = 7.05 p = 0.631) and non-SWJ saccades (*Friedman's test* (5, 9) = 4.85 p = 0.846). Error bars represent the s.e.m. across monkeys (n = 5).

Table 3. Characteristics of SWJs and non-SWJ saccades. Medians and SDs are indicated for each variable and calculated across monkeys (n = 5). * indicates $p < 0.05$, Wilcoxon's signed-rank test.

	SWJ saccades	non-SWJ saccades
Rate (N/s)	0.44 (0.30)	0.82 (0.25)
Magnitude (deg)*	0.42 (0.18)	0.37 (0.13)
Peak velocity (deg/s)*	24.75 (8.95)	22.13 (7.10)
Saccadic slope (deg/s)	48.02 (4.06)	49.85 (3.16)
Vertical component	0.56 (0.25)	0.56 (0.26)
Polar asymmetry*	3.35 (1.93)	8.46 (3.54)

SWJs and fixation correction

As human fixational saccades increase in size, they are more likely to be followed by a return saccade, indicating a role of SWJs in fixation correction (Otero-Millan et al., 2011b). To determine if primate SWJs might be similarly corrective, we examined the relationship between the presence of a fixation error and the likelihood of square-wave coupling. We considered the following two measures of fixation error: a) saccadic magnitude (**Figure 31A**, first gray arrow from the left), and b) the distance between post-saccadic gaze position and fixation target location (**Figure 31A**, second gray arrow from the left). We found that SWJ likelihood increased as a function of the size of the fixation error: The larger the distance between the post-saccadic gaze position and the fixation target location, the more likely the trigger of a return saccade (**Figure 31B**). Likewise, large saccades were more likely than small saccades to lead to square-wave coupling in the form of return saccades (**Figure 31C**).

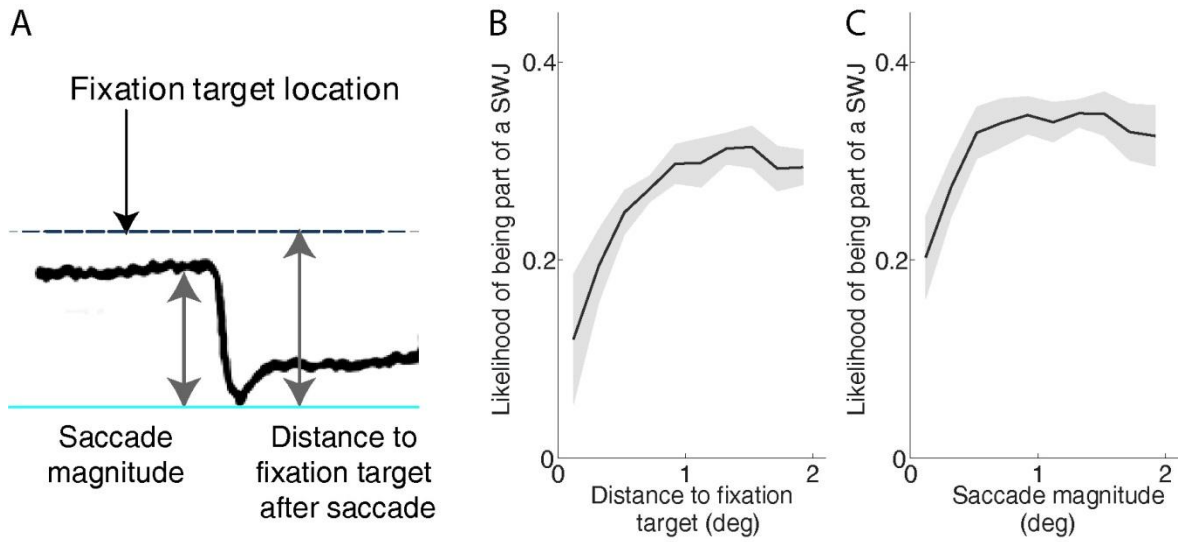

Figure 31. Relationship between fixation error and subsequent SWJ generation. A) Schematic illustration of a fixation error. The fixation target location, the magnitude of the first saccade in the SWJ, and the distance to the fixation target after the first SWJ saccade are indicated. Relationship between a saccade's likelihood of being part of a SWJ and B) the post-saccadic distance to the fixation target and C) the saccade's magnitude. Both relationships follow a logistic regression (p-values < 0.05), where a saccade's likelihood of being part of a SWJ increases with both the distance to the fixation target after the saccade [*Friedman's test* (5, 4) = 10.08 p = 0.039] and the saccadic magnitude [*Friedman's test* (5, 4) = 13.60 p = 0.008)] up to 1 deg, and then plateaus for values > 1 deg [p-values >0.6]. Grey shadows indicate the s.e.m. across monkeys (n = 5).

We also found a significant relationship between the size of the fixation error (defined as a function of either saccade magnitude or post-saccadic distance to the fixation target) and the time lapsed from the end of the first SWJ saccade to the beginning of the second SWJ saccade (Intra-SWJ inter-saccadic interval; ISI; median: 236.20 ms SD +/- 32.82). The larger the fixation error, the quicker the return saccade was triggered, suggesting that greater fixation errors are detected more quickly than smaller errors (**Figure 32**).

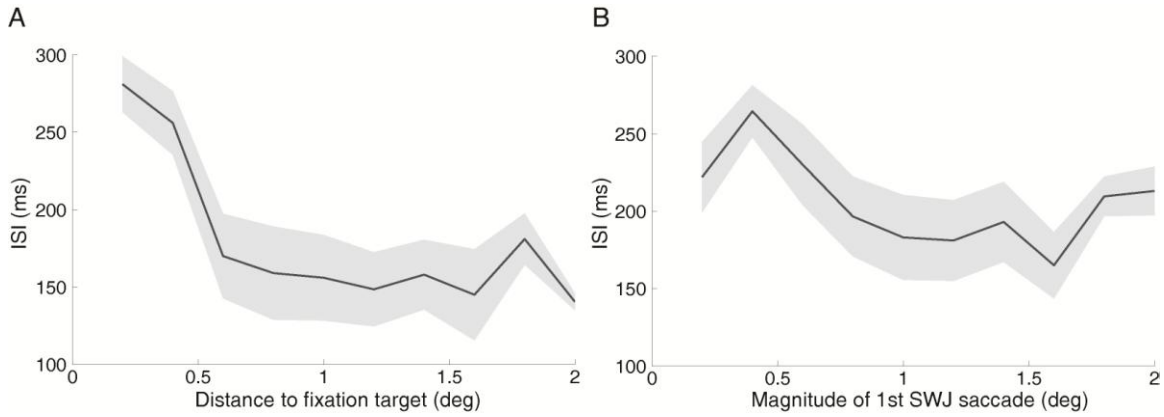

Figure 32. Relationship between fixation error and Intra-SWJ ISI. A) The larger the distance to fixation target, the shorter the intra-SWJ ISI [*Friedman's test* (5, 9) = 26.80 *p* = 0.001)]. B) Likewise, larger saccades tend to be more quickly followed by return saccades [*Friedman's test* (5, 9) = 22.04 *p* = 0.009)]. Shadows indicate the s.e.m. across monkeys (*n* = 5).

Discussion

We set out to investigate the occurrence, and determine the characteristics, of SWJs in the healthy, awake fixating primate. Prior studies found an abundance of SWJs, not only in neurological patients, but also in healthy human subjects (Abadi and Gowen, 2004; Otero-Millan et al., 2011b, 2013b; McCamy et al., 2013b). SWJs have also been reported in monkeys suffering from tectal and cerebellar lesions (Weber et al., 1989; Carasig et al., 2006; Gnadt et al., 2013), but it remains unknown whether healthy nonhuman primates present SWJs during attempted visual fixation, and if so, whether the characteristics of primate SWJs are comparable to those of human SWJs.

Here we set out to determine the characteristics of spontaneous SWJs during attempted fixation in five healthy rhesus monkeys, and found SWJ occurrence to be comparable to that previously reported in healthy human subjects. Also in agreement

with previous human studies, we found that SWJ saccades tended to be larger and faster than non-SWJ saccades, and that both SWJ and non-SWJ saccades fell on the same peak velocity-magnitude relationship main sequence (**Figure 29**). The likelihood of a given saccade to be part of a SWJ increased with increased saccadic magnitude (**Figure 31C**) and distance to the fixation target (**Figure 31B**), also consistent with previous findings for human SWJs. Return saccade latencies were shorter after large fixation errors (**Figure 32**), further supporting the notion that primate SWJs, similarly to human SWJs, help to correct fixation position during normal vision. These combined results suggest a similar coupling mechanism in human and primate SWJs, where large fixational saccades are usually followed by subsequent corrective saccades, thereby producing SWJs as a result.

Whereas fixational saccades tend to be horizontal in humans, and SWJs even more strongly so (Otero-Millan et al., 2011b), fixational saccades in macaques do not typically show a horizontal preference (Weber et al., 1989; Cui et al., 2009). The evolutionary underpinnings of this discrepancy are a matter of speculation, but one possibility is that erect, bipedal locomotion, which imposes vertical head vibrations with each heel strike, made vertical components of fixational saccades less important in human than in macaque vision. Indeed, here we found fixational saccades in the primate to be predominantly vertical, both inside and outside SWJs (**Figure 30**). This dramatic distinction in the directional components of human and primate SWJs seems to make little difference to the coupling mechanisms linking the first and second SWJ saccades though, which appear to be fundamentally common to both species. Thus, our combined data suggest that fixational saccades (including those forming SWJs) have a common

origin in primates and humans, even if the directional biases of monkey and human fixational saccades are grossly different.

These findings constrain the possible brain areas and mechanisms underlying microsaccade generation in both species. Premotor areas in the brain stem separate anatomically horizontal and vertical saccade generation: horizontal saccades are generated in the paramedian pontine reticular formation (pprf) and vertical saccades in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). Thus, there is no single area that can explain the generation of fixational saccades in both primates and humans. Upstream, the superior colliculus (SC) encodes the vectors of saccades of all directions in a single 2D map, making this structure a good candidate for fixational saccade generation in human and nonhuman primates. This is consistent with recent evidence linking microsaccade generation to neural activity in the rostral SC (Hafed et al., 2009) and showing decreased microsaccade rates after rostral SC inactivation (Hafed et al., 2009; Goffart et al., 2012). Other potential areas that may provide a common vertical and horizontal microsaccade-triggering signal include the oculomotor areas in the cerebellum and the cortical frontal eye fields (Izawa et al., 2009).

A recent study (Goffart et al., 2012) has proposed that microsaccade generation results from an imbalance between the left and right superior colliculus. The fact that fixational saccades tended to be vertical in our primate population seems to indicate an alternative mechanism, given that a purely vertical fixational saccade would be accompanied by equivalent activity in the left and right SCs. Other generation models

(Rolfs et al., 2008a; Hafed, 2011; Otero-Millan et al., 2011a) have proposed more general mechanisms that trigger microsaccades when the overall pattern of activity in the SC changes, by increasing the activity level of a given point in the map, and/or changing the location of the center of mass of the population activity.

General Discussion

Visual fixation accounts for approximately 80% of the time spent during visual exploration. Research on the neural, perceptual and cognitive effects of fixational eye movements has increased dramatically in the last decade, with a particular emphasis on the study of microsaccades —the largest and fastest eye movements produced during attempted fixation— (Martinez-Conde et al 2004, Rolfs 2009).

Stationary targets can fade perceptually during steady fixation, a phenomenon known as Troxler fading. Classical studies have shown that, in the absence of fixational eye movements, neural adaptation ensues and observers become blind to stationary objects during fixation, thus fixational eye movements are critical to preventing and restoring loss of vision during fixation (Riggs and Ratliff, 1952; Ditchburn and Ginsborg, 1953; Yarbus, 1957).

There is disagreement about the importance of microsaccades to the visual restoration of foveal versus peripheral targets, and high-contrast versus low-contrast targets, however (Collewijn and Kowler 2008; Rolfs 2009; Kowler and Collewijn 2010; Poletti and Rucci 2010; Kowler 2011).

Recent studies have found that microsaccades enhance vision during fixation in a variety of fading paradigms (Engbert and Mergenthaler 2006; Martinez-Conde et al 2006; Troncoso et al 2008a; Hsieh and Tse 2009, McCamy et al. 2012). Martinez-Conde et al. (2006) found that microsaccade rates increased before peripheral targets became visible, and decreased before the targets faded. McCamy et al. (2012) replicated these findings and extended them to foveal targets. However, the foveal targets tested extended beyond the area of the fovea.

In addition, no study to date has systematically tested the effect of microsaccades on target visibility as a function of stimulus contrast or spatial frequency. The present dissertation provides evidence that microsaccades enhance vision for a variety of spatial frequencies and contrast levels (i.e. their effects are not restricted to peripheral, low-contrast targets). Experiment #1 showed that microsaccade production restored the visibility of targets entirely contained within the fovea. Experiment #2 showed that microsaccade production modulated the visibility of targets with varied spatial frequencies

The potential role of microsaccades versus drifts in the control of eye position has been debated for decades and remains in question today (Martinez-Conde et al 2004; Rolfs 2009). Some studies concluded that microsaccades play no role in the control of fixation position (Ratliff and Riggs 1950; Fiorentini and Ercoles 1966), but others proposed that both microsaccades and drift may be error-correcting as well as error-producing (Nachmias, 1961; Steinman et al., 1973). Previous research carried out in the Martinez-Conde lab found a corrective role for microsaccades in the form of SWJ coupling (Otero-Millan et al 2011). Yet, the ability of microsaccades to improve fixation accuracy remains controversial (Collewijn and Kowler, 2008) and so are the comparative roles of drift and microsaccades in the control of fixation position.

Here we investigated the significance of microsaccades and drift for the correction of gaze position errors caused by eye blinks. If microsaccades do play a general role in oculomotor control during fixation, they should correct fixation errors due to blinks. Experiment #3 showed that eye motion during blinks results in sizable gaze position errors, and that most microsaccades subsequent to blinks decrease such errors.

Large fixation errors were corrected more effectively than small fixation errors, and drifts had a lesser corrective role than microsaccades. We concluded that blinks contribute to gaze instability during fixation and that microsaccades correct blink-induced fixation errors better than do drifts.

Experiment #4 showed that SWJs are as common in healthy nonhuman primates as in human subjects. We moreover found primate SWJs to share several characteristics with human SWJs, including the relationship between the size of a saccade and its likelihood to be part of a SWJ. One main discrepancy between monkey and human SWJs was that monkey SWJs tended to be more vertical than horizontal, whereas human SWJs have a strong horizontal preference. Yet, our combined data indicate that primate and human SWJs play a similar role in fixation correction, suggesting that they share a comparable coupling mechanism at the oculomotor generation level. These findings constrain the potential brain areas and mechanisms underlying the generation of fixational saccades in human and nonhuman primates.

The results from these four Experiments indicate a general role of microsaccades in visual perception and fixation correction.

Future Directions

Future research should investigate the ability of microsaccades to restore faded targets as a function of target size. Future studies may also investigate how microsaccades and other fixational eye movements impact the perception of gradations in fading/visibility (i.e. by obtaining a continuous measure of the subject's perceptual experience, rather than focus on the perceptual transitions to increased or decreased visibility (i.e. as in the present experiments), and also address the perceptual consequences, possibly as a function of both drift speed, size, and retinal eccentricity.

We have developed a novel quantitative analysis to calculate, for the first time, the microsaccadic correction of blink-induced fixation errors. These analyses and results may assist in the development of quantified models of the roles served by fixational eye movements in normal vision and in visual disease. Recent research indicates that a correlation between certain fixational eye movement dynamics and neurological and ophthalmic conditions (Otero-Millan et al., 2011b, 2013b; Kapoula et al., 2013). Thus, noninvasive measures of fixational eye movements may aid medical diagnosis in a variety of pathologies.

Microsaccade production is also relevant to cognitive processes such as working memory and visual attention. In a separate study, my colleagues and I showed that task difficulty can modulate microsaccade rates and magnitudes, even in the absence of visual stimulation (Siegenthaler et al., 2014). This finding points to the potential use of microsaccade dynamics as an indicator of cognitive workload, especially in applied settings. There is no current reliable psychophysiological measure of cognitive workload. The advantages of such a measure might extend to a variety of domains, ranging from the

improvement of working conditions to the optimization of workstation design (Cain, 2007). The same study showed that the microsaccadic peak velocity-magnitude relationship slope decreased significantly with time-on-task. This finding has been attributed to fatigue and is consistent with those reported in previous studies during simulated air traffic control and surgical tasks (Di Stasi et al., 2013, 2014). Different microsaccade parameters may be differentially susceptible to various types of task modulations: microsaccade magnitude could reflect task difficulty accurately while being insensitive to time-on-task, whereas the microsaccade peak velocity–magnitude relationship could behave in opposite fashion.

There is evidence that microsaccade directions are biased as a function of the spatial location of attention during fixation (Hafed and Clark, 2002; Engbert and Kliegl, 2003; Rolfs et al., 2004; Engbert, 2006; Gowen et al., 2007; Laubrock et al., 2007; Turatto et al., 2007). Thus, one may be able to triangulate microsaccade trajectories to pinpoint the focus of covert attention (Martinez-Conde et al., 2010). This could serve as a reliable and non-invasive method to determine the actual position of covert interest of a person within an image. Commercial advertising might benefit from such an approach, as might certain psychiatric and neurological applications.

Conclusions

The proposed dissertation redefines microsaccades as having multiple non-exclusive functional roles during fixation, like large saccades are thought to have during exploration. Current thinking in the field is that microsaccades should stick with one fundamental role or another, to the detriment of other potential functions. This dissertation addresses the major remaining controversies concerning the roles of microsaccades in vision (i.e. the impact of microsaccades on perceptual enhancement as a function of stimulus contrast, spatial frequency, and eccentricity) and oculomotor control (i.e. the potential general role of microsaccades in fixation correction).

The first set of experiments set out to correlate microsaccade production with the visual restoration of low-to-moderate contrast targets contained entirely within the fovea. Despite lower rates of foveal fading (as compared to peripheral fading), microsaccades restored the visibility of faded targets of varied contrasts not only in the visual periphery, but also inside the fovea. Microsaccades also restored the visibility of faded targets of varied spatial frequencies.

The second set of experiments showed that microsaccades play a more general role in error correction during fixation than previously thought, as they serve to rectify gaze position errors due to blinks, and moreover correct fixation errors via square-wave coupling in both humans and monkeys.

We conclude that microsaccades, like saccades, serve multiple non-exclusive important functional roles in vision and oculomotor control (i.e. rather than serving a primary specialized function, as currently believed).

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