Short-term saccadic adaptation in the macaque monkey: a binocular mechanism

K. P. Schultz and C. Busettini
Department of Vision Sciences and Vision Science Research Center, University of Alabama at Birmingham, Birmingham, Alabama

Submitted 4 November 2011; accepted in final form 16 October 2012

Schultz KP, Busettini C. Short-term saccadic adaptation in the macaque monkey: a binocular mechanism. J Neurophysiol 109: 518–545, 2013. First published October 17, 2012; doi:10.1152/jn.01013.2011.—Saccadic eye movements are rapid transfers of gaze between objects of interest. Their duration is too short for the visual system to be able to follow their progress in time. Adaptive mechanisms constantly recalibrate the saccadic responses by detecting how close the landings are to the selected targets. The double-step saccadic paradigm is a common method to simulate alterations in saccadic gain. While the subject is responding to a first target shift, a second shift is introduced in the middle of this movement, which masks it from visual detection. The error in landing introduced by the second shift is interpreted by the brain as an error in the programming of the initial response, with gradual gain changes aimed at compensating the apparent sensorimotor mismatch. A second shift applied dichoptically to only one eye introduces disconjugate landing errors between the two eyes. A monocular adaptive system would independently modify only the gain of the eye exposed to the second shift in order to reestablish binocular alignment. Our results support a binocular mechanism. A version-based saccadic adaptive process detects postsaccadic version errors and generates compensatory conjugate gain alterations. A vergence-based saccadic adaptive process detects postsaccadic disparity errors and generates corrective nonvisual disparity signals that are sent to the vergence system to regain binocularity. This results in striking dynamical similarities between visually driven combined saccade-vergence gaze transfers, where the disparity is given by the visual targets, and the double-step adaptive disconjugate responses, where an adaptive disparity signal is generated internally by the saccadic system.

adaptation; disparity; saccade; strabismus; vergence
Saccadic short-term adaptation to simulated disconjugate gain alterations between the two eyes is another paradigm that can be used to generate asymmetric saccades. In this case, the occurrence of the disconjugacy is causally linked to the occurrence of the saccade, with no prior visual disparity or aniseikonic information. Thus the saccadic system is entirely in charge of generating the disconjugate adaptive response, making this design ideally suited to unmask a monocular mechanism, if present. To compare the metrics of visually driven and adaptive oculomotor behavior in exactly identical conditions, we used the double-step saccadic paradigm (McLaughlin 1967; see Hopp and Fuchs 2004 for an in-depth review). When a target that the animal is actively fixating with both eyes suddenly moves in a stepwise fashion (primary step) to a new location on the same isoversiong circle, i.e., with no change in depth, the animal will produce a conjugate (i.e., identical rotations of the two eyes) saccadic eye movement to bring its eyes to the new target location. In the traditional conjugate double-step saccadic paradigm, while the animal is in the middle of the execution of the saccade elicited by the primary step, the target, continuously presented to both eyes, is stepped a second time (secondary step) to another location on the same isoversiong circle. This generates an apparent conjugate saccadic mismatch between what the animal programmed on the basis of the target’s primary step and the total change in target position. By shifting the target during the saccade, when target motion is not perceived (Brooks and Fuchs 1975; Riggs et al. 1982), the brain interprets the landing error as a mistake in the programming of the primary saccade. Once the landing error is visually detected, the animal will generate a conjugate corrective saccade to move its eyes to the shifted location. If the target is moved this way consistently over many trials, the gain of the primary saccade is adjusted by the animal to compensate for the repeated landing errors. For example, for a primary step of 10° and a secondary step of 2° forward, the animal, if perfect compensation is achieved, will execute 12° primary saccades, despite having only seen 10° target steps throughout the session. This change in saccadic gain remains for a period of time after the stimulus is returned to normal, i.e., with no further delivery of intrasaccadic secondary steps, indicating true adaptation (Albano 1996; Albano and King 1989; Albano and Marrero 1995; Deubel et al. 1986; Frens and van Opstal 1994; Hopp and Fuchs 2004; McLaughlin 1967; Miller et al. 1981; Semmlow et al. 1989; Straube and Deubel 1995). A significant part of this adaptation is achieved inside a single experimental session, and therefore it is referred to as a short-term adaptation. Interestingly, human conjugate adaptation reaches a steady-state level in <100 trials, while monkeys often need 1,000 or more trials (Hopp and Fuchs 2004; Straube et al. 1997a). In a similar fashion, if the secondary step is applied to only one eye with a dichoptonic arrangement—both eyes see the initial conjugate primary step and have uninterrupted view of their respective targets throughout the trial, but there is no secondary step on the other eye—a disconjugate (i.e., different in the two eyes) adaptation can occur (Albano and Marrero 1995; Eggert and Kapoula 1995; Kapoula et al. 1996). We are not aware of studies in which disconjugate double-step saccadic paradigms were tested in macaque monkeys. The key difference with respect to the standard conjugate paradigm is that disconjugate secondary steps introduce a visual disparity. Thus, prior to adaptation, the visual disconjugacy of the landing error is mostly dealt with by a smooth vergence response, i.e., by a nonsaccadic response. How this postsaccadic visual disparity is converted into a saccadic-generated adaptive response is still unresolved. Does a monocular saccadic recalibration independently adjust the gain of each eye? Does the saccadic system generate an internal model of this postsaccadic disparity error, which is then fed to the vergence system? In the latter hypothesis, which is the focus of this work, we expect to see evident similarities in the oculomotor responses between disconjugate controls, where the secondary steps are included in the primary steps to obtain standard single-step disconjugate visual stimuli, and disconjugate adaptive responses. In this binocular mechanism, the visual disparity error is simply replaced by a saccadic-generated adaptive disparity error. In a monocular adaptation mechanism, the adaptation to disconjugate secondary steps will be very similar, in time course and dynamic characteristics, to the adaptation to identical secondary steps in the two eyes, with each eye separately adjusting its gain independently of what is applied to the other eye.

We analyze macaque saccadic adaptation to biocular (identical secondary steps applied to the two eyes), uniocular (secondary step applied to only one eye), and symmetric (equal and opposite secondary steps applied to the two eyes) paradigms. We use these unconventional names for the paradigms to reserve the terms conjugate, monocular, and binocular for the underlying neural mechanisms being tested.

**METHODS**

Binocular horizontal and vertical eye movements were recorded in two rhesus monkeys (*Macaca mulatta*), weighing 6–10 kg, while performing saccadic visually driven controls or adaptive paradigms. The data presented here were acquired from intact animals before the implantation of chambers for single-unit recordings. All procedures and experimental protocols were approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee and complied with U.S. Department of Agriculture, Association for Assessment and Accreditation of Laboratory Animal Care, and U.S. Public Health Service Policy on the humane care and use of laboratory animals.
Surgical Procedures

After the animals were trained to enter a primate chair and acclimated to the lab environment, a series of aseptic surgical procedures were performed. Custom-made PEEK strips were attached to the skull with ceramic bone screws. After full recovery, the strips were used as attachments for an external head post. Coils were implanted underneath the conjunctiva of the right and left eyes for the purpose of binocular eye tracking via the magnetic search coil technique (Fuchs and Robinson 1966).

Behavioral Paradigms

Animals were trained to make saccades and vergence responses between visual targets presented dichoptically to the two eyes for a reward while their heads were immobilized. The dichoptic arrangement was obtained by using matching orthogonal polarizers and a nondepolarizing back-projection screen. The screen was placed at 410 mm from the animal’s corneal apex, equivalent, for the two animals when looking straight ahead, to a vergence angle of 4.4°. With the exclusion of the targets, the room was carefully darkened. The 1° targets were polarized images of bright red LEDs remotely projected by 100-mm lenses onto the nondepolarizing screen, and their position was controlled by mirror galvanometers (GSI Lumonics) in an x-y configuration. The four galvanometers were driven by 1-kHz analog signals generated by the 16-bit D/A converters of the laboratory computer, running a custom package under a real-time Ubuntu kernel. The same computer monitored the animal behavior, timed the stimuli, administered rewards, and acquired, also at 1 kHz with 16-bit A/D resolution, the eye position signals, the feedback signals from the galvanometers, and the signals driving the LEDs. Horizontal and vertical eye position and mirror signals were analogically filtered with antialiasing 200-Hz low-pass 48 dB/octave Bessel filters prior to acquisition.

The study included six main double-step saccadic paradigms, which are described in Fig. 1, top and middle. In all experiments the targets remained on the horizontal meridian, with only horizontal shifts. The primary steps were always identical in the two eyes in all paradigms, and therefore the resulting binocular percept moved in space along isovergence circles. The sizes of the secondary steps were 20% (forward or backward) of the sizes of the primary steps in the biocular (BC, BA) and uniocular (UC, UA) cases and 10% (forward in one eye, backward in the other eye) in the symmetric (SC, SA) cases (see also Robinson et al. 2003). As illustrated in Fig. 1, the difference between the visual controls (Fig. 1, top) and the correspondent adaptive paradigms (Fig. 1, middle) was in the time of delivery of the secondary steps. In the controls, the secondary steps were added on top of the primary steps, which, in Fig. 1, were rightward 10° steps. The delivery of the secondary steps during the adaptive sessions was experimentally set to occur around the peak velocity of the primary saccade. Trials with spurious triggering of the secondary steps, detected by comparing the eye traces with the mirror feedback traces, were manually rejected during the off-line analysis. In the adaptive trials, the LEDs were briefly turned off for 5 ms during the <4-ms movement of the mirrors associated with the secondary steps to even further reduce the possibility for the animal to detect motion. For consistency, the LEDs were also turned off at the same time inside the primary saccade in the control paradigms, even if no secondary steps were delivered at that time.

With the exclusion of the symmetric experiments (SC and SA), which were done only in the fully predictive paradigm (see below), all experiments were done in two configurations. In the fully predictive paradigm, rightward 10° primary target steps were always followed by leftward 10°, followed again by rightward 10°, and so on, until the end of the session. This paradigm is illustrated in Fig. 1, bottom left, reporting the uniocular case with +20% secondary steps applied only on the right eye. Rightward and upward eye movements are reported as positive, while leftward and downward movements are reported as negative. With (horizontal) vergence (VG) defined as $H_L - H_R$, crossed disparities and convergence are reported as positive values and uncrossed disparities and divergence as negative. Starting from point A (cyclopean angle 5.5°, vergence angle 7.4°), which is the end point of the rightward trials in this example, the leftward 10° conjugate primary step is applied, with the binocular percept traveling along the 7.4° isovergence circle. At the end of the primary step, point $A_1$ is at a cyclopean angle of $-4.5°$. The 2° leftward secondary step, applied only to the right eye, causes the binocular percept to move onto the 9.4° isovergence circle and to a cyclopean angle of $-5.5°$ (point $B$), which is the end point of the leftward trials. The next sequence, with a rightward 10° conjugate primary step and a 2° rightward secondary step, again applied only to the right eye, brings the binocular percept back to A. The right-eye mirror and left-eye mirror were calibrated separately with nonlinear look-up tables to obtain these trajectories in space. Thus the animal knew exactly what was going to happen throughout the session after a few trials, both in the control and in the adaptive cases. This fully predictive design (A$\rightarrow$B$\rightarrow$A$\rightarrow$B and so on), obviously artificial, was adopted with the expectation that it would maximize the probability of eliciting pure asymmetric saccades and, in the adaptive paradigm, the speed of the adaptive process. In the pseudorandom design (Fig. 1, bottom right), the primary target steps, still always horizontal and identical in the two eyes, were right 5°, right 10°, left 5°, or left 10°, pseudorandomly intermixed. Thus the sequence of ending points (also starting points for the subsequent trial, as before) followed a nonpredictable trajectory in both vergence and eccentricity (in Fig. 1, bottom right, points A–F as example). At each starting position, any of the four primary steps could be randomly selected, with the only limitation for the targets being to remain inside a horizontal version range of $\pm25°$ and between 4.4° and 12.4° of convergence angle. This forcibly limited the selection of the next primary step when the animal was near the edges of the version and the vergence ranges, and thus the “pseudorandom” term used for this paradigm. The trial lists for the pseudorandom paradigms were computed off-line, with the weights of the random generator adjusted to have an approximately balanced number of 5° and 10° primary steps. Without this correction, because of the imposed target positional limits, the 10° steps had a higher probability of getting rejected because of a higher probability of stepping out of the oculomotor boundaries. This second design was adopted because it more closely resembles what the animal would experience during natural scene scanning while having an altered saccadic gain, and to have an estimate of the influence of prediction in the adaptive process. Although both designs have been used before, this is the first study to compare the two. In both designs, the vergence steps were balanced with respect to the isovergence circle at 8.4°. In pilot experiments, the vergence steps were balanced with respect to the isovergence circle at 4.4°, i.e., to the circle tangent to the screen, in order to minimize the amount of vergence-accommodation dissociation, but during the control sessions both animals had difficulties in diverging beyond the screen, while they had no difficulties in converging to 12.4°. With both control and adaptive cases having identical geometric configurations, we considered it likely that any effects on the responses linked to the vergence-accommodation dissociation would be similar for both paradigms. Thus we rebalanced the paradigms with respect to the 8.4° isovergence circle, which also became the locus of the targets in the biocular paradigm.

The behavioral task required of the animal for a juice reward was limited to responding to the primary steps. The targets defining the primary steps were presented in sequence with no delay or overlap between them. The animal had 2,000 ms to acquire each target. As soon as its eyes were inside the eye position windows associated with the current target, a required fixation period started (a fixed period of 1,000 ms in the fully predictive design and a random period between 800 and 1,200 ms in the pseudorandom design). In the aborted trials, i.e., when the animal’s eyes did not enter inside the required positional

J Neurophysiol • doi:10.1152/jn.01013.2011 • www.jn.org

Downloaded from http://jn.physiology.org/ by IP 10.220.33.2 on November 7, 2017.
windows in the allotted time or exited from them too early by breaking fixation, the LEDs were immediately turned off as soon as the animal’s error was detected and remained off for 3,000 ms, when the next trial in the trial sequence started, to try to minimize the impact of the animal’s errors on the adaptive process. The sizes of the computer eye position windows inside which the animal had to bring its eyes and remain inside to receive a reward were \( \pm 4^\circ \), and were only used to detect that the animal was actively performing the primary saccades.

The list of possible experiments that could be obtained from the two designs was limited by the fact that, for example, in the fully predictive design if the rightward saccades were associated with a convergence secondary step, the leftward saccades had to be associated with a divergence secondary step. Each of the two experiments performed a total of 31 different experiments. Mainly interested in a direct comparison between the fully predictive and pseudorandom paradigms, we analyzed only the 10\(^{\circ}\) pseudorandom data, taking into account that the 10\(^{\circ}\) trials occurred, in this design, only 50% of the time.

After 60 eye calibration trials using a rigid board with embedded horizontal and vertical nonpolarized LED targets, the calibration board was replaced with the nondepolarizing screen. In preliminary sessions we tested, in both animals, whether there were significant differences between a monocular calibration, in which each eye’s data were acquired separately while the other eye was patched, or a single binocular calibration with both eyes viewing. When no differences in the calibration functions were apparent, we decided to use a binocular calibration on both animals to minimize the number of calibration trials. One hundred 10\(^{\circ}\) primary-only saccades (50 rightward, 50 leftward) were then acquired in all sessions, control or adaptive, as baseline. The actual experiment then started. The randomly selected control or adaptive experiment assigned to the session of the day continued until the animal lost interest in the task and the animal was returned to its home cage.

Data Analysis

Horizontal (H) and vertical (V) eye position traces were linearized with third-order polynomials in both horizontal and vertical coefficients, determined with the calibration board, to compensate for possible coil and phase detector horizontal/vertical cross talks, and fit with a cubic spline. Velocity signals (H, V) were then calculated with a 2-point backward differentiation. The primary saccades were manually identified, and the 2-segments fitting process outlined in Busettini and Mays (2005a) was applied to identify the quadrant saccadic onset (\( S_{\text{ON}} \)) and offset (\( S_{\text{OFF}} \)). Once the onset and offset of the primary saccade were determined, all traces were synchronized with respect to saccadic onset or offset, depending on the aspect being addressed.

For the analysis, each trial was divided into four main time segments. The presaccadic (PR) segment started at the onset of the primary target steps and ended at the onset of the primary saccade. The intrasaccadic (IN) segment started at the onset and ended at the offset of the primary saccade. The immediate postsaccadic (\( P_{\text{O-50}} \)) segment started at the offset of the primary saccade and ended 50 ms after the offset. These three segments together defined the PREVISUAL interval. All the response components starting 50 ms after the offset of the primary saccade were defined as VISUAL. Each of these time periods involves specific neural events, which will be briefly discussed here. Busettini and Mays (2003) have shown that during combined vergence-saccadic responses macaque brain stem saccadic omnipause neurons (OPNs) pause only during the IN periods, and are at or near baseline firing elsewhere. Furthermore, the timings of the onset and offset of the OPN saccadic-related pause, both for saccades alone and when associated with an ongoing vergence, were found to be very similar and tightly linked to the onset and offset of the version component of the saccadic response. Similarly, Missal and Keller (2002) have reported that some OPNs slow their firing during conjugate smooth pursuit, but, as observed for vergence, they stopped their firing only in correspondence to the catch-up saccades. When the OPNs are firing at or near baseline, the inhibition of the short-lead saccadic burst neurons by the OPNs blocks any saccadic command from reaching the motoneurons of the extraocular muscles (Keller et al. 1996; Scudder 1988), necessarily implying that, in the monkey, any smooth response outside the actual saccades has no active contributions from the saccadic system. This is also confirmed by direct recordings of short-lead burst neurons during similar visual vergence-saccadic tasks (Van Horn et al. 2008).\(^1\) Excluding corrective saccades or saccadic intrusions, this means that the saccadic system is active at the level of the short-lead burst neurons only during the IN time period. Of interest for our study will be the presence of smooth version or vergence responses during the PR time period, indicating that their onset can precede the onset of the primary saccade. The selection of 50 ms for the duration of the \( P_{\text{O-50}} \) period time derived from the latency values reported in the literature for the visually driven ultrashort-latency version (Busettini et al. 1991; Kawano and Miles 1986; Miles et al. 1986) and vergence (Busettini et al. 1996) responses in the monkey. The 50 ms value guaranteed that no part of the responses observed in the \( P_{\text{O-50}} \) period was elicited by post-saccadic visual feedback. As a consequence, any response after the \( P_{\text{O-50}} \) period was defined as potentially visually driven: the VISUAL segment. \( \text{VIS}_{\text{100-200}} \) was defined as the first 100-ms time period of the VISUAL segment, and \( \text{VIS}_{\text{100-200}} \) was defined as the next 100-ms interval. The extended postsaccadic interval \( \text{PO}_{\text{600}} \) was defined as the interval between the end of the primary saccade and 600 ms after this event. With our definition of VISUAL, \( \text{PO}_{\text{600}} \) included 550 ms of potential visual contributions.

All version, vergence, right eye, and left eye measures reported in this article are horizontal measures. Responses contaminated by vertical movements were rejected during the initial visual inspection. All reported statistical significances are at the \( P < 0.01 \) level, and \( R^2 \) values are mean corrected.

RESULTS

This section is structured into three main segments. The first section illustrates the results associated with the binocular paradigm in the fully predictive design, with particular focus on the adaptive constants, the conjugacy of the adaptive responses, and the nature of the post-saccadic drifts. The second section describes the results associated with the uniconcular and symmetric paradigms, also in the fully predictive design. Of particular importance is a comparison of their adaptive constants and post-saccadic behavior with the binocular case. Finally, the third section briefly reports the main results obtained with the pseudorandom design and how they compare with the fully predictive design to look

\(^1\) There is indirect evidence, supported by the presence of small rapid oscillations in the version trace following the end of the primary saccade, that OPNs in humans might have, sometimes, an extended pause after the primary saccade during combined vergence-saccadic responses. These conjugate oscillations were observed, during combined movements associated with large vergence changes, in approximately one-third of the trials and in all the subjects tested (Ramat et al. 1999). Their frequency of occurrence decreased for smaller vergence changes, and they were not observed for conjugate saccades. There were no evident effects on the version traces in the trials presenting the conjugate oscillations, suggesting that the delayed resuming of the OPN firing, and, as a consequence, the delayed blocking of the saccadic system after the primary saccade occurring in these trials, had little behavioral impact overall. We had no evidence in our monkey data of such oscillations or of a bimodal behavior in the resumption of the OPN firing (Busettini and Mays 2003).
for any influence of prediction in the conjugate and disconjugate short-term adaptive process.

**Fully Predictive Design Biocular Paradigms**

*Adaptive constants and conjugacy.* Two fully predictive biocular adaptive experiments (BA in Fig. 1) and associated controls (BC in Fig. 1) were performed with each animal. In the first adaptive experiment, a \(2^\circ\) forward secondary step was applied during both rightward and leftward \(10^\circ\) primary saccades, which simulated a sudden 20% bidirectional reduction in saccadic gain by causing the animal to consistently undershoot the target. As shown in Fig. 2A (*animal 1*, rightward saccades), the animal reacted to the repeated undershoots by increasing the intrasaccadic version position change of the primary saccade. In the second experiment, a \(2^\circ\) backward secondary step was applied during both rightward and leftward \(10^\circ\) primary saccades, which simulated a sudden 20% bidirectional increase in saccadic gain by causing the animal to consistently overshoot the target. As shown in Fig. 2B (*animal 1*, rightward saccades), the animal reacted to the repeated overshoots by decreasing the intrasaccadic version position change. The gray dots in Fig. 2, A and B, are the 50 initial \(10^\circ\) Saccades.
rightward controls. Trial 1 is defined as the first trial of the actual experiment. The red traces in Fig. 2, A and B, are single adaptive constant exponential fits. With the progress of the adaptation related to the number of exposures to each specific landing error and not to the actual session time, we adopted for the exponential fits the term “adaptive constant” as being more appropriate than the more usual term “time constant.” The value labeled $\Delta_{AS}$ in Fig. 2, A and B, is the asymptotic amplitude of the exponential in degrees, and $A_C$ is the adaptive constant expressed as a function of the total number of trials. In the fully predictive design, the actual number of exposures to each landing error (rightward vs. leftward 10° primary steps) is one-half the total number of trials. As a general feature observed in both humans and monkeys, our two animals found decreasing the gain to be easier than increasing it, as can be seen in Fig. 2 by comparing the adaptive constants $A_C$ for the increasing (Fig. 2A) and decreasing (Fig. 2B) sets. Figure 2, C and D, illustrate our search, in the same data reported in Fig. 2, A and B, for any evidence that biocular adaptation is a binocular process, in the sense that it alters the gain of a common saccadic process, in the sense that it alters the gain of a common process.

Fig. 1. The double-step saccadic paradigms. Top and middle: in these 6 panels, the thin dashed lines (LM and RM) are the calibrated feedback signals from the galvanometers indicating the target positions, while the thick solid lines (LE and RE) are the left-eye and right-eye positions. A dichoptic arrangement using matching orthogonal polarizers and a nondepolarizing screen allowed separate presentation of the targets to the 2 eyes (red traces: left eye; black traces: right eye). The primary target steps were always identical horizontal steps applied to both eyes, 10° rightward steps in the example shown. The secondary steps were $+20\%$ or $-20\%$ of the primary steps, with the exclusion of the symmetric case where they were equally split, in opposite directions, between the 2 eyes. Top: the visual controls, where the secondary steps were delivered with the primary steps. In the biocular control (BC), the secondary steps were identical and in the same direction for the 2 eyes. In the example, the 2 same-direction 2° secondary steps generated a rightward 12° single-step trial to both eyes. In the unocular control (UC), the secondary step was applied only to 1 eye. In the example, with the 2° secondary step added to the right eye, the result is a rightward 10° step on the left eye and a rightward 12° step on the right eye. In binocular coordinates, this translates into a rightward version of 11° and a divergence of 2°. In the symmetric control (SC) example, the 2° step is split, in opposite directions, between the 2 eyes, to still have a divergence of 2° but no alteration in version, which remained 10°. Middle: the matching adaptive tasks. In these, the animal always saw only the conjugate primary steps, with the secondary steps applied while the animal was responding to the primary steps. Bottom: the target trajectories on the horizontal meridian plane for the unocular $+20\%$ secondary step on the right eye paradigms in the fully predictive (left) and pseudorandom (right) designs. In both cases the starting position of the target for the next trial was the position achieved at the end of the previous trial. The main difference was that in the fully predictive design a rightward 10° primary target step was always followed by a leftward 10° and so on, while in the pseudorandom design the primary target step in the next trial could have been, randomly selected, a rightward 5°, a leftward 5°, a rightward 10°, or a leftward 10°. Each paradigm was presented in separate daily sessions in a random sequence, lasting as long as the animal continued to perform the primary saccadic task. Rightward eye movements are reported as positive, leftward movements as negative.

Fig. 2. Examples of intrasaccadic version adaptation as a function of Trial # in the biocular adaptive paradigms (fully predictive design) and associated conjugacy tests from animal 1. A: example of forward biocular secondary steps, which simulate a sudden identical decrease in saccadic gain in both eyes. The animal sees 10° steps in both eyes, but the actual target shift, with the added intrasaccadic second steps, is 12°. The animal gradually adapts by increasing the intrasaccadic version response. B: example of backward biocular secondary steps, simulating a sudden identical increase in saccadic gain in both eyes. The animal sees 10° steps in both eyes, but the actual target shift, with the added intrasaccadic second steps, is 8°. The animal gradually adapts by decreasing the intrasaccadic version response. C: Trial # is the number of trials from the start of the adaptive experiment; the initial control trials, in gray, therefore have a negative Trial #. In the fully predictive design, with alternating rightward and leftward 10° saccades, the number of visual exposures to each of the adaptive trials is 1/2 of the Trial #. Red lines are single adaptive constant exponential fits, with asymptotic amplitude $\Delta_{AS}$ and adaptive constant $A_C$. C and D: relationship between the left-eye intrasaccadic responses and the right-eye intrasaccadic responses for data in A and B, respectively. The red line is the linear regression, with slope $S_r$ reported together with the $R^2$. 

J Neurophysiol • doi:10.1152/jn.01013.2011 • www.jn.org
version drive to the two eyes, or a monocular process, where the gains of the two eyes are independently adjusted. In the first case, we expected little or no alteration in conjugacy, i.e., the level of correlation of the intrasaccadic changes in eye position in the two eyes, between corresponding control and adaptive sets. In the second case, some significant differences were expected, considering it unlikely that the independent right-eye and left-eye adaptive elements would generate exactly identical gain changes and with exactly identical adaptive constants. We therefore computed the linear regression between the intrasaccadic horizontal position change of the left eye and of the right eye for all the experimental data in each biocular control and adaptive session (Trial \# \geq 1). In the eight biocular fully predictive design adaptive sets (2 animals, + and −20%, rightward and leftward saccades) \( R^2 \) ranged from 0.88 to 0.97 (mean 0.91 ± 0.03 SD), while for the associated controls it ranged from 0.87 to 0.98 (mean 0.94 ± 0.04 SD). For the control sets we computed the \( R^2 \) after we restricted the intrasaccadic version range of responses present in the control sets. A mean paired \( t \)-test between the eight correspondent adaptive and control sets was not significant (\( P = 0.08 \)). Furthermore, adding Trial \# as an independent variable in the linear regression improved the \( R^2 \) of the adaptive sets by at most 2%, and its contribution was often not significant. Finally, we plotted the changes in intrasaccadic vergence as a function of Trial \#, and no discernible pattern was observed in animal 1. In animal 2, there was a small, significant increasing convergence for rightward saccades and a small, significant increasing divergence for leftward saccades in all sets, adaptive and control, as the session progressed. Thus it had no relationship with adaptation or its sign. We could not determine whether this was an unspecified slight change in gain in one eye with time or a change in the accommodation/vergence dissociation that was also dependent on saccadic direction. Overall, we found no evidence, in the fully predictive biocular sets, of adaptation altering conjugacy.

The temporal progress of the version adaptation in the biocular fully predictive design was similar, inside each session, for the two saccadic directions. This is illustrated in Fig. 3, which reports the exponential fits of the four rightward/leftward pairs (session with bidirectional simulated gain increases, session with bidirectional simulated gain decreases, 2 animals), expressed as intrasaccadic version gain (1 equivalent to 10°) of the primary saccade. For the gain increases in animal 2 the exponential fit did not converge (sets identified with an asterisk in Fig. 3 tables) and we used a linear fit, defined by the slope \( S_L \). ASE in the tables of Fig. 3 is the asymptotic standard error; the value TN is the experiment trial number when the animal stopped working, and the actual range of trials on which the fits were computed. For clarity, the plots are limited to the first 1,500 trials. The value \( \Delta \) in Fig. 3 indicates the total version gain change, in percentage, achieved during the session, defined as the percent difference between the value of the fit at trial number TN and at trial number 1. For these sets, version full adaptation is +20% or −20%. The \# symbol near the \( \Delta \) value in Fig. 3 indicates that the animal achieved adaptive steady state for that set during the session, which was defined as a set where TN was more than three times \( A_c \), the value \( \Delta \) in these sets is practically the asymptotic amplitude of the exponential expressed as percentage of gain change. Both animals achieved the steady state for the gain decreases and animal 1 for one gain increase [rightward (\( rw \) +20%], Animal 1 achieved good adaptation in all four cases. Animal 2 had clear difficulties with the gain increases, while having a robust adaptation for the gain decreases, albeit with smaller asymptotic values compared with animal 1.

**Dynamical analysis of adapted saccades.** As a first analysis of the dynamics of the adapted saccades in the biocular fully predictive paradigm, we compared the average version velocity profile of the last fifty 10° rightward and the last fifty 10° leftward saccades in the biocular adaptive sessions (BA in Fig. 3 tables) and we used a linear fit, defined by the slope \( S_L \). ASE in the tables of Fig. 3 is the asymptotic standard error; the value TN is the experiment trial number when the animal stopped working, and the actual range of trials on which the fits were computed. For clarity, the plots are limited to the first 1,500 trials. The value \( \Delta \) in Fig. 3 indicates the total version gain change, in percentage, achieved during the session, defined as the percent difference between the value of the fit at trial number TN and at trial number 1. For these sets, version full adaptation is +20% or −20%. The \# symbol near the \( \Delta \) value in Fig. 3 indicates that the animal achieved adaptive steady state for that set during the session, which was defined as a set where TN was more than three times \( A_c \), the value \( \Delta \) in these sets is practically the asymptotic amplitude of the exponential expressed as percentage of gain change. Both animals achieved the steady state for the gain decreases and animal 1 for one gain increase [rightward (\( rw \) +20%], Animal 1 achieved good adaptation in all four cases. Animal 2 had clear difficulties with the gain increases, while having a robust adaptation for the gain decreases, albeit with smaller asymptotic values compared with animal 1.

**Dynamical analysis of adapted saccades.** As a first analysis of the dynamics of the adapted saccades in the biocular fully predictive paradigm, we compared the average version velocity profile of the last fifty 10° rightward and the last fifty 10° leftward saccades in the biocular adaptive sessions (BA in Fig.
1) with, respectively, the average version velocity profile of the last fifty rightward and the last fifty leftward 8°, 10°, and 12° saccades from the associated control sessions (BC in Fig. 1) to take into account the changes in saccadic dynamics due to fatigue (Prsa et al. 2010; Straube 1997b). This approach was preferred to a comparison made on adaptive and control trials within the same range of Trial # because it probably better matched the animal alertness and interest in the primary saccadic task. Figure 4, top, shows an example of a backward-step adaptive case (animal 1, biocular −20% adaptive paradigm, fully predictive design, rightward saccades). Figure 4BA illustrates the average version position (HVS) and version velocity (HVS˙) of the last 50 rightward saccades (continuous lines) of the adaptive set, with the dashed lines indicating ±SD. All traces were synchronized with respect to primary saccade onset before averaging. The decrease in gain near the end of this session was quite robust, as evident in Fig. 4BB, which compares the adapted position and velocity version averages from Fig. 4BA (traces labeled −20% AD) with the averages of the last fifty 8° (CONT) and 10° (CONT) saccades of the correspondent control session. The adapted saccades had profiles, on average, similar to gain-reduced 10° “fatigued” control saccades. This opens the possibility of the adapted saccades being elicited by the primary steps as 10° saccades unaltered by the adaptive process, only further downstream scaled down by the adaptation. Note, as evident in Fig. 4BB, that this mechanism would make the adapted saccades appear slower and last longer than similarly “fatigued” 8° control saccades if, for that animal, following the duration/size main sequence (Bahill et al. 1975), 10° control saccades are of significantly longer duration than 8° control saccades. No actual adaptive dynamical changes would have occurred, just an amplitude decrease of larger and longer 10° saccades. Figure 4, FA and FB, show an example of a forward-step adaptive case (animal 1, biocular +20% adaptive paradigm, fully predictive design, rightward saccades) with the same layout. In Fig. 4FB, the adapted averages (+20% AD) from Fig. 4FA are now compared with the averages of the last fifty 10° (CONT) and 12° (CONT) saccades of the control session. The profile was, again, similar to gain-altered 10° “fatigued” control saccades. In this case, if the

**Fig. 4.** Comparison of average version profiles between biocular fully predictive adaptive and associated control sets. Top: backward adaptive step (animal 1, biocular −20% adaptation, rightward saccades). Bottom: forward adaptive step (animal 1, biocular +20% adaptation, rightward saccades). BA and FA: average version position (HVS) and version velocity (HVS˙) of the last 50 rightward saccades (continuous lines) of the 2 adapted sets, with dashed lines indicating ±SD. BB: comparison of the version position and velocity averages (AD) from BA with the averages of the last fifty 8° (CONT) and 10° (CONT) saccades of the correspondent control session. FB: averages (AD) from FA compared with the averages of the last fifty 10° (CONT) and 12° (CONT) saccades of the correspondent control session.
animal had its 12° control saccades significantly longer in duration than its 10° control saccades (not true for this set), adapted saccades obtained by upward rescaling of 10° saccades would actually appear faster than 12° control saccades at a similar level of fatigue. We attempted to quantify these dynamical changes for both control and adaptive sets by morphing the average version velocity profile of the initial fifty 10° same-direction control trials of the session onto the version velocity profile of each associated experimental trial (TN ≥ 1). This morphing was obtained with a minimum square error procedure that quadratically altered the timescale and linearly the amplitude scale of the associated control average profile. This was seen as a much more robust estimate of the temporal alteration of the main component of the saccade than standard pointwise duration and amplitude measures. The vast majority of both control and adaptive sets (biocular, uniocular, and symmetric) showed highly significant increases in duration of the version velocity profiles with Trial # with respect to the initial fifty 10° controls of the session, quantified as a significant deviation of the distorted timescale from the 1:1 line (no time distortion). Most interestingly, there were no consistent differences in the level of time distortion between biocular (BC vs. BA), uniocular (UC vs. UA), or symmetric (SC vs. SA) control and adaptive sets. This was also true for the pseudorandom paradigms, strongly suggesting that an unspecific fatigue effect, shared with the controls, was most likely the cause of the increase in duration of the version velocity profiles of the adapting saccades as the session progressed. For the uniocular and symmetric cases, part of the saccadic slowing might have been caused by vergence-saccadic interactions, which are known to generate slower and longer saccades (Collewijn et al. 1995; Walton and Mays 2003), but we did not see an additional slowing in these sets when compared with the biocular sets. In both fully predictive and pseudorandom biocular paradigms, we also attempted to see whether the adapted profiles, as amount of time distortion, were significantly different from the last fifty 8° saccades in the control sets in the −20% cases and from the last fifty 12° saccades in the control sets in the +20% cases (Fig. 4), supporting the concept that adaptation in the biocular paradigms is a downward or an upward linear gain scaling of unadapted 10° primary saccades. The alternative hypothesis was for the adapted saccades to be generated directly as 8° or 12° movements, respectively, and therefore having dynamics similar to control 8° or 12° saccades. The results were inconclusive. Perhaps slight differences in the fatigue level between the control and adaptive sessions, acquired on different days, were sufficient to mask the small dynamical differences that would have allowed us to determine the mechanism of biocular adaptation, although it is also possible that biocular adapted saccades do not follow the unadapted main sequence.

**Extrasaccadic adaptive components.** Are there contributions to the adaptation in the biocular paradigms outside the primary saccade, like presaccadic or postsaccadic smooth responses or secondary saccades with short, nonvisual latencies? As we will see below, smooth postsaccadic components play an important role in uniocular and symmetric adaptation and, in the monococular adaptive hypothesis, they also have to be present in the biocular sets as, similar in the two eyes to preserve conjugacy, adaptive monococular postsaccadic drifts. The scatter in Fig. 2 also raised the question about the animals being truly engaged in the saccadic task. This was particularly important in the fully predictive paradigms where, because of their predictability, it was possible that the animals were just following a rightward/ leftward pattern to receive their reward without precisely following the targets. Figure 5A illustrates an example of the changes in presaccadic version position from the onset of the primary 10° target step to the onset of the animal’s primary saccade as a function of Trial # (animal 2, biocular −20% adaptive paradigm, fully predictive design, rightward saccades). The animal had no anticipatory responses in the PR segment. In the biocular cases there were no presaccadic adaptive components, even in the fully predictive design. As described above, there was a rapid intrasaccadic adaptive change in version, evident when comparing the 50 initial 10° controls (open gray circles) with the adaptive responses (open black circles and filled gray circles) in Fig. 5B. The amount of biocular landing error introduced by the secondary steps that was not compensated by the intrasaccadic version adaptation was accurately corrected (Fig. 5C) during the extended postsaccadic period (0–600 ms from primary saccadic offset). As the biocular secondary steps were introduced, the total change in version position (from onset of the primary target steps to 600 ms after the end of the primary saccade) presented an immediate sharp transition from 10° to 8° (Fig. 5D), indicating that the animal was fully engaged in the saccadic task to the very end of the session and carefully corrected the landing errors. The nature of the postsaccadic correction in Fig. 5C is illustrated in Fig. 5E, reporting the version position profiles and version velocity profiles, synchronized with respect to primary saccade offset, of the last 15 saccades of the session, identified with the filled gray circles in Fig. 5, C–D.

All postsaccadic corrections were visually driven corrective saccades, as evident from their latency, longer than 180 ms from primary saccadic offset (the vertical dashed line in Fig. 5E identifies the location of the onset of the earliest corrective saccade in the set). To verify that these corrective saccades were truly linked to the residual postsaccadic visual error, for these 15 saccades we plotted the intrasaccadic v

---

J Neurophysiol • doi:10.1152/jn.01013.2011 • www.jn.org
images show the averages of the horizontal version velocity HVS, horizontal left eye velocity HL, horizontal right eye velocity HR, and vergence velocity VG. The postsaccadic overshoots were very similar between the 50 initial controls of the session and the last 50 adapted saccades. Strikingly, practically identical overshoots were present in the +20% case, illustrated in Fig. 6, bottom, with the same layout.

To better elucidate the development in time of the biocular postsaccadic drifts as the adaptive sessions progressed, Fig. 7 shows examples of the time course of the changes in horizontal right eye position (Fig. 7, A and E), horizontal left eye position (Fig. 7, B and F), vergence position (Fig. 7, C and G), and horizontal version position (Fig. 7, D and H) in the first 50-ms time interval after the end of the primary saccade (PO[0-50] measures) as a function of Trial #. Figure 7,
A–D, report the data for the rightward saccades in the −20% biocular adaptive fully predictive session in animal 2. Figure 7, E–H, report the same measures for the leftward saccades in the same session. The quality of the measures is quite remarkable, with clear and highly significant changes occurring inside the \( \text{PO}_{[0-50]} \) interval as the session progresses, particularly for the horizontal version measures. The red lines in Fig. 7 are second-order polynomial fits. The asymmetries between the right-eye measures and the lefteye measures are most likely due to the divergence/convergence transients, in this late part of the response being convergence responses (positive sign of the vergence measures in Fig. 7, C and G). The inversions with saccadic direction in sign and trend with Trial # of the version measures are quite evident when comparing Fig. 7, D and H. For both rightward and leftward saccades, the movement ends with small overshoots (negative values for rightward saccades, positive values for leftward saccades) presenting a clear trend to decrease their amplitude as the session progressed. To verify whether these results are specific to the biocular adaptive paradigms or whether they also apply to the control sets, Fig. 8 shows the second-order polynomial fits of the \( \text{PO}_{[0-50]} \) horizontal version measures for the two biocular fully predictive adaptive sets and for the associated control sets superimposed (animal 1 in Fig. 8, left; animal 2 in Fig. 8, right). The postsaccadic horizontal version overshoots are clearly determined by saccadic direction [rightward (rw) or leftward (lw)], with direction of the adaptation (+20% or −20%) having a small, if any, impact on their time course compared with the controls (CONT). Identical results were found in the biocular sets following the pseudorandom design. It is likely that the decrease in the amplitude of the overshoots is another unspecific aspect of fatigue, with the \( \text{PO}_{[0-50]} \) values gradually converging toward zero for both control and adaptive sets. The data show no evidence of the postsaccadic drifts being affected by or contributing to biocular adaptation, or, indirectly, of adaptation affecting the pulse-step ratio of the primary saccade. Biocular adaptation seems to equally scale the pulse and the step components of the primary saccade.

**Summary.** Our analysis of the biocular adaptive results in the fully predictive design suggests that the adaptive process in these paradigms is likely conjugate and strictly limited to the main component of the primary saccade. There were no presaccadic adaptive contributions, and the analysis of the \( \text{PO}_{[0-50]} \) postsaccadic drifts identified them as overshoots related to the saccadic direction and not to the adaptive process. The oculomotor responses inside the \( \text{PO}_{[0-600]} \) interval were found to be visually driven corrective saccades. These observations.

---

**BI-OCULAR PARADIGM - FULLY-PREDICTIVE DESIGN**

**POSTSACCADIC DRIFTS**

![Fig. 6. Postsaccadic drifts in the biocular fully predictive paradigms. Top: version velocity average (HVS ± SD) of the 50 initial primary-only leftward control saccades (left) and of the last 50 leftward downward-adapted saccades of the biocular −20% session (right). Magnified insets (location identified by blue boxes): horizontal version velocity HVS, horizontal left eye velocity HL, horizontal right eye velocity HR, and vergence velocity VG. Bottom: upward-adapted (+20%) data. All traces were synchronized with saccade end prior to averaging. Animal 1, fully predictive design, −20% or +20% biocular adaptive paradigms, leftward saccades. \( S_{\text{OFF}} \), saccade offset.](http://jn.physiology.org/DownloadedFrom)
also extended to the biocular data in the pseudorandom design, which are not shown for brevity. We also found that the changes in version dynamics observed in the adapted saccades were mostly nonspecific effects due to fatigue, and this observation, not shown for brevity, also extended to the uniocular and symmetric paradigms and to both fully predictive and pseudorandom designs.

Fully Predictive Design Uniocular and Symmetric Paradigms

General observations. If saccadic short-term adaptation is a monocular process, in which each eye recalibrates its gain independently from the other on the basis of its own landing errors, the adaptive behavior for the uniocular and symmetric paradigms provides an important test of this hypothesis. If a change in version dynamics is the result of a nonspecific process like fatigue, or a visual artifact, this change would also extend to the symmetric paradigm.

Fig. 7. Postsaccadic overshoots in the biocular tasks. A and E: changes in horizontal right eye position in the PO[0–50] interval as a function of Trial #. B and F: changes in horizontal left eye position. C and G: changes in vergence position. D and H: changes in horizontal version position. A–D: data for the rightward saccades in the −20% biocular adaptive fully predictive session in animal 2. E–H: the same measures for the leftward saccades in the same session. Red lines are second-order polynomial fits.

BI-Ocular Paradigm - Fully-Predictive Design
Postsaccadic Drifts PO[0–50] Values

Fig. 8. Postsaccadic overshoots in the biocular paradigms are determined by saccadic direction and fatigue. Superimposed second-order polynomial fits of the changes in version position in the PO[0–50] interval for the 4 biocular fully predictive adaptive sets (lw +20%, rw +20%, lw −20%, and rw −20%) and for the associated controls (lw CONT and rw CONT) as function of Trial # are shown. Left: animal 1. Right: animal 2.
paradigms will necessarily match the adaptive behavior described above for the biocular paradigms. A biocular adaptation, in this view, is simply a monocular adaptation where both eyes receive the same secondary steps, and therefore the right-eye and left-eye monocular gain controllers are asked to achieve identical gain changes. In the uniocular paradigms, the eye seeing the backward or forward 20% secondary step will adapt exactly the same way it does in the biocular paradigms, unaware that there is no secondary step in the other eye. In the symmetric paradigms, each eye will adjust its gain by equal and opposite half amounts. Furthermore, post-saccadic drifts in the PO_{[0–50]} interval are expected to give no contribution to the adaptive process and only to depend on saccadic direction and fatigue. Already at the single-trial level things look quite incompatible with the monocular view, with three single-trial examples reported in Fig. 9 (animal 1, +20% uniocular step on

**UNI-OCULAR PARADIGM - FULLY-PREDICTIVE DESIGN**

**SINGLE TRIALS AND DEVELOPMENT OF DISCONJUGACY**

**Fig. 9.** Single-trial examples from a uniocular fully predictive design adaptive paradigm and test of the vergence adaptation/prediction hypothesis. Top: eye positions (LE, left eye; RE, right eye; VG, vergence) and calibrated feedback signals from the mirrors (LT, left eye mirror; RT, right eye mirror). Middle: eye velocities. A: an initial 10° primary-only control trial. B: an early adaptive trial, with the disparity landing error entirely compensated by a post-saccadic visually driven smooth vergence response. C: a late adaptive trial, presenting a large post-saccadic component (arrow). Some presaccadic vergence response is also present (asterisk). Note that the entire disparity error in this late trial is compensated perisaccadically, with no need for a later visually driven corrective smooth vergence response. These panels report the time intervals used in the analysis as vertical dashed lines, and are labeled in C. The vergence velocity traces (VG) (middle) are amplified 5 times with respect to the right-eye and left-eye velocity traces for clarity. Trials from animal 1, +20% uniocular step on the right eye (crossed disparity), leftward saccades. Bottom: changes in vergence position (ΔVG) in the IN, PO_{[0–50]}, VIS_{[0–100]}, and VIS_{[100–200]} intervals as a function of Trial # for animal 2, +20% uniocular step on the left eye (crossed disparity) rightward saccades.
the right eye, leftward saccades). Figure 9, top, reports eye positions (left eye, right eye, vergence) together with the calibrated feedback signals from the mirrors (left eye mirror, right eye mirror). Figure 9, middle, reports eye velocities with the same color scheme. Traces are synchronized with the onset of the primary target steps. The initial fifty 10° primary-only trials were obviously not different from the initial fifty primary-only trials in the biocular sets. Figure 9A reports one of these to highlight the vergence transient, also present in these initial control saccades. In the initial adaptive trials, where there was no time for adaptation to have developed, the primary saccades were also identical to the initial primary-only controls as expected. One example is reported in Fig. 9B. The first striking difference with respect to the biocular case (compare with Fig. 5E) is that the visual correction of the disparity error introduced by the secondary step being applied to only one eye is achieved by a smooth vergence response. Small corrective saccades could also be present in the VISUAL time interval to compensate for the 10% change in version introduced by the unbalanced secondary step (Fig. 1, UA case). The second difference is that even in the cases where the animal achieved a steady state, a large postsaccadic component was present after the end of the primary saccade (arrow in Fig. 9C). As the asterisk near the vergence velocity trace in Fig. 9C indicates, some presaccadic vergence responses were also present in some trials.

With the data reported in Fig. 9 from a fully predictive set, we initially suspected that what we were observing was a vergence-driven predictive process, where the smooth visually driven vergence correction of the disparity error introduced by the unocular secondary step (Fig. 9B) gradually travelled in the direction of the saccade (Fig. 9C) driven by prediction. To test this hypothesis, we plotted the changes in vergence position (ΔVG) in the IN, PO\(_{0–50}\), VIS\(_{0–100}\), and VIS\(_{100–200}\) intervals as a function of Trial # (Fig. 9, bottom). These time intervals are identified in the single-trial panels as vertical dashed lines, and are labeled in Fig. 9C. Following this hypothesis, as the vergence wave traveled toward the saccade and we expected a gradual decrease in the VIS\(_{100–200}\) values and at least a transient increase in the VIS\(_{0–100}\) values. During the time needed for this wave to encroach the saccade, the IN and PO\(_{0–50}\) values were expected to remain stationary at least for a short period. In all adaptive unocular and symmetric fully predictive paradigms, the values in VIS\(_{0–100}\) remained pretty flat throughout the session or showed a trend toward zero, and no initial plateaus in the IN or PO\(_{0–50}\) measures were detected. Furthermore, the same behavior was observed in the unocular pseudorandom paradigms, where prediction was not expected to play a role. The behavior described in these panels is much more consistent with the development of a perisaccadic adaptive process influencing both the IN and PO\(_{0–50}\) measures, and with the postsaccadic visually driven vergence corrections, stationary in latency, becoming smaller and smaller as the perisaccadic adaptation increased.

**Postsaccadic components.** For a given saccadic direction, identical disparity landing errors can be generated by a decrease in gain in one eye or by an identical increase in gain in the other eye. For example, for rightward saccades we can introduce a crossed disparity error by applying a backward secondary step in the right eye or by applying a forward secondary step in the left eye. Both paradigms require a convergence adaptive response. In a binocular adaptive modality, this convergence response will be driven by the vergence system and will symmetrically affect both eyes, with the direction of the primary saccade and which eye saw the step being irrelevant factors. In a monocular adaptive modality, we will have an adaptive response affecting only the eye that saw the secondary step, with the uniocular adaptation achieved by pure asymmetric saccades (Fig. 5E). From the biocular results, we also expect, in the monocular modality, any postsaccadic drift to be only related to saccadic direction. Figure 10, top, illustrates the averages of the velocity profiles, after alignment with saccadic offset, of the initial 50 rightward 10° primary-only saccades (Fig. 10, top left) and of the last 50 rightward adapted saccades (Fig. 10, top right) in the two uniocular fully predictive rightward saccades convergence sets (−20% secondary step on the right eye and +20% secondary step on the left eye) from animal 1. The layout is similar to Fig. 6, with the only difference that the ±SD of the HVS traces in the main panels in Fig. 6 are now the HL (red) and HR (green) velocity averages; horizontal version velocity averages (HVS) are in black, and vergence velocity averages (VG) are in violet. The similarities in adapted average postsaccadic profiles between the −20% secondary step on the right eye and the +20% secondary step on the left eye are truly striking, clearly suggesting the presence of a symmetric adaptive convergence response affecting both eyes. Note that these data are from different days. Figure 10, bottom, illustrates the averages, with identical schema, of the velocity profiles in the two uniocular fully predictive rightward saccades divergence sets (+20% secondary step on the right eye and −20% secondary step on the left eye) from animal 1, also acquired on different days. Again, the evidence is for the presence of a symmetric adaptive divergence response affecting both eyes. Similar results were obtained in the fully predictive symmetric and the pseudorandom uniocular paradigms.

**Version adaptation.** If the hypothesis suggested by Fig. 10 about the presence of a saccadic-controlled symmetric adaptive vergence response is correct, it is possible that the version landing errors and the disparity landing errors are dealt with by independent adaptive mechanisms. This would mean that the adaptation to the 1° version landing errors introduced by the unocular 2° secondary step is a version-only process that necessarily follows the same behavior observed in the biocular adaptive paradigms. In the context of the immediate postsaccadic behavior, this implies that the version responses in the PO\(_{0–50}\) interval are nonadaptive saccadic overshoots, i.e., determined only by the saccadic direction, that gradually converge toward zero as the session progresses because of fatigue. This hypothesis also requires that they are unaffected by which eye experienced the secondary step and by its sign. Furthermore, the intrasaccadic version adaptation (IN time interval) will have adaptive constants similar to the biocular data, and present the typical asymmetry between increasing and decreasing gain paradigms. The data presented in Fig. 11, from animal 2, clearly support a version-only adaptation that is acting independently of the mechanism dealing with the correction of the disparity landing errors. Figure 11A illustrates the single-trial changes in horizontal version position in the PO\(_{0–50}\) interval for the leftward saccades in the +20% uniocular step
on the right eye paradigm as a function of Trial #. Figure 11C shows the same measure for rightward saccades in the −20% unioocular step on the right eye paradigm. Both are convergence tasks, but the PO_{0−50} Version measures clearly have opposite sign and follow similar trends toward zero. The red lines in Fig. 11, A and C, are second-order polynomial fits, which are used in Fig. 11, B and D. With a striking similarity with this animal’s biocular behavior, reported in Fig. 8, right, Fig. 11B shows that the immediate posttaccadic version drifts for leftward saccades for all unioocular fully predictive paradigms, irrespective of the sign of the disparity or which eye saw the step, were overshoots (positive sign) with a trend toward zero as the session progressed. Mirror-image results were observed for rightward saccades (Fig. 11D). The associated unioocular controls (not shown) gave very similar results, again supporting the observation, made with the biocular sets, that version adaptation does not affect the immediate posttaccadic behavior. This pattern was confirmed in the unioocular fully predictive paradigms in animal 1 and in the fully predictive symmetric paradigms in both animals. In the pseudorandom unioocular sets, because of the saccades ending at different version position values (Fig. 1), there was more scatter in the posttaccadic version overshoots, but the behavior, again, was not affected by the direction of the disparity error or by which eye saw the step. Overall, the version behavior in the PO_{0−50} interval was practically identical to the biocular data. As for the biocular paradigms, the presaccadic version behavior showed no evidence of presaccadic version contributions to the adaptive process. Thus version adaptation was found to be strictly limited to the intrasaccadic period as in the biocular cases. Figure 11, E–H, with a similar layout, illustrate the version position changes in the IN period for the same sets in Fig. 11, A–D. The only difference is that Fig. 11, F and H, now report the intrasaccadic version gain of the primary saccade, and the fits are single adaptive constant exponential or linear fits. The similarities with Fig. 3, animal 2, reporting the same measures for the biocular sets of this animal, are evident, even if the version adaptation goal is only half of the biocular case. The very strong biocular asymmetry between increasing version gain and decreasing version gain in this animal is preserved in the unioocular sets. The adaptive constants are very similar to the biocular sets and independent of which eye saw the step and/or the direction of the disparity error. Identical results were obtained from animal 1. No version errors are introduced in the symmetric paradigms, and, accordingly, the data showed no consistent version changes as the sessions progressed. In summary, the version analysis for the biocular and unioocular paradigms strongly suggests that version saccadic adaptation is an independent, likely conjugate, adaptive process strictly limited to the intrasaccadic period. We also have preliminary evidence (Figs. 9 and 10) that adaptation to the disparity landing errors might be achieved by saccadic-controlled symmetric vergence responses in the two eyes, which behavior we explore next.

Vergence dynamics. Similar to the version dynamical analysis for the biocular data illustrated in Fig. 4, for the unioocular
and symmetric paradigms we compared the vergence position and velocity profiles of the last 50 trials of the adaptive sessions with the last 50 trials of the associated control sessions. Traces were synchronized with respect to the onset of the primary saccade. As evident in the single trial in Fig. 9A, the initial fifty 10° control saccades of both control and adaptive sessions already presented a pronounced vergence response, usually termed the “vergence transient,” which is also present in saccades with no net change in depth (Busettini and Mays 2005a; Collewijn et al. 1988; Maxwell and King 1992; Sylvestre et al. 2002). Figure 12 presents data from the +20% uniocular step on the left eye control and adaptive paradigms in the fully predictive design from animal 1. Rightward saccades (Fig. 12, top) are associated with a crossed disparity, and leftward saccades (Fig. 12, bottom) with an uncrossed disparity. The vergence transients in the 50 primary-step only 10° initial controls (Figs. 12, 1st and 3rd columns) were almost machinelike, although with some variability between the daily sessions. This reproducibility is consistent with the vergence transient being the result of a dynamical asymmetry of the abducting and adducting elements of the oculomotor plant (Zee et al. 1992) and not an active vergence response (but see Sylvestre et al. 2002), although temporal differences in the premotor drives between the two eyes are also possible (Maxwell and King 1992; Zee et al. 1992). Some of this daily variability is likely due to small variations in the right-eye and left-eye calibrations. With the peak version velocity of 10° saccades as high as 400°/s, even a small 1% gain calibration error in one eye would introduce a 4°/s distortion in the intrasaccadic vergence velocity profiles. Small variations in the offset adjustments and thermal drifts of the mirror galvanometers or of the coil detectors may also play a role, although we turned the laboratory on at least 1 h before the start of the session to thermally stabilize the electronics and recalibrated coil detectors and galvanometers daily. The trial-by-trial reproducibility of the last 50 rightward and leftward trials in the session is also remarkable, if one considers that these are the last saccades of the session before the animal stopped working. The key observation is the striking similarity in vergence dynamics between the last 50 saccades in the control and the adaptive sessions, particularly remarkable for the rightward saccades set of this example. The strong similarity is also present for the leftward saccades if one visually subtracts from the last 50 vergence profiles the profile differences in the control vergence transients between the control and the adaptive sets. This is quite surprising, if one considers that in the control paradigms the vergence responses are driven by a visual disparity, while in the adaptive paradigms they are the nonvisual result of a saccadic adaptation. The slowing of the late saccades when compared with the initial controls is also quite evident in both control and adaptive paradigms by

---

Fig. 11. Version adaptive components in the uniocular fully predictive tasks. A: single-trial change in horizontal version position in the PO(0–50) interval for the leftward saccades in the +20% uniocular step on the right eye task for animal 1. C: same measure for rightward saccades for the −20% uniocular step on the right eye task. Red lines are second-order polynomial fits, which are reported in B and D and for all 4 uniocular sets with that saccadic direction. E–H (similar layout): version changes in the IN time interval for the same sets in A–D. Red lines are single-exponential or linear fits, reported in F and H as version primary gain fits (1 / 1°) for all 4 uniocular sets with that saccadic direction.
observing the change in average version velocity profiles (gray dotted lines in the average plots in Fig. 12).

**Development in time of the vergence adaptation.** The analysis of the vergence adaptive process was similar to the analysis of the version components. The presaccadic analysis showed some smooth vergence preceding the primary saccades in both control and adaptive sets, particularly for late primary saccades, like the example in Fig. 9C. The overall contribution...
was small and mostly indicated that smooth vergence adaptive contributions can precede the primary saccade, as visually driven smooth vergence contributions often precede the primary saccade in 3D gaze transfers. Our main focus was on three measures: IN, \( \text{PO}[0–50] \), and PREVISUAL changes in vergence position. The PREVISUAL (PR + IN + \( \text{PO}[0–50] \)) measure derives from the observation that smooth vergence responses can precede the primary saccade, i.e., anticipate the onset of the pause of the OPNs associated with the primary saccade, and can continue after the OPNs have resumed their baseline firing (Busettini and Mays 2003; van Horn et al. 2008). Therefore, \( \text{PR} \) and \( \text{PO}[0–50] \) contributions are an integral part of the nonvisual vergence adaptive process, making PREVISUAL a more appropriate measure of the vergence adaptation than the intrasaccadic (IN) measure. Adaptive nonvisual components may also be present during the initial VISUAL period and add to the responses elicited by visual feedback, but, because they were indistinguishable from visually driven responses, we could not include them in the computation. The \( \text{PO}[0–50] \) vergence analysis will test whether the postsaccadic component in Fig. 9C (arrow) is a true vergence adaptive component.

Sample single-trial measures are reported in Fig. 13 from two convergence and two divergence uniocular fully predictive sets from animal 2, with the secondary steps applied to one or the other eye. The first column of Fig. 13 reports the change in vergence position inside the intrasaccadic (IN) interval, the second column inside the \( \text{PO}[0–50] \) interval, and the third column inside the entire PREVISUAL interval, all as a function of Trial #. The fourth column of Fig. 13 illustrates an estimate of the relative contribution of the intrasaccadic (IN) change in vergence with respect to the entire PREVISUAL change. In the first three columns of Fig. 13 the red lines are single adaptive constant exponentials, while the red lines in the fourth column are second-order polynomial fits. Note that the \( y \)-scale factor for the \( \text{PO}[0–50] \) data is twice as large with respect to the IN and PREVISUAL plots for clarity. Also, plots of sets with more than 1,500 adaptive trials were truncated at 1,500, although the fits were computed with the entire set. The key difference with respect to the version adaptation is that the \( \text{PO}[0–50] \) vergence position change is a robust adaptive component, necessarily driven by the vergence system. The saccadic system is inhibited by the OPNs from the start of the postsaccadic period. It is also evident, from the plots in the fourth column of Fig. 13, that there is a precise ratio between the IN and the PREVISUAL vergence contributions; the dashed line in these plots represents the entirety of the PREVISUAL response being contained inside the intrasaccadic period. As the overall PREVISUAL adaptive contribution increases, the IN relative contribution decreases, with more adaptive contribution coming from the \( \text{PO}[0–50] \) interval and also from the small presaccadic vergence responses, if present. An important feature of the plots in the fourth column of Fig. 13 is the absence of any evident breaking point that would suggest that up to a certain PREVISUAL value the saccadic system can monocularly deal, strictly intrasaccadically, with the disparity correction by itself, and only after a certain threshold must rely on the vergence system, solely responsible for the post-saccadic component. The properties illustrated in Fig. 13 are accurately preserved irrespective of the eye seeing the uniocular secondary step or the crossed or uncrossed disparity landing error and, for the \( \text{PO}[0–50] \) measures, irrespective of the saccadic direction. With the evidence that the \( \text{PO}[0–50] \) vergence responses are integral contributions to the vergence adaptive process, the analysis of the adaptive constants in the next section was performed on the PREVISUAL vergence measures.

**Vergence adaptive constants.** Critical evidence in support of an independent saccadic-controlled, but vergence-driven, adaptive mechanism dedicated to the correction of post-saccadic disparity landing errors would be that the time course of the adaptation is determined by the sign of the disparity error alone, with saccadic direction, which eye saw the step, and the modality of how the error was introduced (uniocular or symmetric) being mostly irrelevant factors. Figure 14, left and right (animal 1 and animal 2, respectively), report the single adaptive constant exponential or linear fit of the adaptive change in vergence position inside the PREVISUAL interval as a function of Trial # for all the uniocular fully predictive design sets. The top table in Fig. 14, with layout and symbols identical to the tables in Fig. 3, with the exception of the version gain being replaced by the vergence change in degrees, applies to the same sets illustrated in Fig. 14, top. One property is immediately apparent. The time course of the vergence-driven adaptation is univocally determined by the sign of the disparity introduced by the secondary step, independently of saccadic direction, which eye saw the step, and most importantly, the sign of the secondary step. Increasing or decreasing the gain of one eye, which directly affects, also in these data, the time course and amount of the version adaptation, is an irrelevant factor for the vergence-driven adaptation. Most humans and monkeys, including our two animals, presented visually driven convergence responses that were somewhat faster than similar-size divergence responses (Hung et al. 1997).

This is also reflected in the rate of adaptation \( (\Delta C_S \text{ or } S_I) \) and the PREVISUAL amount of adaptation in degrees achieved during the session \( \Delta \) between convergence and divergence sets, the latter estimated as the difference of the value of the fits at trial TN and at trial 1. The vergence velocity trace \( \dot{V}_G \) in Fig. 9C suggests that the adaptive response can extend into the VIS[0–100] interval (arrow). Our \( \Delta \) values, which ignore these responses, are probably underestimations of the overall vergence-driven adaptation, but we preferred to strictly limit our measures to the previsial period. Vergence adaptation steady state was reached in only one set (# symbol in \( \Delta \) column of top

---

**Fig. 12.** Sample comparisons of vergence position and velocity profiles in a uniocular fully predictive set. First column: initial 50 primary-only controls of the control paradigm. Second column: last 50 same-saccadic-direction trials of the same control set. Third column: initial 50 primary-only controls of the associated adaptive paradigm. Fourth column: last 50 same-saccadic-direction trials of the same adaptive set. The single vergence position traces are in black, and the single vergence velocity traces are in red. The same single-trial data are also plotted as averages in the row below, with red lines the average vergence velocity and green lines indicating \( \pm 2 \text{SD} \). Black solid line is the average version velocity trace, and dotted profile is the average version velocity trace. Both the single-trial vergence positions traces (as a group to maintain the original scatter) and the position averages were offset with respect to their actual values to not superimpose on the velocity traces for clarity. **Top:** uniocular +20% with the step on the left eye fully predictive set, rightward saccades. **Bottom:** leftward saccades. From animal 1.
fig. 13), vergence adaptation being, on average, slower than version adaptation.

The analysis of the symmetric fully predictive design data (bottom table of Fig. 14) did not unmask any indication for these adaptive paradigms to be harder than uniocular paradigms. Divergence adaptation was, again, harder to achieve than convergence adaptation. In a uniocular paradigm, the requirement is to increase or decrease the gain in one eye while leaving the gain in the other eye as unchanged as possible. In the symmetric case, there is the need for a gain increase in one eye while the other eye decreases, and this process is more challenging.
eye and a gain decrease in the other eye for the same saccadic direction, which conflicts even more with the eye gain covariation in the two eyes observed when adapting one eye while the other eye is patched (Abel et al. 1978; Albano and Marrero 1995; Optican and Robinson 1980; Snow et al. 1985). For an independent saccadic-controlled but vergence-driven correction of the disparity landing errors, the two paradigms are functionally identical, the presence or absence of a simultaneous version landing error being irrelevant.

Relative weight of postsaccadic vergence contributions. Figure 13, fourth column, suggests that, for the adaptive data, there is a precise relationship between total vergence change in the PREVISUAL interval and the intrasaccadic (IN) period. If the vergence responses in the 3D gaze transfers and in the adaptive paradigms share the same downstream circuits and also the same vergence-saccadic interactions, we expected the postsaccadic vergence “leaks,” i.e., the deviations from the 1:1 lines, to also be similar. This is tested in Fig. 15, which reports the second-order polynomial fits of the vergence position change in the IN (intrasaccadic) interval as a function of the vergence position change in the PREVISUAL interval (similar to Fig. 13, 4th column) for all uniocular fully predictive adaptive (in color) and associated control (gray) sets; the control fits (gray) also include the initial 50 rightward and leftward primary-only saccades to overlap in range with the adapted data at the beginning of the adaptive process. There is a clear continuity in the deviation from the 1:1 line between the adaptive and control sets for both divergence and convergence tasks. The larger the amount of previus vergence, the smaller

is the relative contribution of the intrasaccadic vergence and, consequently, the larger the presaccadic (if present, and usually very small for <3° vergence changes associated with 10° saccades) and postsaccadic vergence contributions. There was no evidence, for both control and adaptive sets, of a breaking point that would suggest that only after a certain threshold in the asymmetry does the saccadic system have to rely on the vergence system, which is solely responsible for the postsaccadic “leaks.”

Pseudorandom Design Paradigms

The technical issues related to the setting up and the analysis of the pseudorandom experiments were truly daunting, from the nonlinear tables that we had to implement to drive the mirror galvanometers for the targets to follow the trajectories in space illustrated in Fig. 1 to the difficulties in precisely calibrating the eyes inside much larger version and vergence ranges. Furthermore, half of the data (the 5° primary saccades) and postsaccadic vergence contributions. There was no evidence, for both control and adaptive sets, of a breaking point that would suggest that only after a certain threshold in the asymmetry does the saccadic system have to rely on the vergence system, which is solely responsible for the postsaccadic “leaks.”

Pseudorandom Design Paradigms

The technical issues related to the setting up and the analysis of the pseudorandom experiments were truly daunting, from the nonlinear tables that we had to implement to drive the mirror galvanometers for the targets to follow the trajectories in space illustrated in Fig. 1 to the difficulties in precisely calibrating the eyes inside much larger version and vergence ranges. Furthermore, half of the data (the 5° primary saccades) and postsaccadic vergence contributions. There was no evidence, for both control and adaptive sets, of a breaking point that would suggest that only after a certain threshold in the asymmetry does the saccadic system have to rely on the vergence system, which is solely responsible for the postsaccadic “leaks.”
**Biocular paradigms.** The biocular pseudorandom design had four adaptive experiments and associated controls, with same or opposite gain changes for the two saccadic directions, the latter not feasible in the fully predictive design. In Fig. 16, *top*, which follows the same layout of Fig. 3, we used a color code to identify each of the four biocular adaptive sessions. The fact that in the pseudorandom design each adaptive trial type was presented only one-fourth of the time and the animal could not predict the size of the saccade (5° or 10°) or, sufficiently away from the edges of the stimulus ranges, its direction had little effect on the time course of the adaptation or its amount (Δ), particularly for the decreases in gain (−20% traces). Asking for an increase in gain in one saccadic direction and a decrease in the other (green and black traces in Fig. 16, *top*) also had minor effects. In the pseudorandom design, gain increasing was even harder than gain decreasing, now quite evident also in *animal 1*, and half of the gain increasing sets (identified with an asterisk in Fig. 16 tables) had to be fitted with a linear regression. Interestingly, even when the animal reached the adaptive steady state (sets with # in Δ entry in Fig. 16 tables), the Δ for gain increases was consistently smaller than the Δ for gain decreases, indicating it was not just a different speed of the adaptive process. It is also evident that the time course for the gain increases was more variable between sessions. The intrasaccadic version gain change for the lw +20% matched in the same session with the rw −20% (black code) in *animal 2* and reported in gray in the top table in Fig. 16 was not significant. On the contrary, the adaptive process was remarkably consistent for gain decreases. The overall average adaptive constant for gain decreases in the biocular pseudorandom design sets (4 cases, 2 animals) was 252 (±56 SD; range 173 to 370; n = 8). This is remarkably similar to the average value for the fully predictive design (2 cases, 2 animals), which was 253 (±87 SD; range 196 to 381; n = 4). The Δ values were also practically identical: −15.5 (±3.6 SD; range −20.5 to −9.8; n = 8) for the pseudorandom design and −16.3 (±2.3 SD; range −18.6 to −14.1; n = 4) for the fully predictive design. For the gain increases, the Δ was better in the fully predictive design for *animal 1*, and this is probably also true for *animal 2* if we consider that in the two fully predictive sets the adaptation was still increasing linearly when the animal lost interest in the task.
We also repeated all the other biocular version analyses described for the fully predictive design. We confirmed, also for the pseudorandom design, that conjugacy is not altered by the adaptive process, the adaptation is strictly limited to the intrasaccadic period, and the postsaccadic drifts are related to the saccadic mechanism for the two designs, with prediction playing only a minor, inconsistent role.

Uniocular paradigms. Very similar results, although somewhat noisier, were obtained when control and adaptive uniocular vergence profiles were compared in the pseudorandom biocular paradigms. Version gain primary saccade data do not support a different biocular adaptive mechanism to recalibrate its cyclopean (conjugate) responses in the event of an external misalignment. Consistent postsaccadic version errors generated by the saccade, an internal compensatory disparity signal, which is then sent to the vergence system to reestablish binocular alignment. Why a Binocular Short-Term Saccadic Adaptive Process?

Primates have binocular vision. From a sensory point of view, a saccadic system that relies on a version-driven adaptive mechanism to recalibrate its cyclopean (conjugate) responses and on a vergence-driven adaptive mechanism that relies on postcranial disparity information to maintain binocular alignment makes perfect sense. On the contrary, from a point of view of recovery from pathology/injury along with the effects of aging, an independent monocular recalibration of the two eyes would be much better optimized to deal with focal damages or deficits at the level of single extraocular muscles or their innervation. Surprisingly, we found no behavioral evidence, using the double-step saccadic paradigm, of a monocular mechanism. Our results support a saccadic adaptive mechanism that relies on the visual detection of consistent postcranial disparity errors to generate, during the motor planning of the saccade, an internal compensatory disparity signal, which is then sent to the vergence system to reestablish binocular alignment. Consistent postcranial version errors generated independent, likely conjugate, recalibrations of the version commands. The ratio between the intrasaccadic (IN) vergence response and the overall PREVISUAL response (Fig. 13, 4th column, and Fig. 15) did not present, in both control and

Fig. 16. Pseudorandom design: overall results. Top: graphs and tables with layout and symbols identical to Fig. 3 showing intrasaccadic version change as a function of Trial # in the pseudorandom biocular adaptive paradigms. Left: single adaptive constant exponential or linear fits of the primary saccadic gain as a function of Trial # for the 4 biocular adaptive sessions (rw +20% lw +20%; rw +20% lw −20%; rw −20% lw +20%; and rw −20% lw −20%) from animal 1. Right: from animal 2. Color coding is used to identify the pairs. The slope for the lw +20% matched with the rw −20% (black pair) in animal 1 was not significant, and is reported in gray. Bottom: the PREVISUAL vergence change as a function of Trial # for the pseudorandom uniocular adaptive paradigms: animal 1 (left) and animal 2 (right). Same layout of tables as in Fig. 14.
adaptive paradigms, breaking points suggesting a disconjugacy threshold below which the saccadic system consistently generated pure asymmetric saccades. By definition, these saccades present the entirety of the disconjugacy during the intrasaccadic period, and thus with ratios along the 1:1 line. Above this threshold, the engagement of vergence would have become necessary, as proposed by Bush et al. (1994).

As the time analysis described in Fig. 9, bottom, indicates, this disconjugate response is a true saccadic-generated perisaccadic vergence response driven by an internal disparity adaptive signal. This signal is treated by the vergence system in the same way as a visual disparity. It cannot be the result of a gain modulation of an already existent visually driven vergence response (Munoz et al. 1999), with the primary steps being conjugate: there is no vergence activity to act upon. Midbrain vergence burst cells are silent during conjugate saccades, which carry zero disparity. Furthermore, as Erkelens et al. (1989b) have reported, saccadic disconjugate adaptation, once developed, persists during monocular viewing, where there is also no visual disparity-driven vergence to modulate.

Several studies, among others those of Seeberger et al. (2002) and Wallman and Fuchs (1998), have demonstrated that version post-saccadic visual errors, and not proprioceptive or efferent copies of the burst commands associated with the visually driven corrective saccades, drive the version adaptive process. This is likely also true for the vergence-driven component, with the adaptive process using the post-saccadic visual disparity information and not an efferent copy of the corrective vergence response. A cyclopean/disparity dual-adaptive mechanism well matches the observation that adapting one eye while the other eye is patched (Abel et al. 1978; Albano and Marrero 1995; Optican and Robinson 1980; Snow et al. 1985) generated conjugate adaptive changes, i.e., equally affecting the patched eye. With no disparity information available because of the patching, only the version adaptation was activated, with the errors in the viewing eye treated, by default, as version errors. Scudder et al. (1998) presented evidence that muscle tenectomy and biocular double-step saccadic paradigms most likely engage the same version adaptive mechanism.

It is possible that, in the long-term, a true asymmetric monocular recalibration may take over by utilizing the short-term corrections as a guide. There is indication that short-term and long-term saccadic version adaptation rely on different mechanisms (Robinson et al. 2006). Using an adaptive biocular paradigm and blindfolding the animals between the daily sessions, the authors observed that when a new version adaptive challenge was introduced after allowing the animal to long-term adapt to the previous challenge, the animal presented a normal short-term amount of version adaptation, as if the previous challenge was, with time, transformed into a new baseline. If too little time was allowed to pass between challenges, the adaptation to the previous challenge significantly reduced the next one. Small lesions of the cerebellar oculomotor vermis impaired short-term version adaptation, but long-term recovery was still present (Barash et al. 1999).

Why should the saccadic system need to rely on the vergence system to adaptively maintain binocular alignment when there is substantial evidence that the saccadic system, during 3D transfers of gaze, can generate different commands to the two eyes (for review, see Cullen and Van Horn 2011 and King 2011), with resulting intrasaccadic vergence changes much larger than our adaptive vergence goals of 2°? We entertain the possibility that disconjugate saccades, whether visually driven, aniseikonic, or short-term adaptive, can only occur when there is an ongoing smooth vergence response, i.e., they are the result of vergence-saccadic interactions at the immediate pre-motor level, with the saccadic system otherwise set to be strictly conjugate by long-term monocular recalibrations. Thus, during uniocular and symmetric short-term adaptation, the saccadic system is forced to generate its own disparity signal, which then activates the vergence system, in order to control its binocular alignment. Monocular asymmetric saccadic contributions (Cullen and Van Horn 2011) and/or intrasaccadic vergence enhancements (Busettini and Mays 2005b; Erkelens 2011; Zee et al. 1992), elicited as the result of downstream saccadic-vergence interactions, are added to the ongoing smooth vergence response, which we unmasked with our POxOy measures in both control and adaptive sets. Busettini and Mays (2005b) found that, after the contribution of the smooth vergence component was subtracted, the amount of intrasaccadic asymmetry was linked to the vergence motor error at the time of the saccade and not to the initial visual goal of the movement. Erkelens (2011) suggested a multiplicative interaction between vergence velocity and saccadic burst signals. An obvious and quite radical consequence of our hypothesis is that short-term adaptive, 3D visually driven, or aniseikonic pure asymmetric saccades, i.e., without vergence coactivation, do not exist. A logical explanation for this behavior would be that the saccadic system only has access to cyclopean information. At the same time, we do expect long-term monocular gain corrections, needed to maintain long-term saccadic conjugacy when no depth changes are called for. Indirect evidence for such a long-term mechanism is that the vergence system is silent during conjugate saccades (Judge and Cumming 1986; Mays et al. 1986), indicating that there are no long-term vergence-driven corrections of saccadic binocular misalignments. We consider it quite unlikely that all the midbrain vergence cells reported in the literature are from animals with perfectly balanced saccadic signals to the two eyes. This long-term adaptive mechanism would make, paradoxically, conjugate saccades the only true pure asymmetric saccades, in the sense that their conjugacy is the result of different long-term adaptive commands to the two eyes that do not require vergence coactivation.

Although we are well aware that this is a novel idea on which much further work is needed, strong evidence for this hypothesis is the fact that saccades elicited by stimulation of the superior colliculus (SC) are, in the absence of an ongoing vergence, always strictly conjugate. Evident intrasaccadic asymmetries occurred only when the SC stimulation was delivered during an ongoing disparity-driven smooth vergence eye movement (Chaturvedi and van Gijsbergen 1999). There is no evidence for coding of asymmetric saccades at the level of the SC during 3D gaze transfers (Walton and Mays 2003), suggesting that any vergence-saccadic interaction occurs further downstream, at the level of the midbrain vergence burst neurons and/or the saccadic long-lead and short-lead burst neurons, with the SC inherently a conjugate structure. Unfortunately, most of the studies describing the effects of partial lesions of the SC or of stimulation or lesions in the downstream structures, including saccadic-related cerebellar areas, used

J Neurophysiol • doi:10.1152/jn.01013.2011 • www.jn.org
only one eye coil, and consequently measures of saccadic conjugacy during these experiments were not taken. A recent work, using binocular recordings, reported that stimulation in some locations inside the monkey central mesencephalic reticular formation generated asymmetric saccades (Waitzman et al. 2008). The closeness of this region to the supraoculomotor area (SOA), where vergence cells are located (Judge and Cumming 1986; Mays 1984; Mays et al. 1986), makes these stimulation results, as pointed out by the authors, somewhat problematic, and most conclusions about monocular saccadic encoding in this region were derived from recordings while the animal executed 3D gaze transfers, and therefore when the vergence system was also active. This observation also applies to all other studies reporting monocular saccadic encoding (Cullen and van Horn 2011; King 2011).

In the past, the strongest criticism for the asymmetry of a pure asymmetric saccade, i.e., with no visible pre- or postsaccadic smooth vergence responses, to be vergence driven, directly or indirectly by vergence modulating the asymmetry of the saccadic bursts in the two eyes, was that the vergence system was seen as a “smooth,” i.e., slow, system with a long-delay visual feedback loop (Rashbass and Westheimer 1961). The dual model of the vergence system (Hung et al. 1986) also has the final reaching of the goal controlled by visual feedback. Following this reasoning, because of its slow dynamics and low gain needed to maintain stability, and the time delay in the visual detection of the goal being already reached inside the very short duration of the saccade, any intrasaccadic disparity-driven smooth vergence response would have necessarily extended in time well beyond the end of the saccade. Thus, not surprisingly, these saccades were automatically attributed to a monocular saccadic mechanism. The evidence, initially proposed by Zee et al. (1992) and confirmed by Busettini and Mays (2005b), of the existence of a rapid vergence local feedback loop similar to the one proposed for saccades has greatly weakened this criticism. In this schema, an internal rapid estimate of the progress of the vergence response allows for a saccadic-like, nonvisual correction of the vergence motor error driving the vergence response. It is important to observe that this evidence implies that any monocular contribution also has to be delivered to the vergence local feedback loop, in order to properly adjust the postsaccadic smooth vergence response to avoid overshooting. Thus the lack of pre- and postsaccadic smooth vergence is not necessarily evidence of no vergence coactivation during the intrasaccadic period, as it was generally assumed.

**Comparisons with Previous Studies**

Biocular double-step saccadic paradigms applied to macaques are reported by Albano and King (1989) and Straube et al. (1997a), together with studies aimed at the determination of the ability of the adaptive process to adjust for context and to transfer to other saccades (Noto et al. 1999; Tian and Zee 2010; Watanabe et al. 2000). The paradigm used in the Albano and King (1989) study was a biocular pseudorandom task, but with each saccade starting straight ahead and with the secondary step a fraction of the saccadic size, not of the primary target step. The paradigm used in Straube et al. (1997a) was practically identical to our biocular pseudorandom task, and the results were similar to ours in terms of adaptive constants, amount of adaptation, and $R^2$. Increasing gain presented a longer adaptive constant (their average value 1,178 saccades for a 30% increase) than decreasing gain (368). As for our data, the variability between the daily sessions was significant. Their attempt to quantify the dynamics of the adapted saccades was also mostly inconclusive, varying between animals, although for the 50% gain reduction there was an indication, for the most reduced saccades, of further slowdown compared with similarly “fatigued” saccades. The postsaccadic behavior was not quantified. Our study is the first with a systematic comparison between fully predictive and pseudorandom designs, both reported in studies with humans but never together. We found that the simpler, in terms of setup and data analysis, fully predictive design gave very similar results, with prediction playing a very minor role.

We are not aware of uniocular or symmetric studies using the double-step saccadic paradigm in monkeys. Oohira and Zee (1992) had normal monkeys wearing laterally displacing prisms in front of one eye for several days. Interestingly, even after 15 days of wearing the prism, 2.3° convergence disconjugacies were achieved with a still significant postsaccadic component in the patched eye during their monocular controls (their Fig. 3). For 2.3° divergence deviations, the correction was mostly intrasaccadic (their Fig. 2). Viirre et al. (1988) used surgical alterations in one horizontal rectus muscle (in some animals the medial rectus, in others the lateral rectus) to elicit disconjugate misalignments. After the operated eye was kept patched for 7 days after surgery the patch was taken off, and after 1 wk five of the eight animals had a good recovery of function. The animal with the largest eye deviations failed to recover. Two other animals, albeit with deviations in the same range of three animals that recovered, did not. Unfortunately, no data are available regarding the ability of the animals that failed to recover to short-term adapt prior to surgery, or whether they presented binocular sensory or motor abnormalities.

**Neural Substrate**

Very little is known about the neural substrate of saccadic adaptation to uniocular and symmetric gain alterations and whether it is monocularly or binocularly organized. Cerebellum, SC, and the vergence supraoculomotor and dorsal areas are the most obvious targets for single-unit recordings during uniocular and symmetric adaptive paradigms. A detailed review of the extensive literature regarding version adaptation and its neural substrate can be found in Hopp and Fuchs (2004).

**Cerebellum.** Cerebellum plays an important role in vergence and accommodation (Gamlin et al. 1996), as is evident in patients with cerebellar lesions (Sander et al. 2009). It is the most logical location to search for the generator of the adaptive vergence signal unmasked by our study. Several of the cerebellar areas described below are also associated with saccadic eye movements. May et al. (1992) have reported that the fastigial and interpositus nuclei of the cerebellum have reciprocal connections with the SOA, the main premotor vergence area. Little is known about the function of the fastigial nucleus in vergence or accommodation, although Zhang and Gamlin (1996) found, in the posterior region of this nucleus, cells related to vergence and accommodation. Stimulation of the
fastigial oculomotor region (FOR) elicited, depending on the location of the electrode, ipsiversive or contraversive saccades (Noda et al. 1988). The caudal fastigial nucleus presented modifications in its firing consistent with this area being involved in version saccadic adaptation (Inaba et al. 2003; Scudder and McGee 2003). Its direct connections with the oculomotor brain stem make this area the main relay of the adaptive version signals (Noda et al. 1990). The posterior interposed nucleus presents cells related to divergence and relaxation of accommodation and insensitive to conjugate saccades (Zhang and Gamlin 1998), as well as cells with activity mostly related to vertical saccades (Robinson 2000), but its contribution to adaptive processes, if any, is unknown.

Although conjugacy is most likely controlled by the cerebellum, the only evidence for this is a report by Takagi et al. (2003) showing that lesions of the dorsal cerebellar vermis affect both binocular alignment and disconjugate prism adaptation. This observation is consistent with preliminary results by Gamlin and Zhang (1996) that muscimol lesions in the posterior portion of the fastigial nucleus, which receives input from the dorsal cerebellar vermis, caused vergence abnormalities. Patients with cerebellar dysfunctions show both conjugate dysmetria and deficits in binocular alignment (Versino et al. 1996). These authors suggested that the flocculus and paraflocculus might be in charge of calibrating the yoking of the eyes and both conjugate (Optican et al. 1986) and disconjugate postsaccadic drifts. These areas are known to be involved with vestibular adaptation (Anzai et al. 2010; Nagao and Kitazawa 2003; Rambold et al. 2002). Total cerebellectomy in monkeys completely abolished adaptive reaction of the animal to the saccadic dysmetria and postsaccadic drifts elicited by tenectomy in the recti muscles of one eye (Optican and Robinson 1980). These animals presented long-term uncompensated saccadic hypermetria and postsaccadic drifts. Animals with partial midline cerebellar lesions affecting the vermis, paravermis, and fastigial nuclei, but not the floccular area, continued to present saccadic dysmetria but were able to reduce the postsaccadic drifts. Conversely, floccular lesions alone preserved the capability to eliminate the dysmetria, but the animal was not able to eliminate the postsaccadic drifts (Optican et al. 1986).

Nitta et al. (2008) have observed cells in the dorsal vermis with activity related to vergence and fronto-parallel pursuit. A number of reports confirmed that lesions of lobules VIc and VII of the cerebellar vermis—commonly termed the oculomotor vermis (OV)—abolished the ability of monkeys to compensate for saccadic dysmetria surgically induced by tenectomy (Optican and Robinson 1980) or by biocular double-step saccadic paradigms (Barash et al. 1999). Analysis of the simple spike activity (Kojima et al. 2010) and of the complex spike activity (Soetedjo et al. 2008) of Purkinje cells in the OV supports the involvement of this area in version saccadic adaptation. Pharmacological inactivation and disinhibition seem to indicate that each OV controls the metrics of ipsiversive saccades, with no consistent effects on contraversive saccades. Unfortunately, all these studies recorded the movement of only one eye. As noted above, binocular recordings suggest that OV is also related to convergence and the maintenance of binocular alignment.

The precerebellar nucleus reticularis tegmenti pontis (NRTP) is an important relay of SC activity (Harting 1977) to the OV (Brodal 1980), and it would be logical to expect NRTP to be unaffected by saccadic adaptation, being located upstream of the main cerebellar adaptive centers. Surprisingly, changes in the firing behavior during biocular saccadic adaptation were found to be present already at the level of NRTP (Takeichi et al. 2005). The authors proposed the existence, in addition to the known connection between NRTP and OC, of a feedback connection from the caudal fastigial nucleus, which receives direct inputs from the OC (Noda et al. 1990). NRTP is involved in several oculomotor functions, including stabilization of Listing’s plane (Van Opstal et al. 1996), vergence (Gamlin and Clarke 1995), smooth pursuit (Suzuki et al. 2003), and eye-head gaze pursuit (Suzuki et al. 2009). Its multimodality and its inputs from cortical areas that carry in-depth information (frontal eye field: Huerta et al. 1986; Stanton et al. 1988a, 1988b; supplementary eye field: Shook et al. 1990) make NRTP one of the most likely candidates for the encoding of the adaptive disparity signal.

**Superior colliculus.** With regard to biocular adaptation, Quessy et al. (2010) found that the locus of activity in the motor map at the level of the deep layers of the SC did not change during adaptation, which is consistent with a downstream gain recalibrating mechanism. Frens and van Opstal (1997) reported similar conclusions. On the contrary, Takeichi et al. (2007) found changes in SC firing consistent with the SC being the site of the adaptation or at least receiving signals related to it, although if, as proposed by Soetedjo et al. (2002) and others, the SC is inside the saccadic local feedback loop, modifications downstream would likely be mirrored in the SC firing. Saccades are preceded by a shift of the focus of visual attention. Ditterich et al. (2000) did not see changes in the metrics of the shift of attention after adaptation, which is consistent with a premotor gain correction and not a visual remapping.

The stimulation results from the study of Chaturvedi and van Gisbergen (1999) and the behavior of the SC during 3D transfers of gaze (Walton and Mays 2003) do not support the hypothesis of involvement of the SC in the generation of visually driven asymmetric saccades or uniocular and symmetric saccadic adaptation. Walton and Mays (2003) reported that an ongoing vergence affected the SC, but in an unspecified way not consistent with monocular encoding. It would be of some interest to verify whether the vergence adaptive component also modifies the SC activity. The evidence of neural activity related to smooth pursuit in the rostral area of the SC (Krauzlis 2001; Krauzlis et al. 2000) suggests an involvement of the SC beyond just saccades. In the cat, the rostral SC is related to accommodation (Sawa and Ohtsuka 1994) and vergence (Suzuki et al. 2004) and the visual layers of the SC present disparity sensitivity (Mimeault et al. 2004), but these properties do not seem to be present in the primate SC.

**Vergence supraoculomotor and dorsal areas.** Two groups of vergence cells have been described in the monkey midbrain. One group of these midbrain vergence-related cells is localized in the mesencephalic reticular formation just above the oculomotor nucleus (Judge and Cumming 1986; Mays et al. 1986; Zhang et al. 1991, 1992), and is so named the supraoculomotor area (SOA). The second group is located just slightly more superficially (Mays et al. 1986), in front of the SC. This is often termed the dorsal area. There is no known difference in behavior when comparing SOA and dorsal groups, although...
their target neurons and source of inputs are likely different. Both contain convergence and divergence neurons, with some cells firing only during the phasic part of the response (burst cells) and others presenting a tonic firing related to the vergence angle (tonic and burst-tonic cells). There is evidence, from antidromic activations, of direct excitatory monosynaptic connections from SOA convergence burst-tonic cells to ipsilateral medial rectus motoneurons (Zhang et al. 1991). Our hypothesis expects these cells to have similar firing patterns during both control and adaptive uniconal and symmetric tasks.

Implications for Strabismus

Our results, if confirmed by single-unit recordings, have evident impact on the short-term saccadic adaptation of subjects with impaired disparity detection, and perhaps also long-term, if the short-term saccadic-controlled but vergence-driven adaptation is the needed first step in guiding the long-term adaptive process. During patching experiments, Das et al. (2004) found that the conjugate transfer of adaptation to the nonviewing eye, while adapting the viewing eye with a double-step adaptive saccadic task, is preserved in monkeys with very large sensory-induced strabismus. These animals, tested monocularly, presented disconjugacy in their saccadic eye movements and postsaccadic drifts (Fu et al. 2007), but their version adaptive mechanism was apparently still functional. No data are available on whether these animals had a normal AC/A ratio, i.e., the relative amount of vergence elicited by an accommodative stimulus applied to one eye while patching the other eye. A normal AC/A would indicate that these animals have a functional vergence system from a motor point of view even if, of course, they had no disparity sensitivity whatsoever, having never experienced binocular vision during their critical developmental period. Interestingly, in the study by Quick et al. (1994) on natural strabismic animals, the strabismic animal that experienced bilateral retinal hemorrhage at birth (INDUCED animal), and therefore probably presenting a sensory-induced strabismus, had a normal AC/A. With these animals unable to detect post-saccadic disparity errors, and therefore unable to engage the vergence-driven disconjugate adaptive process, their binocular misalignment might just be their vergence-driven adaptive default value.

ACKNOWLEDGMENTS

We thank S. Hayley for computer programming, Christopher Williams for help in the data analysis, J. Millican and A. Yildirim for technical assistance, and L. Phillips for administrative assistance.

GRANTS

This research was supported by the National Eye Institute, with a grant to C. Busettini (ARRA supplement to R01 EY-017283) and Core Grant P30 EY-03039 to the University of Alabama at Birmingham Vision Science Research Center, and by The EyeSight Foundation of Alabama, with Grants FY2006-2007-42 and FY2011-12-274 to C. Busettini.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


