Primate Translational Vestibuloocular Reflexes. IV. Changes After Unilateral Labyrinthectomy

DORA E. ANGELAKI,1 SHAWN D. NEWLANDS,2 AND J. DAVID DICKMAN3

1Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri 63110; 2Department of Otolaryngology, University of Texas Medical Branch, Galveston, Texas 77555; and 3Department of Research, Central Institute for the Deaf, St. Louis, Missouri 63110

Angelaki, Dora E., Shawn D. Newlands, and J. David Dickman. Primate translational vestibuloocular reflexes. IV. Changes after unilateral labyrinthectomy. J. Neurophysiol. 83: 3005–3018, 2000. The effects of unilateral labyrinthectomy on the properties of the translational vestibuloocular reflexes (trVORs) were investigated in rhesus monkeys trained to fixate near targets. Translational motion stimuli consisted of either steady-state lateral and fore-aft sinusoidal oscillations or short-lasting transient displacements. During small-amplitude, steady-state sinusoidal lateral oscillations, a small decrease in the horizontal trVOR sensitivity and its dependence on viewing distance was observed during the first week after labyrinthectomy. These deficits gradually recovered over time. In addition, the vertical response component increased, causing a tilt of the eye velocity vector toward the lesioned side. During large, transient lateral displacements, the deficits were larger and longer lasting. Responses after labyrinthectomy were asymmetric, with eye velocity during movements toward the side of the lesion being more compromised. The most profound effect of the lesion was observed during fore-aft motion. Whereas responses were kinematically appropriate for fixation away from the side of the lesion (e.g., to the left after right labyrinthectomy), horizontal responses were anticomparative during fixation at targets located ipsilateral to the side of the lesion (e.g., for targets to the right after right labyrinthectomy). This deficit showed little recovery during the 3-mo post-labyrinthectomy testing period. These results suggest that inputs from both labyrinths are important for the proper function of the trVORs, although the details of how bilateral signals are processed and integrated remain unknown.

INTRODUCTION

Translational vestibuloocular reflexes (trVORs) are elicited in response to translational head displacements. Even though trVOR responses are either absent or rudimental in lateral-eyed species (Baarsma and Collewijn 1975; Dickman and Angelaki 1999; Hess and Dieringer 1991), they constitute a robust pattern of highly specific and geometrically complex eye movement responses in primates and humans (Angelaki and McHenry 1999; Angelaki et al. 2000b; McHenry and Angelaki 2000; Paige and Tomko 1999a,b; Schwarz and Miles 1991; Telford et al. 1997). Although the properties and performance of the reflex have been extensively studied, our knowledge of the neural mechanisms underlying the trVOR circuitry remains quite limited. Among the complicating factors that have impeded our understanding of the neural and computational organization of the trVORs is the highly distributed arrangement of motion signals in the otolith maculae. For example, during lateral motion while looking straight ahead, appropriate afferent signals to generate the compensatory eye movements could arise from multiple sources. First, there exists the bilateral structure of the peripheral vestibular system and commissural inputs to central neurons (Uchino et al. 1999). Second, there also exists the opposite spatial vector organization of hair cells on opposing sides of the striola. Thus a potential redundancy in directional signals appears to exist within a single labyrinth or in restricted regions of both labyrinths that could provide the necessary signals for a push-pull arrangement of otolithocular signals in the trVORs. In fact, the problem of redundancy is even greater when one considers that spatially appropriate vestibular signals could be provided through either labyrinth, either side of the striola, and either saccular or utricular macula.

Examination of the eye movement pattern after unilateral labyrinthectomy represents one of the first steps needed to understand the bilateral neural organization of the trVORs. In primate studies examining the effects of labyrinthectomy on the horizontal rotational VOR, it has been demonstrated that static deficits (e.g., spontaneous nystagmus) are the first to recover, whereas dynamic reflex properties slowly follow (Fetter and Zee 1988; Takahashi et al. 1977; Wolfe and Kos 1977). Acutely after unilateral labyrinthectomy, rotational VOR gain is reduced, primarily during rotation toward the injured side, resulting in a relatively large asymmetry that is exaggerated during high-frequency or -acceleration rotations (Allum et al. 1988; Fetter and Dichgans 1990; Fetter and Zee 1988; Maïoli and Precht 1984; Maïoli el al. 1983; Vibert et al. 1993). In the otolith system, it is possible that a single labyrinth might suffice to generate the trVORs. In fact, despite a complete loss of the early (<100 ms) transient responses in human subjects with bilateral vestibular loss, a “relatively normal,” bidirectional trVOR has been reported in chronic patients with unilateral labyrinthectomy or unilateral vestibular damage (Bronstein et al. 1991). In a group of unilaterally labyrinthectomized patients tested 1 wk after surgery, a deficient trVOR was reported during transient motion toward the operated ear (Lempert et al. 1998). On the other hand, symmetric, roughly conjugate trVOR responses have been reported during steady-state linear motion in the dark after unilateral labyrinthectomy in squirrel monkeys (Paige et al. 1996). In preliminary results obtained after unilateral labyrinthectomy in two canal-plugged rhesus monkeys, we observed a significant impairment in the reflex dependence on target distance and eccentricity, as well
as in the dynamics of the tVORs (Angelaki et al. 1999b). The recovery from canal plugging, however, might cause adaptive changes in the otolith system that would complicate interpretation of the effects of unilateral labyrinthectomy. In the present study, we have extended these investigations by directly comparing tVOR properties in labyrinthine-intact and unilaterally labyrinthectomized animals. The two most conspicuous deficits are a disruption in the tuning of the fore-aft VOR as a function of gaze eccentricity and a reduction in sensitivity during large amplitude transient lateral displacement. Both of these deficits persist in compensated animals.

**METHODS**

**Animal preparation, eye movement recording, and behavioral training**

Five juvenile rhesus monkeys were chronically implanted with a circular delrin ring that was anchored to the skull by inverted stainless T-bolts and dental acrylic. In addition, animals were also implanted with a dual eye coil on one or both eyes (Hess 1990). Once animals were satisfactorily trained to fixate far and near targets for juice reward and after control responses were obtained (see following text), animals were subjected to unilateral labyrinthectomy. In two of the animals (B and E), the left labyrinth was destroyed. The other three animals (H, P, and R) underwent right labyrinthectomy. Animals B and R were labyrinthectomized 3–4 mo after all semicircular canals were inactivated as part of a different study (Angelaki et al. 1999a). In animals E, H, and P, the semicircular canals were intact at the time of unilateral labyrinthectomy.

Binocular three-dimensional (3-D) eye movements were recorded in a 16-in side-length two-magnetic field system (CNC Engineering). During experimental testing, the monkeys were seated in a primate chair with their heads statically positioned such that the horizontal semicircular canals were tilted 18° nose-down relative to an earth-horizontal plane. All animals participating in these experiments were pretrained using juice rewards to fixate targets paired with auditory cues, then to maintain fixation in the presence of the auditory tone (≥1 s). Details for surgical procedures, eye movement calibration, experimental testing, and training have been reported previously (Angelaki and McHenry 1999; Angelaki et al. 2000b; McHenry and Angelaki 2000). All surgical procedures were performed under sterile conditions in accordance to National Institutes of Health guidelines.

**Experimental protocols**

The goal of the present study was to investigate changes in the tVORs after unilateral labyrinthectomy. For this, 3-D eye movements were recorded during both lateral and fore-aft motions. The following experimental protocols were tested before (control responses) as well as at different times after unilateral labyrinthectomy: 1) All animals were oscillated at different frequencies between 4 and 12 Hz (0.3–0.4 g) while fixating on one of several target light-emitting diodes (LEDs). These stimuli were characterized by small peak head displacement and velocity (<18 cm/s; see Table 1 in Angelaki et al. 2000b) and were thus used to study the effects of unilateral labyrinthectomy on the small-signal range of the tVORs. 2) Four animals (B, E, P, and R) were also tested with a transient stimulus consisting of a step-like linear acceleration profile, followed by a short period of constant velocity (peak linear acceleration: 0.5 g; peak linear velocity: ±22 cm/s). To determine the frequency content of these transient stimuli, we used 1,000-order finite-impulse-response filters (as in Minor et al. 1999). The frequency response characteristics of three such filters with corner frequencies of 15, 25 and 40 Hz are plotted in the inset of Fig. 1 (plots of gain vs. frequency). The head acceleration signal was then digitally processed through each of these filters

![FIG. 1. Frequency content of the transient stimuli. The raw head acceleration signal (—) is compared with the signal after passing through finite-impulse response filters with corner frequencies of 15, 25, and 40 Hz (dotted and dashed lines). The frequency response characteristics of these filters are displayed in the inset.](http://jn.physiology.org/)

(Matlab, Mathworks), and the result was compared with the raw head acceleration signal in Fig. 1. As seen from the large differences between the filtered and raw signals, the frequency content of the transient linear acceleration stimulus used in these studies was much higher than the 4- to 12-Hz frequency bandwidth that was used for sinusoidal testing (but most of the power was <50 Hz). These large transient stimuli were primarily used to examine the labyrinthectomy effects on the large-amplitude range of the tVORs. These large transient stimuli evoke viewing distance-dependent nonlinearities in animals with intact labyrinths. In addition, the transient responses were also used to examine changes in response asymmetry for the two directions of motion.

For lateral motion stimuli, animals fixated an approximately centered target LED located 40, 30, 20, 15, and 10 cm from the eyes. For fore-aft motion, animals fixated one of several targets on a flat screen at a distance of 20 cm: centered approximately in between the two eyes, ~6 cm to the left/right, as well as ~6 cm up/down (relative to the right eye, i.e., eye positions of ~17°).

After unilateral labyrinthectomy, animals were characterized by the well-described postural and eye movement static syndromes, including a static head tilt toward the side of the lesion and a spontaneous nystagmus with the slow phase directed toward the side of the lesion (e.g., Fetter and Zee 1988). Animals were first tested between 3 and 7 days after unilateral labyrinthectomy. The strong spontaneous nystagmus prevented satisfactory fixation on the targets for the first 2 days after the operation. On the third day after the operation, the spontaneous nystagmus had decreased significantly and some animals were able to fixate the presented LED targets. Animals were subsequently tested at different times, ≤3 mo after the labyrinthectomy. Because of differences in the eye-movement deficits during lateral motion stimuli for the two animals whose canals were plugged before the unilateral labyrinthectomy compared with the other three animals (without canal plugging), data presented here have primarily focused on lateral motion responses from the three animals whose canals were intact prior to the labyrinthectomy (animals E, H, and P). Results in the two animals that had undergone prior plugging of all semicircular canals have been presented in detail elsewhere (Angelaki et al. 1999b). Here, these data are primarily presented and discussed for comparison. The deficits observed during fore-aft motion were similar for the two groups of animals, thus canal-intact and canal-plugged data are presented together.

For all behaviorally controlled experiments, each trial was initiated under computer control when the animal had satisfactorily fixated the
target light in a dimly-illuminated environment for a random period of ~300–1,000 ms. After successful fixation had been satisfied, the sled was commanded to deliver either between 5 and 25 cycles (the first and last cycles were excluded from analyses) or the transient motion profile. During sinusoidal motion, which usually involved a recording period of ≤1 s, the target remained illuminated. This was necessary to maintain vigilance (particularly after labyrinthectomy). Because of technical restrictions, only head-fixed target presentation was possible during motion. Even though visual effects are minimal at frequencies higher than ~4 Hz, we cannot exclude the possibility that the presence of the head-fixed targets reduced the amplitude of the elicited eye movements. Since, however, the stimulus conditions were identical for all experiments, any suppression effect due to the presence of the head-fixed targets would not have influenced the comparisons between the responses before and after unilateral labyrinthectomy. For the transient stimuli, the target was extinguished ~20 ms prior to the onset of movement, such that animals were in completely darkness during motion. Since our analyses only focus on the very early part of the response after motion onset, illumination of the target during motion was not necessary. Intermingled with these protocols also were runs where no movement occurred even though satisfactory fixation was obtained. Stimulus presentation and behavioral control during motion have been described in detail in the preceding papers (Angelaki et al. 2000b; McHenry and Angelaki 2000).

For each recording session, the eight voltage signals of the two eye coil assemblies, the three output signals of a 3-D linear accelerometer (mounted on fiberglass members that firmly attach the animal’s head ring to the inner gimbal of the rotator), as well as velocity and position feedback signals from the linear sled were low-pass filtered (200 Hz, 6-pole Bessel), digitized at a rate of 833.33 Hz (Cambridge Electronics Design, model 1401, 16-bit resolution), and stored on a PC for off-line analysis. The majority of the data reported were from binocular 3-D recordings. Because of broken torsion coils at the time of labyrinthectomy, only monocular data are presented for animals R and H.

**Data Analyses**

Calibrated 3-D eye positions were expressed as rotation vectors, E (Haustein 1989; van Opstal 1993, the reference position was straight ahead). The eye angular velocity vector, Ω, was computed from 3-D eye position, as previously described (c.f. Angelaki and Hess 1996a,b). Both eye-position and angular eye-velocity vectors were expressed relative to a head-fixed right-handed coordinate system, as defined in the 18° nose-down position. Torsional, vertical, and horizontal eye position and velocity were the components of the eye-position and eye-velocity vectors along the nasooccipital, interaural, and vertical head axes, respectively. Positive directions were clockwise (as viewed from the animal, i.e., rotation of the upper pole of the eye toward the right ear), downward and leftward for the torsional, vertical, and horizontal components, respectively.

The horizontal, vertical, and torsional components of the calibrated eye position vectors were smoothed and differentiated with a Savitzky-Golay quadratic polynomial filter with a 15-point forward and backward window (Press et al. 1988; Savitzky and Golay 1964). For frequencies >6 Hz, response amplitudes have been corrected for the gain attenuation of the filter (Angelaki 1998; Angelaki et al. 2000b). For steady-state sinusoidal runs, no fast phase removal was usually necessary. For each run (corrected for head movement) (see Angelaki et al. 2000b), average response cycles were computed from the respective steady-state horizontal, vertical, and torsional velocity components (usually from 3–10 custom-selected saccade-free cycles). Since the selected segment did not include fast eye movements, the obtained slow phase eye velocity responses were not contaminated by post-saccadic drift. Because of gaze-holding deficits that are commonly present after labyrinthectomy, it has been previously pointed out that a traditional slow phase analysis is problematic when post-saccadic drift is not taken into account in the estimation of VOR time constants (Cannon and Robinson 1987; Fetter and Zee 1988; Rey and Galiana 1993). The slow phase eye velocity analysis performed here was not subject to this limitation.

Sensitivity and phase were determined by fitting a sine function (and a DC offset) to both response and stimulus (output of the 3-D linear accelerometer) using a nonlinear least-squares algorithm based on the Levenberg-Marquardt method. Translational VOR sensitivity was expressed as the ratio of peak eye velocity to peak linear velocity (computed as the integral of linear acceleration). Phase was expressed as the difference (in degrees) between peak eye velocity and peak stimulus velocity. Positive head motion was defined as rightward and backward. Based on these sign definitions, the phase of the compensatory horizontal response during sinusoidal lateral motion should be ≤0° (Angelaki et al. 2000b). For fore-aft motion, a compensatory horizontal response phase would be ≤0° when looking to the right and ≥180° when looking to the left (McHenry and Angelaki 2000). The trVOR vector angle in the roll plane was defined as the arc tangent of vertical over horizontal response sensitivities. In animals with intact labyrinths, the phase difference between the horizontal and vertical modulations was close to 180° (e.g., Fig. 2A). That is, an upward vertical accompanied generation of a leftward horizontal eye movement. Based on the coordinate system used, this is defined as a positive tilt angle. When the phase of the vertical modulation changed more than 90° after (relative to the values before) labyrinthectomy, the trVOR tilt angle was defined to be negative. Otherwise it was computed as a positive angle.

For transient responses, a grand-average was computed for each
stimulus and prior viewing condition in each animal. A semi-auto-
mated analysis routine displayed each experimental run sequentially
and allowed the experimenter to select only saccade-free runs to be
included for grand averages and further analysis. In addition, this step
allowed direct inspection of vergence throughout the motion profile. If
there was an obvious loss of vergence (usually associated with a
saccade), the run was discarded and excluded from further analysis.

The onset times of stimulus (linear acceleration) and response (hor-
izontal eye velocity) were computed based on the 3-SD method, as
previously described (Angelaki and McHenry 1999). Only the first
239 ms after stimulus onset and the last 50 ms prior to stimulus onset
were quantitatively analyzed. The actual binocular fixation and ver-
geence angles were measured from mean eye position during the 50 ms
prior to motion onset. To describe the response profiles across differ-
ent viewing conditions, the left and right eye velocity were computed
at different time intervals after stimulus onset.

Statistical comparisons are based on ANOVAs. In addition, regres-
sions were used to quantify the dependence on viewing distance.
Based on previous findings, a first-order regression was sufficient to
approximate the viewing distance dependence of the sinusoidal re-
sponses (Angelaki et al. 2000a,b). However, a second-order regres-
sion was necessary to describe the nonlinearities characterizing the
viewing distance dependence of the transient responses (see RESULTS).
Data points for each animal were obtained at different times following
labyrinthectomy. Thus statistical comparisons (ANOVA and regres-
sions) were performed only on data collected before, within the first
week and 2–3 mo following labyrinthectomy.

RESULTS

Changes in the trVORs during lateral oscillations

Unilateral labyrinthectomy resulted in small but consistent
decreases in the horizontal response sensitivity of the trVORs
during lateral motion. Table 1 summarizes the relevant statisti-
cal comparisons. An example of responses before and after
unilateral labyrinthectomy is illustrated in Fig. 2. In addition to
a decrease in the horizontal response, the vertical response
modulation was increased. The elicited eye movement during
lateral motion should be primarily horizontal for fixation on the
target with a small vertical elevation. In animals with intact
labyrinths, the vertical response component is small, resulting
in a tilt of the eye velocity vector that is <10° from a purely
horizontal direction (Angelaki et al. 2000b). As seen in Fig. 2,
however, the vertical component significantly increased after
unilateral (right) labyrinthectomy (see also Table 1). In fact,
peak-to-peak vertical eye velocity oscillations after the lesion
could be almost as large as those of the horizontal component
(e.g., Fig. 2). Torsional response sensitivity did not signifi-
cantly change after labyrinthectomy ($F(1,81) = 0.6, P > 0.05$).

The decrease in the horizontal response sensitivity, as well
as the increase in vertical response sensitivity, were both
viewing distance dependent, as shown in Fig. 3, A and B,
respectively (Table 1, statistical comparisons in second row).
This dependence was characterized using first-order regres-
sions (Table 2) (see also Angelaki et al. 2000a). The horizontal
and vertical response components were characterized by simi-
lar viewing-distance dependencies such that the tilt of the
trVOR vector away from a purely horizontal response was
independent of viewing distance ($F(4,160) = 1.8, P > 0.05$).
In both canal-intact animals that underwent a right labyrinthec-
tomy, the trVOR response vector tilted further to the right
(positive tilt angle). That is, a negative (upward) vertical eye
movement accompanied generation of a positive (leftward)
horizontal eye movement (e.g., Fig. 2B). In the third canal-
intact animal whose left labyrinth was destroyed, the trVOR
response vector tilted to the left (negative tilt angle). Specifi-


**TABLE 2. Dependence of horizontal response sensitivity on the inverse of viewing distance during 10-Hz sinusoidal lateral motion: linear regression parameters**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Before Labyrinthectomy</th>
<th>2–7 Days after Lesion</th>
<th>2–3 mo after Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression R²</td>
<td>Regression R²</td>
<td>Regression R²</td>
</tr>
<tr>
<td>(P)</td>
<td>(y = 0.20(1/D) + 0.53)</td>
<td>(y = 0.10(1/D) + 0.32)</td>
<td>(y = 0.06(1/D) + 0.45)</td>
</tr>
<tr>
<td>(E)</td>
<td>(y = 0.15(1/D) + 0.70)</td>
<td>(y = 0.11(1/D) + 0.43)</td>
<td>(y = 0.17(1/D) + 0.91)</td>
</tr>
<tr>
<td>(H)</td>
<td>(y = 0.22(1/D) + 0.73)</td>
<td>(y = 0.14(1/D) + 0.56)</td>
<td></td>
</tr>
</tbody>
</table>

Data from the 3 animals whose semicircular canals were intact at the time of unilateral labyrinthectomy. The ideal equation for maintaining fixation on the target is \(y = 0.57(1/D)\). Based on a larger number of animals, a linear regression was considered sufficient to describe the dependence on the inverse of viewing distance (Angelaki et al. 2000b; Telford et al. 1997). The 2–3 mo data were not available in animal \(E\).

Cyclically for the first week after the operation, the vector tilt averaged \(-14.4 \pm 3.5^\circ\) for animal \(E\) (left labyrinthectomy; mean ± SD) and \(13.6 \pm 1.7^\circ\) and \(29.1 \pm 1.6^\circ\) for animals \(H\) and \(P\) (right labyrinthectomy). In all three cases, these values were statistically significantly different from those in the intact animals, which averaged \(5.4 \pm 3.7^\circ\), \(5.9 \pm 0.6^\circ\), and \(5.5 \pm 1.6^\circ\) for each of the three animals, respectively \([F(1,160) = 32.3, P < 0.01]\). These changes in trVOR vector tilt exhibited some recovery over time \([F(1,146) = 49.8, P < 0.01; \text{Fig. 4B}]\).

The decrease in horizontal response sensitivity also tended to recover over time (see statistical comparisons in Table 1). Figure 4A illustrates the changes in the horizontal sensitivity slope (i.e., the slopes of the regression lines as a function of inverse viewing distance, as in Fig. 3A) as a function of time after unilateral labyrinthectomy. In all three nonplugged animals, horizontal response sensitivity recovered significantly within 2 mo after the operation (Fig. 4A, ●, ■, ▲, and Table 1). Figure 4A also illustrates the respective responses from the two animals whose semicircular canals were plugged several months prior to the labyrinthectomy (Angelaki et al. 1999b). The effects of unilateral labyrinthectomy on horizontal trVOR sensitivity tended to be larger in the two animals whose semicircular canals were plugged 3–4 mo prior to the labyrinthectomy (Fig. 4A, ○, □) (see also Angelaki et al. 1999b). The effects of unilateral labyrinthectomy on trVOR response dynamics were also different between canal-plugged and canal-intact animals. Whereas horizontal response dynamics were altered after labyrinthectomy in the canal-plugged animals (Angelaki et al. 1999b), no systematic changes in trVOR dynamics were observed after unilateral labyrinthectomy in the canal-intact animals.

**Changes in the trVORs during transient lateral motion**

During the high-acceleration transient lateral motion stimuli in labyrinthine-intact animals, eye velocity did not exhibit a linear dependence on viewing distance throughout the motion profile (Table 3). The smallest nonlinearities were observed early into the movement. Twenty-five milliseconds after motion onset (and while the movement of the two eyes was conjugate), the eye velocity dependence on inverse viewing distance was rather linear (linear regression coefficients: 0.75–0.97; see Table 3). The nonlinear dependence was strong for the adducting eye and became apparent as soon as the two eyes diverged from each other for the near target viewing conditions (>25 ms into the motion). 239 ms after motion onset, there was little dependence of eye velocity on the inverse of viewing distance (Table 3).

The decrease in horizontal response sensitivity observed after unilateral labyrinthectomy during the small-amplitude, sinusoidal oscillations was also observed during transient lateral motion. As shown in Fig. 5, which compares responses before (top) with those 1 wk and 1 mo after right labyrinthectomy (bottom), the largest changes were observed in the responses during near target viewing and ipsilateral motion (i.e.,...
toward the side of the lesion). That is, positive (leftward) horizontal eye velocity responses elicited during rightward (ipsilateral) motion were lower after unilateral labyrinthectomy compared with control responses. The differences between the lesioned and control data were generally the largest for the smallest viewing distances. During contralateral (leftward) motion, the early part of the response also decreased.

Since transient trVOR velocities are robust and exhibit a systematic viewing distance-dependent behavior only during the early (~100 ms) part of the response, quantitative analyses of the effects of labyrinthectomy have primarily focused on eye velocity within 70 ms after motion onset. The latter corresponded approximately to the time that horizontal eye velocity reached its peak value. These eye velocity values have been plotted in Fig. 6 as a function of the inverse of viewing distance before and 1 wk and 1 mo after right labyrinthectomy (E and □, ● and ■, ○ and □, respectively). Because of the nonlinear dependence of response amplitude on the inverse of viewing distance during large transient displacements (Table 3), a second-order linear regression has been fitted through the data from each eye (Fig. 6, · · ·, —, and - - -). The regression coefficients have been included in Table 4. Unilateral labyrinthectomy significantly decreased the 70-ms responses in all animals \[ F(1,40) = 7.8, P < 0.01; \text{Table 4} \]. The response decline after unilateral labyrinthectomy was larger for ipsilateral (i.e., toward the side of the lesion) compared with contralateral motion. These differences between ipsilateral versus contralateral motion responses were statistically significant in three of the animals \[ F(2,43) = 7.2, P < 0.01; \text{animal E was not included in the comparison} \]. For the two animals with complete data at all viewing distances (P and B), recovery was small and statistically insignificant \[ F(1,17) = 2.4, P > 0.05 \]. Similar to steady-state sinusoidal responses, the effects of unilateral labyrinthectomy during these transient stimuli tended to be larger in those animals that had undergone canal plugging in comparison with those that had not.

Changes in the trVORs during fore-aft motion

Unilateral labyrinthectomy resulted in a large and persistent deficit in the tuning of fore-aft trVOR as a function of target (and gaze) eccentricity. A typical example of responses before and after labyrinthectomy during sinusoidal fore-aft transla-

![Fig. 5. Horizontal eye velocity of the right and left eyes during transient lateral motion and different viewing distances (40, 20, and 10 cm). Data (mean ± SD) before, 1 wk after, and 1 mo after right labyrinthectomy. Within each plot, the dashed line shows zero velocity and the small solid line at the beginning of the trace shows the initial portion of stimulus acceleration. Data from animal P.](https://jn.physiology.org/loi/jn)

<table>
<thead>
<tr>
<th>TABLE 3. Dependence of eye velocity on the inverse of prior viewing distance during transient lateral motion in labyrinthine-intact animals: first- and second-order regression coefficients ( R^2 )</th>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>25 ms</td>
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<tr>
<td>R eye velocity</td>
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<tr>
<td>L eye velocity</td>
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<tr>
<td>50 ms</td>
</tr>
<tr>
<td>R eye velocity</td>
</tr>
<tr>
<td>L eye velocity</td>
</tr>
<tr>
<td>100 ms</td>
</tr>
<tr>
<td>R eye velocity</td>
</tr>
<tr>
<td>L eye velocity</td>
</tr>
<tr>
<td>239 ms</td>
</tr>
<tr>
<td>R eye velocity</td>
</tr>
<tr>
<td>L eye velocity</td>
</tr>
</tbody>
</table>

Average data (5 animals) prior to unilateral labyrinthectomy at different times after stimulus onset (25, 50, 100, and 239 ms).

![Fig. 6. Dependence on viewing distance. Horizontal right and left eye velocity amplitude at 70 ms after motion onset has been plotted as a function of inverse viewing distance before and 1 wk and 1 mo after right labyrinthectomy (○ and □, ● and ■, ○ and □, respectively). · · ·, —, and - - -: second-order regression fits to the before, 1 wk, and 1 mo data. Regression parameters are included in Table 4. Data from animal P.](https://jn.physiology.org/loi/jn)
specified (since there were 3 unknown parameters in the fit, Left labyrinthectomy

* (Right labyrinthectomy)

transient lateral motion

B, of the lesion, i.e., to the left after right labyrinthectomy (Fig. 7)

sponses were qualitatively similar to controls (albeit generally

the right (Fig. 7)

canal-plugged animals.

TABLE 4. Parameters for second-order regression fits of eye velocity (at 70 ms) as a function of inverse viewing distance during transient lateral motion

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ipsilateral Motion</th>
<th>Contralateral Motion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R eye</td>
<td>L eye</td>
</tr>
<tr>
<td></td>
<td>R eye</td>
<td>L eye</td>
</tr>
<tr>
<td>Animal P (Right labyrinthectomy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>( y = -2.0 + 7.5x - 0.39x^2 )</td>
<td>( y = -7.7 + 10.2x - 0.53x^2 )</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>6 days</td>
<td>( y = 0.7 + 2.4x - 0.23x^2 )</td>
<td>( y = -2.4 + 4.6x - 0.36x^2 )</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.76</td>
<td>0.77</td>
</tr>
<tr>
<td>1 mo</td>
<td>( y = 1.1 + 0.2x - 0.06x^2 )</td>
<td>( y = 7.6 + 3.2x - 0.24x^2 )</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>2 mo</td>
<td>( y = 1.0 - 2.3x + 0.41x^2 )</td>
<td>( y = -0.1 + 4.5x - 0.17x^2 )</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Animal P* (Right labyrinthectomy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>( y = -6.1 - 2.2x - 0.00x^2 )</td>
<td>( y = 0.6 - 4.2x + 0.28x^2 )</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.64</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Data were usually collected at 5 viewing distances (10, 15, 20, 30, and 40 cm). Whenever data were only collected at 3 viewing distances, no \( R^2 \) value is specified (since there were 3 unknown parameters in the fit, \( R^2 = 1 \)). Only monocular data were collected in animal R. The eye movements elicited during transient motion in labyrinthine-intact animals were asymmetric. Specifically, the movement of the adducting eye was smaller than that of the abducting eye for near target viewing. This asymmetric behavior is evident in the first order regression coefficients of the control responses before labyrinthectomy. *, canal-plugged animals.

tion at 10 Hz is illustrated in Fig. 7 for fixations at three different targets. In labyrinthine-intact animals, horizontal eye velocity modulated sinusoidally and out of phase for the targets to the left and to the right. Even though the amplitude of modulation was generally less than that required for binocular fixation at the target (Fig. 7A, compare \( \Omega_{hor} \) with Ideal), responses were appropriately tuned to target eccentricity. For example, in line with the kinematic requirements of the reflex, purely vergence responses were observed during fixation at the center target, whereas a combination of vergence and version responses were seen during fixation of targets to the left and to the right (Fig. 7A) (see also McHenry and Angelaki 2000; Paige and Tomko 1991b).

After unilateral labyrinthectomy, the elicited horizontal responses were qualitatively similar to controls (albeit generally larger) during fixation at targets located contralateral to the side of the lesion, i.e., to the left after right labyrinthectomy (Fig. 7B, left). In contrast, kinematically inappropriate horizontal binocular responses were elicited during fixation at ipsilateral targets, i.e., to the right after right labyrinthectomy (Fig. 7B, right). Compared with responses before labyrinthectomy, horizontal eye velocity during right target fixation was of reverse phase. That is, responses were anticipatory for fixation at ipsilateral targets. A deficit was also seen during center target viewing. Rather than purely vergence responses where the modulation of the right and left eyes were out of phase, a combination of version and vergence responses were observed after unilateral labyrinthectomy (Fig. 7, A and B, middle).

The changes in the horizontal response phase during fixation at ipsilateral targets are further illustrated in Fig. 8 where horizontal sensitivity and phase of the right eye as a function of frequency are compared for nine different targets located at different horizontal/vertical eccentricities on a flat screen at a distance of 20 cm (see METHODS). In this case, data 3 days after left labyrinthectomy are compared with those prior to the operation (Fig. 8, ● and ○ circles, respectively). The organization of the plot reflects the positions of the fixation targets (relative to the animal), with center, up/down, left/right in the plot corresponding to the respective location of the targets on the screen. In the intact animal, trVOR phase was ~0° for right target fixation (i.e., eye velocity in phase with linear head velocity), with a consistent tendency for small lags at the highest frequencies (Fig. 8, ○: right groups of plots). Based on the coordinate definitions used here, a phase of zero corresponded to a positive (leftward) eye movement being elicited during backward (positive) motion. For left target fixations, trVOR phase was about ~180° (Fig. 8, ○: left groups of plots). In this case, eye velocity was also in phase with linear velocity, albeit the eye movement direction was reversed (i.e., a rightward eye movement was elicited during backward motion; see also Fig. 7A). For targets in the midsagittal plane (where right eye position is to the left), the response sensitivities of the right
eye were small with phases about \(-180°\) (Fig. 8; middle groups of plots). After the lesion, responses were compromised for ipsilateral targets: during fixation to the left, response sensitivity decreased and response phase shifted 180°. During fixation to the right, responses were compensatory and response sensitivity was consistently increased. Even though it
was not systematically investigated, no consistent changes in vertical response sensitivity were observed in the one animal tested during fixation on vertical targets in the midsagittal plane.

Little recovery of function was seen in the fore-aft VOR for as long as 2–3 mo post-lesion (Fig. 9). The phase of the reflex shifted and remained shifted through 180° for left target fixation after left labyrinthectomy (Fig. 9, left, □ and ▪) and for right target fixation after right labyrinthectomy (Fig. 9, right, □ and ▪). These observations were common to all animals; thus canal-plugged and canal-intact data were considered together. A selective destruction of responses for gaze eccentricities ipsilateral to the side of the lesion was also observed during transient fore-aft displacements (Fig. 10). Three weeks after right labyrinthectomy, for example, responses for gaze directions contralateral to the lesion side remained indistinguishable from those before the lesion (Fig. 10, left). For gaze directions ipsilateral to the lesion, however, responses were severely compromised, particularly during backward motion (Fig. 10, right).

DISCUSSION

We have studied the changes in the translational VORs after unilateral labyrinthectomy. Based on the redundant representation of motion direction in the peripheral vestibular organs (Flock 1964; Lindeman 1969), it could be possible that destruction of one labyrinth did not significantly alter the reflex properties. We found this not to be true. During high-frequency lateral oscillations, a small decrease in the trVOR sensitivity and its dependence on viewing distance was observed when animals were tested 3–7 days after the lesion. These deficits of the trVOR tended to gradually recover over the next 2–3 mo. In addition, a misalignment in the eye velocity vector was revealed after unilateral labyrinthectomy. The vertical response component was increased such that the eye velocity vector tilted in the roll plane away from a purely horizontal direction toward the side of the lesion. This misalignment exhibited some recovery over the time period tested. A tilt in the eye velocity response during lateral motion has been observed after unilateral labyrinthectomy in squirrel monkeys but reported to be in the opposite direction (Paige et al. 1996).

The decrease in horizontal eye velocity after labyrinthectomy was also present during transient motion stimuli. Responses were also asymmetric for the two motion directions. During translation toward the lesioned labyrinth, eye velocity was smaller than that during motion toward the intact labyrinth. The closer the target, the larger the decrease in horizontal sensitivity. Even though these responses recovered over time, severe deficits and large asymmetries were still present 2–3 mo after the operation. Interestingly, no systematic difference in deficits was seen for the ipsilateral versus the contralateral eye, suggesting that each labyrinth contributes to a binocular trVOR organization.

The most profound effect of the lesions was observed during fore-aft motion. In this case, the effects of unilateral labyrinthectomy were asymmetric not to the direction of motion, as was the case for lateral motion, but to the direction of gaze. Whereas responses were kinematically appropriate for fixation away from the side of the lesion (e.g., to the left after right labyrinthectomy), horizontal responses were anticompenatory during fixation at targets located ipsilateral to the side of the lesion (e.g., for targets to the right after right labyrinthectomy). In other words, the single remaining labyrinth could only generate the same horizontal eye movement direction, independently of horizontal gaze eccentricity. This deficit showed little recovery in the 3 mo post-labyrinthectomy. In contrast to these changes in horizontal eye movements, vertical response sensitivities during fixation at up/down targets remained qualitatively the same.
eventually reached after 3 mo (Fetter and Zee 1988). After unilateral deafferentation of the otolith organs in squirrel monkeys, the VOR gain enhancement during eccentric rotations was compromised acutely after the lesion but compensated to relatively normal values 6–8 wk after the operation (Takeda et al. 1990). It is possible that had we tested trVOR responses acutely (i.e., within hours) after unilateral labyrinthectomy, the deficits would be greater. The goal of this study, however, was not the early deficits that could be at least partly due to the loss of spontaneous activity in the deafferented side but rather the prevailing deficits in the trVORs once static vestibular imbalance had been mostly restored. For this reason (and because animals could not consistently fixate acutely after labyrinthectomy), our earliest quantitative data presented here were obtained 3–7 days after the operation.

Response asymmetry

Several studies of the rotational VOR in humans and monkeys have clearly demonstrated that the observed recovery in the gain of the reflex varies depending on the stimuli used. First, it depends on peak head acceleration. The higher the peak acceleration, the smaller the recovery and the larger the asymmetry to ipsilateral and contralateral rotation responses (Gilchrist et al. 1998; Halmagyi et al. 1990; Tabak et al. 1997; Vibert et al. 1993). For low-acceleration sinusoidal rotations, in particular, a nearly complete recovery of the horizontal VOR has been shown in both humans and monkeys (Allum et al. 1988; Baloh et al. 1984; Fetter and Dichgans 1990; Fetter and Zee 1988; Takahashi et al. 1977, 1984; Wolfe and Kos 1977). Second, horizontal VOR recovery and symmetry has also been shown to be smaller for impulsive rotations that had the same peak head acceleration compared with sinusoidal oscillations (Crane and Demer 1998; Gilchrist et al. 1998). Differences between the ipsilesional and contralesion movement directions have also been reported during center and eccentric rotations in subjects with unilateral vestibular deafferentation (Crane and Demer 1998). Ewald’s second law (Ewald 1892) has been often proposed as an explanation for such response asymmetries in the horizontal canal system (Crane and Demer 1998; Curthoys et al. 1991b). Recent studies have recently further addressed this issue during head rotations (Broussard et al. 1999; Baloh et al. 1999a; Minor et al. 1999).

Similarly to the results during head rotations, asymmetric responses were also observed here during large-amplitude transient lateral movements. We have also found that the transient response asymmetry does not totally recover within the 2–3 mo of post-lesion testing. Asymmetric responses to ipsilateral/contralateral motion directions have been also previously reported during transient linear motion in darkness one week after unilateral labyrinthectomy (Lempert et al. 1998). Responses regained symmetry when tested 6–10 wk after the operation. In addition, a “relatively normal,” bidirectional trVOR was reported in chronic patients with unilateral labyrinthectomy or unilateral vestibular damage (Bronstein et al. 1991). The transient stimuli used here differ from those of Lempert et al. in two ways. First, the head displacement and peak head acceleration, as well as the frequency content of the transient stimulus, were all higher in the present study. Second, animals in the present study fixated near targets (at 10 cm, vergence angles were 14–18°). Most likely the lack of a large

Unilateral labyrinthectomy and vestibular compensation

Based on previous work regarding the rotational VOR, it appears that there are two phases in compensation (Curthoys and Halmagyi 1995; Fetter and Zee 1988; Ris et al. 1995; Smith and Curthoys 1989). Within approximately the first week, recovery is fast and involves mainly compensation of the static imbalance and recovery of central vestibular neuron discharge. The VOR reflex gain recovery observed during this first week could be at least partly due to the restoration of spontaneous activity in central vestibular neurons. The dynamic compensation is slower and takes place within several weeks or months after unilateral labyrinthectomy. Because of the confounding problems associated with the strong spontaneous nystagmus and difficulties in fixation, the present work has not examined the changes in the trVORs during the first couple of days after unilateral labyrinthectomy. Rotational VOR gains, which have been reported to decrease to ~0.5 immediately after labyrinthectomy, exhibited a fast recovery within the first 2–3 days after exposure to light. For low-velocity stimuli, in particular, rotational VOR gain tested after 2–3 days increased to ~80–90% of the value that was
recovery in the transient responses reported here is due at least in part to the large acceleration and/or frequency content of the transient stimulus. The deficits reported here are most likely due to the removal of specific connections from the lesioned utricular/saccular macula to the brain stem. It is unlikely that the observed asymmetries, particularly those pertinent to long-lasting effects during fore-aft oscillations or transient lateral motion, are due to a decrease in the spontaneous activity of central neurons after unilateral labyrinthectomy. The restoration of spontaneous activity in guinea pig central neurons is complete within a week after unilateral labyrinthectomy (Ris et al. 1995). The recovery of neural discharge in primates has not yet been investigated, although behavioral data suggest that spontaneous nystagmus in complete darkness decreases to less than half within 10 days after operation (Fetter and Zee 1988).

Differences between canal-intact and canal-plugged animals

The observation that the unilateral labyrinthectomy deficits during lateral movements were larger in canal-plugged than in canal-intact animals suggests that otolith and semicircular canal signals are not independent in their central processing and adaptation. We have recently shown, for example, that a nonlinear interaction between semicircular canal and otolith signals is necessary for an appropriate central decomposition of linear accelerations into translational and gravitational components (Angelaki et al. 1999a). The differences in adaptation between canal-intact and canal-plugged animals constitute further evidence that otolith and semicircular canal signals are subject to extensive central processing and convergence.

Deficits for fore-aft motion stimuli

Perhaps the largest and most consistent effect of unilateral labyrinthectomy in all five animals tested was the destruction in the tuning of the fore-aft trVOR as a function of gaze eccentricity. Whereas responses were qualitatively unchanged during fixation of contralateral targets, responses were anti-compensatory during fixation of targets ipsilateral to the lesion side. In contrast to fore-aft responses in intact animals where the direction of the elicited eye movement reverses for leftward and rightward eye positions (McHenry and Angelaki 2000; Paige and Tomko 1991b), forward motion elicited leftward eye movements for all gaze directions following right labyrinthectomy. The opposite was true after left labyrinthectomy. The deficits reported here are most likely due to the removal of specific connections from the two labyrinths.

Implications for otolith-ocular connectivity

For the present results to be extrapolated in a simple conceptual diagram that could be used to generate the trVORs, knowledge of the main excitatory otolith-ocular connectivity is fundamental. For example, depending on whether the main excitatory projections are to the ipsilateral or contralateral abducens, either the medial or the lateral side of the striola could elicit compensatory horizontal eye movements during lateral motion. In fact, the observation that ipsilateral translations (that cause excitation to utricular afferents innervating the lateral side of the striola) were more severely compromised following unilateral labyrinthectomy led Lempert et al. (1998) to conclude that afferents in the trVOR originate from the lateral side of the striola. However, an implicit assumption for the conclusions of Lempert et al. (1998) is the existence of a (semicircular canal-like) contralateral excitatory utriculoabducens pathway. Currently, there is no experimental evidence regarding a short-latency excitatory contralateral utriculoabducens pathway. In fact, there is growing evidence that the main, excitatory utriculoocular pathway is ipsilateral, in sharp contrast to the horizontal canal-ocular pathway (Schwindt et al. 1973; Uchino et al. 1979). Intracellular recordings from cat motoneurons and internuclear neurons have demonstrated the existence of di- and (mono-) synaptic excitatory postsynaptic potentials (EPSPs) in the ipsilateral abducens nucleus during stimulation of the utricular nerve (Uchino et al. 1994, 1997). In contrast, only small hyperpolarizations with a longer latency were reported in some cells in the contralateral abducens nucleus during utricular nerve stimulation. Even though the existence of similar connections is yet to be documented in primates, we consider it inappropriate to embrace the conclusion of Lempert et al. (1998) at this point.

If indeed the main excitatory horizontal trVOR pathway in primates is ipsilateral (as is the case in cats) and to generate a compensatory eye movement during lateral translation, cells in the excitatory horizontal trVOR pathway should originate from the medial side of the striola. For example, left utricular afferents originating from the medial side of the striola would be excited during a rightward head acceleration. Left utricular afferents would excite the left abducens nucleus, thus eliciting a leftward (compensatory) eye movement. Such a connectivity, however, would have predicted the opposite asymmetries from those seen after unilateral labyrinthectomy. Following lesions of the left labyrinth, for example, it should be rightward (contralateral) head movements that should have been more severely compromised. The fact that the electrophysiological and lesion data are not mutually consistent with any such simplified scheme suggests that the actual organization of the translational VORs is more complex. The extensive convergence of the two sides of the striola, as well as the two labyrinths, on single second-order neurons (Uchino et al. 1999) would also
suggest that no simple connectivity scheme would be the answer to the organization of the translational VORs.

Finally, it should be pointed out that no data are currently available on changes in the neural coding of linear acceleration after unilateral labyrinthectomy in any species that has been shown to exhibit functionally-appropriate trVORs (i.e., horizontal/vertical eye movements that are scaled by target distance and eccentricity). Even though such data are available in nonprimate species (e.g., Chan 1997; Wadan and Dieringer 1994), their relevance to the neural organization of the trVORs is questionable since they might reflect signal processing in the orienting otolith-ocular reflexes (counter-rolling/counter-pitching). It is nevertheless interesting to notice that, although ipsilateral ear-down responses predominated, the best response orientations of vestibular nuclei neurons in unilateral labyrinthectionized cats pointed in all directions in the horizontal plane (Chan 1997). Such a result provides further evidence that both sides of the striola project (either directly or indirectly) onto vestibular nuclei neurons. Indeed, monosynaptic EPSPs were observed during electrical stimulation of both sides of the striola in ~20% of secondary utricular neurons in the cat (Uchino et al. 1999). An additional 40% of secondary utricular neurons exhibited monosynaptic EPSPs and disynaptic inhibitory postsynaptic potentials, suggesting cross-striolar inhibition (Uchino et al. 1999).

Considering the present and previous results together, we are faced with a serious limitation in our current understanding of the neuroanatomy and functional connectivity of the system. The labyrinthectomy results in both humans and monkeys are not easily reconciled with what has been observed electrophysiologically in cats. As mentioned above, this apparent discrepancy might be at least partly due to extensive convergence of utricular afferents from both sides of the striola. Nevertheless despite a remaining uncertainty in the neuroanatomical architecture of the trVORs, the fact that the deficits during lateral motion were small during small-amplitude sinusoidal lateral oscillations suggest that a commissural pathway probably exist in the trVORs. Earlier work had suggested that otolith-related commissural projections to the lateral vestibular nucleus might have a purely excitatory effect on second order neurons in the cat (Shimazu and Smith 1971). However, more recent work in the same species has suggested that approximately half of the secondary utricular neurons receive commissural inhibition, whereas the remaining do not receive commissural signals at all (Uchino et al. 1999).

The neuroanatomical architecture seems to be less controversial for other aspects of the otolith-ocular system. For example, there is consistent experimental evidence that the main excitatory drive for the orienting components of the otolith-ocular system (i.e., counter-rolling and counter-pitching) might arise from the medial side of the striola. First, patients with unilateral vestibular neurectomies have been shown to underestimate the magnitude of roll head tilt when the resultant acceleration is directed toward their operated ear (Curthoys et al. 1991a; Dai et al. 1989). Second, patients with unilateral lesions have also been shown to elicit smaller ocular counter-rolling for ipsilateral head roll tilts (albeit with largely inconsistent results) (e.g., Diamond and Markham 1981; Kanzaki and Ouchi 1978; Krecjova et al. 1971; Nelson and House 1971). Finally, electrical stimulation of the utricle elicited torsional eye movements appropriate to compensate for an ipsilateral roll tilt (Curthoys 1987; Fluur and Mellström 1970; Suzuki et al. 1969). These torsional and vertical eye movements, albeit of small amplitude in primates and humans, constitutes the primary otolith-ocular responses in lateral-eyed species, including frogs (Hess et al. 1984), rats (Hess and Dieringer 1991), rabbits (Baarsma and Collewijn 1975), and pigeons (Dickman and Angelaki 1999).

If indeed there is extensive convergence from both sides of the striola in central vestibular neurons participating in the trVORs, the neuronal architecture of the trVORs will be harder to understand using tools and principles that have been proven very successful for the rotational VOR. At present, several pieces of the puzzle remain missing and so is also a basic neuroanatomical diagram that could be consistent with both the electrophysiological, lesion, and stimulation data regarding the trVORs.

REFERENCES


