

Asymmetric Recovery in Cerebellar-Deficient Mice Following Unilateral Labyrinthectomy

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¹Department of Physiology, McGill University, Montreal, Quebec, Canada; and ²Laboratoire de Neurobiologie des Réseaux Sensorimoteurs, Unité Mixte de Recherche Centre National de la Recherche Scientifique 7060, UFR Biomédicale, Université Paris Descartes, Paris, France

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Beraneck M, McKee JL, Aleisa M, Cullen KE. Asymmetric recovery in cerebellar-deficient mice following unilateral labyrinthectomy. *J Neurophysiol* 100: 945–958, 2008. First published May 28, 2008; doi:10.1152/jn.90319.2008. The term “vestibular compensation” refers to the resolution of motor deficits resulting from a peripheral vestibular lesion. We investigated the role of the cerebellum in the compensation process by characterizing the vestibuloocular reflex (VOR) evoked by head rotations at frequencies and velocities similar to those in natural behaviors in wild-type (*WT*) versus cerebellar-deficient Lurcher (*Lc/+*) mice. We found that during exploratory activity, normal mice produce head rotations largely consisting of frequencies ≤ 4 Hz and velocities and accelerations as large as $400^\circ/\text{s}$ and $5,000^\circ/\text{s}^2$, respectively. Accordingly, the VOR was characterized using sinusoidal rotations (0.2–4 Hz) as well as transient impulses ($\sim 400^\circ/\text{s}$; $\sim 2,000^\circ/\text{s}^2$). Before lesions, *WT* and *Lc/+* mice produced similar VOR responses to sinusoidal rotation. *Lc/+* mice, however, had significantly reduced gains for transient stimuli. After unilateral labyrinthectomy, VOR recovery followed a similar course for *WT* and *Lc/+* groups during the first week: gain was reduced by 80% for ipsilesionally directed head rotations on day 1 and improved for both strains to values of ~ 0.4 by day 5. Moreover, responses evoked by contralesionally directed rotations returned to prelesion in both strains within this period. However, unlike *WT*, which showed improving responses to ipsilesionally directed rotations, recovery plateaued after first week for *Lc/+* mice. Our results show that despite nearly normal recovery in the acute phase, long-term compensation is compromised in *Lc/+*. We conclude that cerebellar pathways are critical for long-term restoration of VOR during head rotation toward the lesioned side, while noncerebellar pathways are sufficient to restore proper gaze stabilization during contralesionally directed movements.

INTRODUCTION

The term “vestibular compensation” refers to the partial or complete normalization of postural and ocular motor deficits that result from a peripheral vestibular lesion. Such lesions trigger static deficits, which affect posture and eye position at rest (i.e., a spontaneous nystagmus with slow phase and head-tilt directed toward the lesioned side) as well as changes in the ability of the vestibuloocular (VOR) and vestibulocollic (VCR) reflexes to stabilize gaze and posture (reviewed in Curthoys 2000; Dieringer 1995; Vibert et al. 1997). While static deficits disappear over the course of few days in most species (Darlington et al. 2002; de Waele et al. 1989; Sirkin et al. 1984; Smith and Curthoys 1989), the response dynamics of vestibularly driven reflexes never fully recover. For example, despite

an initial improvement in response to head movement with relatively low velocities/accelerations that are in the low- and middle-frequency range (~ 0.1 – 10 Hz), the performance of the VOR in response to higher frequency and velocity/acceleration stimulation remains impaired on the long term (e.g., cat: Broussard et al. 1999; guinea pig: Gilchrist et al. 1998; macaque: Fetter and Zee 1988; Sadeghi et al. 2006; squirrel monkey: Lasker et al. 2000; Paige 1983; human: Crane and Demer 1998; Halmagyi et al. 1990). Notably, an asymmetry in the responses persists such that VOR responses evoked by ipsilesionally directed movements are less robust than those evoked by contralesionally directed movements.

In normal animals, the VOR produces compensatory eye movements required to stabilize gaze and ensure clear vision during everyday activities. This reflex shows impressive adaptation in response to environmental requirements. For example, in humans, VOR motor learning is required to compensate for the magnification of corrective lenses that are worn for common visual conditions; the VOR gain in myopic individuals who wear concave lenses will be lower than for individuals with normal vision. The results of single-neuron recording and lesion studies have shown that the flocculus and ventral paraflocculus (herein called the floccular complex) of the vestibulocerebellum are critical for VOR motor learning (e.g., Ito et al. 1974, 1982; Lisberger et al. 1984; Nagao 1983; Robinson 1976). Effectively, the vestibular-cerebellar-vestibular pathway provides a parallel inhibitory side loop that can modulate the gain of the direct VOR pathway (Fukuda et al. 1972; Highstein 1973; Ito et al. 1977; Sato et al. 1988). Recent studies suggest that the gain changes required for VOR motor learning are initially stored in the floccular complex and in turn drive the formation of long-term synaptic changes at the level of the vestibular nuclei such that long-term memory is chiefly consolidated in the brain stem rather than the cerebellum (reviewed in Broussard and Kassardjian 2004).

While the vestibular cerebellum's role in motor learning is well established, only a few investigations have explicitly addressed whether this region plays a comparable role in the vestibular compensation process following peripheral lesions (Johnston et al. 2002; Kitahara et al. 1998a). Nevertheless, the evidence that is available to date supports the proposal that the floccular complex plays a comparable role during VOR postlesional recovery and motor learning. First, lesions of the cerebellum in cats eliminate the initiation but not the maintenance

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of behavioral recovery following unilateral labyrinthectomy (Courjon et al. 1982; Haddad et al. 1977). Similarly, in rats, lesions of the vestibulocerebellum impair the resolution of static symptoms, including ocular nystagmus, following unilateral labyrinthectomy (Kim et al. 1997a,b; Kitahara et al. 1997, 1998b, 2000). While these findings support the proposal that the cerebellum participates in the vestibular compensation process, prior studies have not yet established whether the vestibular cerebellum contributes equally to the recovery across the full range of physiologically significant head movements nor have they fully described the time course of its contribution (see for a review Darlington and Smith 2000).

The mouse is an attractive model to examine the role of the cerebellum in the recovery of vestibular reflexes following a unilateral labyrinthectomy. In the present study, we took advantage of a cerebellar-deficient Lurcher (*Lc/+*) mouse strain to characterize the cerebellum's contribution to the vestibular compensation process. This strain is characterized by a mutation in the *GLUR δ 2* (glutamate receptor delta-2 subunit) gene, causing increased activity of the receptor, which in turn leads to the apoptotic programmed death of the output neurons of the cerebellar cortex (i.e., the Purkinje cells) within the first three postnatal weeks (Doughty et al. 2000; Hirano 2006; Wullner et al. 1995; Zuo et al. 1997; for review, see Vogel et al. 2007). As a result, the cerebellum is severely deformed and undersized (Caddy and Biscoe 1975; Swisher and Wilson 1977; Yue et al. 2002; Zuo et al. 1997) and the mice show typical ataxia among various other motor skill deficits (Vogel et al. 2007). Thus the *Lc/+* provides a useful model of a complete ablation of cerebellar cortex (Van Alphen et al. 2002).

The results of previous investigations of vestibular compensation in both normal and cerebellar mutant mice have proven inconclusive regarding several critical questions (Faulstich et al. 2006; Funabiki et al. 1995; Kitahara et al. 1998; Murai et al. 2004). First, the question of whether the cerebellum plays a critical or supportive role remains unresolved. On the one hand, the findings of Faulstich et al. (2006) in the *Lc/+* mutant mouse suggest that the vestibular compensation process depends completely on an intact cerebellar circuitry. In contrast, Murai et al. (2004) found that recovery in another cerebellar mutant strain (the *GLUR δ 2* knock-out mouse; $\delta 2^{-/-}$) was similar to that of wild-type (*WT*) mice. In addition, compared with other species (e.g., Sadeghi et al. 2006), VOR asymmetries following unilateral vestibular loss in either normal or cerebellar-deficient mice have not been investigated.

Accordingly, the goal of the present study was to study the time course of the compensation process in *WT* versus *Lc/+* mice and to establish whether the vestibular cerebellum contributes equally to behavioral recovery across the full range of physiologically significant head movements. We first measured head rotations made by normal mice during natural exploratory behavior and determined their frequency content as well as velocities and accelerations. The time course of VOR recovery was then established in normal mice following labyrinthectomy in response to both ipsi- and contralesionally directed rotations for similar stimuli to quantify directionally dependent asymmetries. Next, responses in *Lc/+* mice were compared with those of *WT* mice during both acute and chronic periods to assess the role of the cerebellum in recovery. As compared with *WT* mice, we found that long-term compensation is compromised in cerebellar-deficient mice. However, surpris-

ingly mutant mice demonstrated significant improvement within 1 wk after the lesion. After this period, the behavioral recovery plateaued in *Lc/+* mice, whereas in contrast, *WT* mice continued to show improvement over the next 2 wk. Thus noncerebellar pathways were sufficient to restore proper gaze stabilization for contralesional-directed head movements in *Lc/+* mice, but the restoration of VOR for head movements directed toward the lesioned side was incomplete compared with *WT* mice.

METHODS

Animals

Ten normal C-57Bl6 (Charles River Laboratories) and 9 Lurcher male adult mice (~ 30 g) were used in this study. Two pairs of Lurcher mice (2 heterozygous males and 2 wild-type females) were initially purchased (B6CBACaAW-J/A-Grid2Lc, Jackson Laboratory), and breeding was subsequently done in our institution. Ataxic mice were separated from normal animals 3 wk following birth, and experiments were performed on mice at ≥ 2 mo of age. All procedures were approved by McGill University Animal Care Committee and were in strict compliance with the guidelines of the Canadian Council on Animal Care.

Surgeries

Surgical preparation and postoperative care for head implant surgery have been described elsewhere (Beraneck and Cullen 2007). Briefly, anesthesia was induced using an intramuscular injection of a mixture of atropine (5.10^{-4} mg/g), ketamine (10^{-1} mg/g), acepromazine maleate ($2.5.10^{-2}$ mg/g), xylazine (10^{-1} mg/g), and sterile saline. A custom-built head holder was then cemented (C&B Metabond) to the skull of each animal. Following the surgery, animals were isolated in specific cages and closely surveyed for 48 h. Buprenorphine (0.05 mg/kg) was provided for postoperative analgesia, and care was taken to avoid hypothermia and dehydration.

Unilateral labyrinthectomy was performed during a second surgery for which the procedures for surgical preparation and postoperative care were the same as those described above. The semicircular canals, utricle, and saccule were exposed via a retroauricular approach. Hemostasis control was performed using a portable cautery device (Allegiance Healthcare). The bony labyrinth was drilled, and the ampullae of all three canals and the otolithic maculae were removed using suction. A small piece of surgifoam (Ferrosan A/S) was then placed in the cavity. Following surgery, animals were allowed to compensate in a normal visual environment (Shinder et al. 2005). For both normal and Lurcher mice, eight animals were studied both before and after labyrinthectomy.

Data acquisition

To quantify natural head movements, normal mice ($n = 5$) were placed in a 30×30 -cm box in which food pellets had been distributed. Markers were fixed on the mouse headpost, and the animals' natural exploration of the environment was captured using a high-resolution 250-Hz camera. Off-line processing of the resultant images was performed using a free-licensed software (Video-spot tracker; courtesy of the National Institutes of Health/National Institute for Biomedical Imaging and Bioengineering; Computer-Integrated Systems for Microscopy and Manipulation, University of North Carolina), and the resultant data were imported into the Matlab (Mathwork) programming environment for further analysis. Analyzed sequences ($n = 16$) were restricted to epochs of 3-s duration when the animal was actively exploring the field.

The experimental setup, apparatus, and method of data acquisition used to record eye movements were similar to those that have been previously described (Beraneck and Cullen 2007). Briefly, during the experiment, animals were placed in a custom-built Plexiglas tube that was fixed to the center of the superstructure of a vestibular turntable. The mouse's head was fixed 35° nose down to align the horizontal semicircular canals with the horizontal plane (Calabrese and Hullar 2006; Vidal et al. 2004). Eye movements were recorded using an infrared video system (sampling rate: 120 Hz; ETL-200, ISCAN, Burlington, MA) with optics modified for the mouse eye following the approach described by Stahl et al. (2000). Vestibular turntable velocity was measured using an angular velocity sensor (Watson). Data acquisition and vestibular stimulation were controlled by a QNX-based real-time data-acquisition system (REX) (Hayes et al. 1982). Recorded eye- and head-position signals were low-pass filtered at 250 Hz by an 8-pole Bessel filter and sampled at 1 kHz. Eye and head positions as well as table velocity were recorded on digital audio tapes for later playback and off-line analysis.

Mice were tested before the labyrinthectomy to obtain prelesion VOR data as well as on days 1, 5, 10, and 20 following labyrinthectomy. The VOR elicited by rotation in the yaw axis during each of the stimulation paradigms was then measured both in the light (VORI) and in the dark (VORD). Pilocarpine (4%, Alcon Canada) was applied to the eye to keep the pupil size constant in the latter condition (Iwashita et al. 2001). Whole-body rotations were applied by sinusoidally rotating head-restrained mice en bloc at frequencies of 0.2, 0.5, 1.0, 2.0, 3.0, and 4.0 Hz, 40°/s. Fifteen consecutive stimulus cycles were applied within each trial. Segments of data with quick phases were excluded from analysis. Quick phases were identified using an algorithm based on the method previously described by Ebisawa et al. (1988). In addition, rapid (~400 ms), high-velocity (250–400°/s) perturbations were randomly applied in either the contra- and ipsilateral directions to test the VOR response evoked by rapid transient rotations (Gilchrist et al. 1998; Halmagyi et al. 1990).

Data analysis

To quantify VOR response dynamics, the recorded data were imported into the Matlab (The MathWorks) programming environment for analysis as previously detailed (Beraneck and Cullen 2007). Briefly, horizontal eye- and head-movement data were digitally low-pass-filtered using a 51st-order finite-impulse-response (FIR) filter (cut-off frequency = 40 and 75 Hz for sinusoidal rotations and transient head perturbations, respectively), and position data were differentiated to obtain velocity traces.

To analyze data from sinusoidal rotations, the head velocity signal was divided into right and left half cycles based on zero crossings of the stimulus. At least 10 half-cycles were analyzed for each frequency in each direction. VOR gain and phase were determined by the least-squares optimization of the equation $E'(t) = (\text{gain}) * \{ [H'(t + \text{td})] + \text{bias} \}$ where $E'(t)$ is eye velocity, $H'(t)$ is head velocity, gain is a constant value, td is the dynamic lag time (in ms) of the eye movement with respect to the head movement, and bias is a DC offset. Because mice frequently exhibited spontaneous nystagmus following labyrinthectomy, $E'(t)$ was typically offset by the slow phase velocity (defined as the mean velocity 5–40 ms prior to the onset of the perturbation (see also: Sadeghi et al. 2006)). The dynamic lag time (td) was used to calculate the corresponding phase (φ°) of eye velocity relative to head velocity. The variance-accounted-for (VAF) of each fit was computed as $\{1 - [\text{var}(\text{est} - E')/\text{var}(E')]\}$, where var represents variance, est represents the modeled eye velocity, and E' represents the actual eye velocity. VAF values were typically between 0.70 and 1, where a VAF of 1 indicates a perfect fit to the data. Trials for which the VAF was <0.5 were excluded from the analysis.

In addition, ≥ 10 trials, which were free of quick phase/saccades during the initial rising phase of the velocity response, were analyzed to characterize the VOR response to high-velocity (250–400°/s)

perturbations. The VOR gain was defined as the change in eye velocity (i.e., peak eye velocity – bias velocity), divided by the peak head velocity of the perturbation.

Statistical processing of all results was carried out using the Systat10.0 software (SPSS, Chicago, IL). For each parameter, normality of the distributions was assessed using one-sample Kolmogorov-Smirnov tests with significance set at $P = 0.05$. Statistical comparisons between numerical values were achieved through either parametric (if the distribution of the parameter was normal for all the samples involved and each sample included ≥ 15 values) or otherwise, nonparametric tests with the threshold for significance set at $P = 0.05$. Accordingly, two-by-two comparisons between the different groups were performed using Student's *t*-test or the nonparametric Mann-Whitney *U* tests.

RESULTS

Range of natural head movements

The principal goal of our study was to compare VOR response dynamics following labyrinthectomy in normal mice versus cerebellar-deficient mice in the range of natural head movements. We first characterized voluntarily generated head rotations to establish the range of physiologically relevant head movements. Horizontal head movement was recorded in unrestrained mice as described in METHODS. Figure 1A illustrates the Fourier analysis of active head motion produced while the animal freely explored its environment. During periods of exploratory activity, mice produced head movements with frequency contents of ≤ 20 Hz (Fig. 1A). Within this range, however, most movement magnitude (~70%), was composed of frequencies of ≤ 4 Hz. Additionally, movements reached angular velocities of $\leq 400^\circ/\text{s}$ (Fig. 1B) and accelerations of $\leq 10,000^\circ/\text{s}^2$ (Fig. 1C). In all animals, velocities and accelerations were typically symmetrically distributed between left and right movements. The vast majority (85%) of movements consisted of velocities of $< 100^\circ/\text{s}$ and accelerations of $< 5,000^\circ/\text{s}^2$.

Accordingly, we compared the response dynamics of the VOR before and following labyrinthectomy, using both sinusoidal rotations over a frequency range of 0.2–4 Hz and transient perturbations that produced velocities and accelerations $\leq 400^\circ/\text{s}$ and $2,000^\circ/\text{s}^2$, respectively.

VOR responses in wild-type and Lurcher mice before lesion

We first tested the VOR elicited by passive sinusoidal rotations at 0.2, 0.5, 1.0, 2.0, 3.0, and 4.0 Hz. Figure 2A, 1 and 2, shows examples of eye- and head-velocity profiles of the responses of *WT* mice for two of the six frequencies of head oscillation that were tested within this frequency range (0.5 and 2.0 Hz). In these examples, mice were rotated in darkness, and head velocity was kept constant at 40°/s. The VOR evoked in both light and dark were then compared for *WT* and *Lc/+* mice.

Bode plots quantifying the frequency response of the VOR during sinusoidal oscillations are shown in Fig. 2B, 1 and 2, for both *WT* and *Lc/+* mice, respectively. In *WT* mice, the gain of evoked eye movements in the dark (Fig. 2B1) increased as a function of frequency, ranging from 0.50 ± 0.04 at 0.2 Hz to 0.84 ± 0.03 (mean \pm SE) at 4 Hz (Fig. 2B1). VOR responses evoked by rotation in the light showed a comparable trend, but gain values were significantly higher (compare black and white squares in Fig. 2B1; $P > 0.05$ at all frequencies except 1 Hz),

reaching a maximum gain of 0.95 ± 0.05 at 4 Hz. Correspondingly, the VOR gains of the *Lc/+* mice were similar to those of *WT* mice in both dark and light conditions (VORd and VORl, respectively) at all tested frequencies ($P > 0.15$ at all frequencies except at 1 Hz for VORd gain $P = 0.016$). *Lc/+* mice also

had consistently greater VOR gains for rotations in the light versus dark; gains were significantly greater during VORl for all frequencies >0.2 Hz ($P < 0.05$). When data from *WT* and *Lc/+* mice were grouped together, average VORl gains were significantly higher than VORd gains across the entire frequency range ($P < 0.05$).

The phase of the response was also similar for the two groups of mice prior to labyrinthectomy. For both *WT* and *Lc/+* mice, the phase of the VOR (Fig. 2B) was most compensatory for lower frequencies of stimulation. Response phases were comparable at all frequencies for both VORd and VORl ($P > 0.15$ except at 0.5 and 1 Hz for VORl) and increasingly lagged that of the stimulus as a function of increasing frequency, approaching a lag of 15 [deg] at 4.0 Hz. Note, this finding markedly contrasts with the near perfect phase compensation that has been reported in previous studies of rhesus monkeys for frequencies <5 Hz (Huterer and Cullen 2002). This dissimilarity highlights differences across species which are further considered in the discussion.

Transient head perturbations were used to further characterize the response dynamics of the VOR. The stimulus (Fig. 2C1; solid line) had a peak acceleration in excess of $\sim 2,000^\circ/\text{s}^2$, reached velocities of 250–400 $^\circ/\text{s}$, and was completed within ~ 400 ms. The frequency content of the perturbation was computed by Fourier analysis of the head velocity profile, which revealed frequencies of up to ~ 6 Hz. Thus overall the transient perturbation had higher frequency, velocity and acceleration content than did the sinusoidal head-on-body rotations applied in our first series of experiments. The gray line in Fig. 2C1 shows an example of a wild-type mouse's eye movement response superimposed on the inverted head velocity profile during stimulation in the dark. In response to these abrupt stimulations, control animals produced compensatory eye movements with gains approaching unity. The mean VORd gain for *WT* animals was 0.92 ± 0.02 ; a value that was significantly higher than that of the *Lc/+* mice when tested in the same conditions (0.84 ± 0.02 , $P = 0.015$ see Fig. 2).

Vestibular compensation following labyrinthectomy

Having evaluated the gain and phase of the VOR induced by sinusoidal and transient rotations in *WT* and *Lc/+* mice before lesion, we next studied VOR responses in the same mice after unilateral labyrinthectomy. To address the role of the cerebellum in the compensation process, we compared the time course of vestibular compensation in the two strains. In the following text, we first describe the time course of the resolution of static signs, and then present the results of our analysis of the VOR response dynamics for sinusoidal and transient rotations.

Static signs in wild-type and Lurcher mice

Spontaneous nystagmus in dark and head tilt along with a postural imbalance were observed in both strains of mice imme-

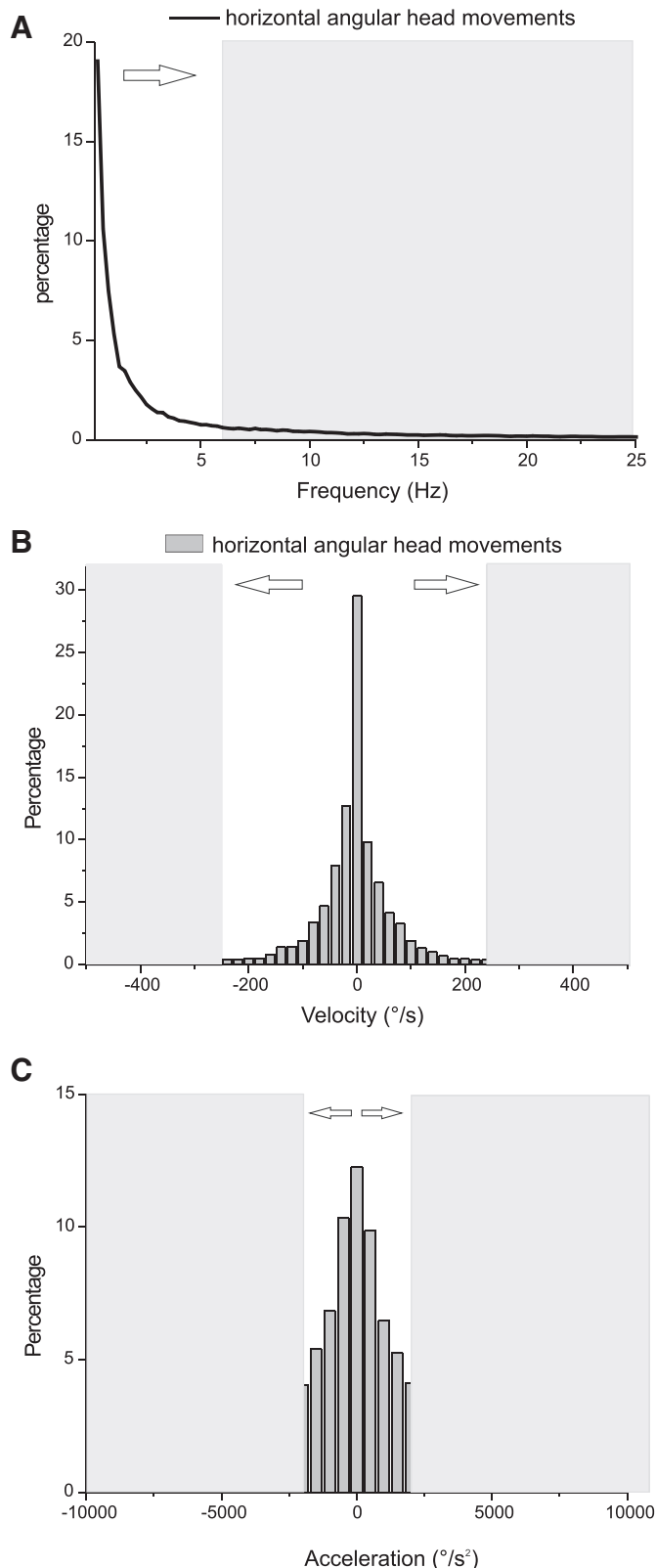


FIG. 1. Dynamics of natural head movements. Head movements were recorded in unrestrained wild-type (*WT*) mice while they explored their environment. **A**: Fourier analysis of angular head-velocity profiles reveals little frequency content >5 Hz. **B** and **C**: analysis of corresponding velocities (**B**) and accelerations (**C**) shows that majority ($>85\%$) consisted of movements with peak velocities $<100^\circ/\text{s}$ and peak accelerations $<5,000^\circ/\text{s}^2$. Note, movements were symmetrically distributed between left and right. Shaded areas represent the range of stimuli used in the study to probe the vestibuloocular reflex (VOR).

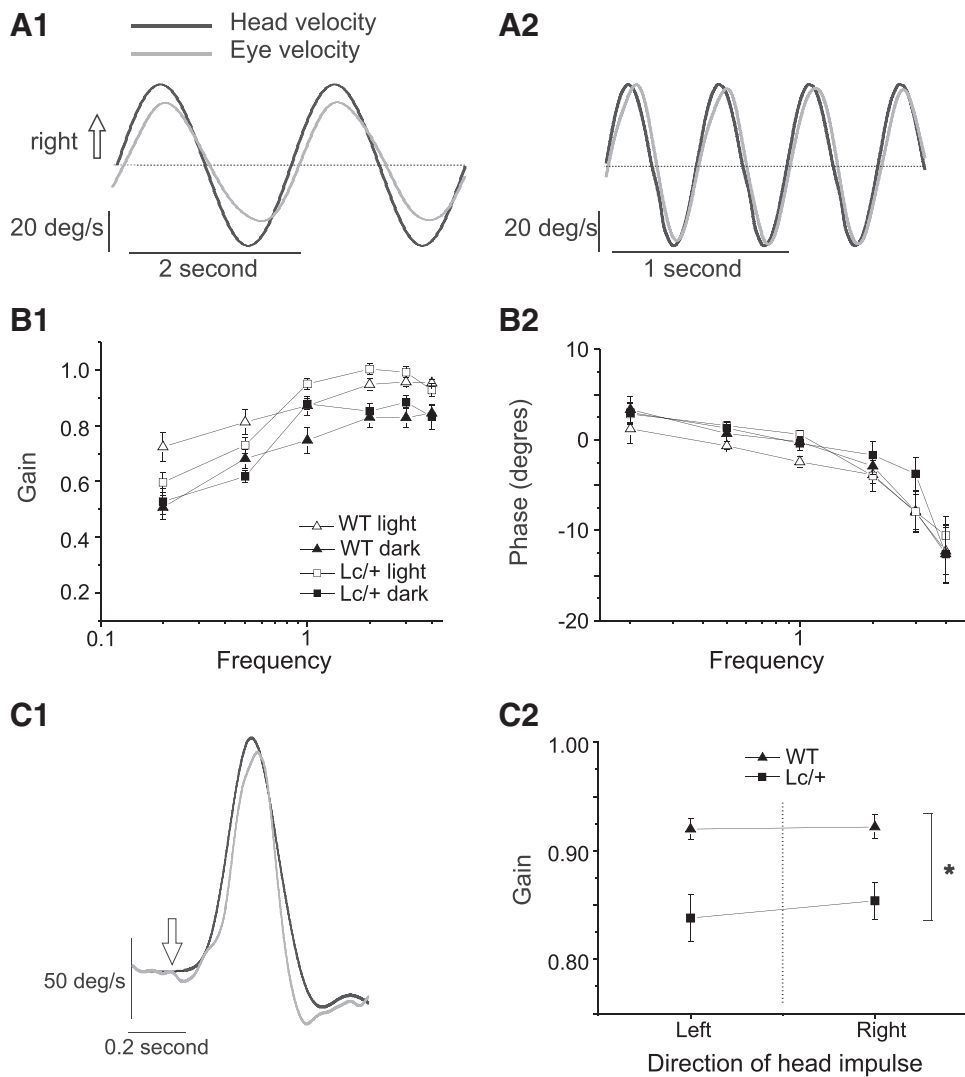


FIG. 2. VOR in wild-type and Lurcher mice before lesion. *A*: example eye and head (table) velocities during sinusoidal rotations in the dark at 0.5 (*A1*) and 2 Hz (*A2*) for a *WT* mouse. *B*: gain (*B1*) and phase (*B2*) plots of responses to 0.2- to 4-Hz rotations averaged across the groups of *WT* (Δ and \blacktriangle) and *Lc/+* (\square and \blacksquare) mice. No significant differences were observed between the 2 strains before lesion. *C*: responses to transient impulses. *1*: example of a *WT* mouse's response to a transient rotation applied in the dark. *2*: gains of VOR responses to abrupt stimulations responses averaged across the groups of *WT* (Δ and \blacktriangle) and *Lc/+* (\square and \blacksquare) mice; *WT* produced almost perfect compensatory responses, whereas *Lc/+* mice showed relatively lower gains. No difference between right and left responses was observed before lesions. *, significant differences ($P < 0.05$) between *WT* and *Lc/+* mice. Note, that in this and the following figures: \uparrow , the onset of the stimulation; head velocity traces have been inverted to facilitate comparison with eye velocity; and error bars indicate means \pm SE.

diately following labyrinthectomy. In *WT* mice, these static symptoms disappeared in the course of the next 10 days. The spontaneous nystagmus that was acutely observed nearly completely disappeared within 5 days of the lesion (64 ± 4 beat/min at day 1 compared with 3.6 ± 4.9 at day 5). Analysis of the slow phase velocity when the eye was centered in the orbit (i.e., eye position $0 \pm 5^\circ$) showed a further decrease in nystagmus from day 5 to 20 (8.2 ± 2.9 to $4.1 \pm 2.7^\circ/s$, respectively; $P < 0.01$). Similarly, the marked head tilt that was observed acutely ($44 \pm 7^\circ$ on day 1) decreased to $12 \pm 4^\circ$ by day 10. Similar static symptoms were observed in the first 24 h after labyrinthectomy in *Lc/+* mice. At day 1, mice produced a spontaneous nystagmus (71.6 ± 10.9 beat/min; $P > 0.1$ relative to *WT*) and head tilt of $\sim 50^\circ$ ($P > 0.1$ relative to *WT*). The resolution of these symptoms, however, was far less substantial in the course of the next 3 wk. As a result, at day 20, mice showed a spontaneous nystagmus of 18 ± 4.4 beat/min ($P < 0.01$ relative to *WT*) with slow phase velocity of $7.62 \pm 3.2^\circ/s$ ($P = 0.039$ relative to *WT*) and head tilt of $\sim 31 \pm 6^\circ$.

Time course of compensation in wild-type mice

Vestibular compensation was evaluated in *WT* and *Lc/+* by quantifying VOR in response to rotation in the dark. Because

previous studies have demonstrated marked asymmetry in gain characterized by diminished responses to rotations that would be excitatory for the lesioned side (e.g., guinea pig: Smith and Curthoys 1988a,b; Vibert et al. 1993; monkey: Lasker et al. 2000; Sadeghi et al. 2006; human: Allum et al. 1988; Crane and Demer 1998; Curthoys and Halmagyi 1995), analysis was performed separately for movements directed toward the lesioned side (ipsilesional) versus the nonlesioned side (contralesional).

Figure 3A shows examples of a *WT* VORd response 1 day after lesion. Note the pronounced asymmetry between the response gains evoked by ipsilesionally versus contralesionally directed rotations (*A1* at 0.5 Hz; *A2* at 2 Hz). In response to ipsilesionally directed rotations, VORd gains were significantly reduced at all tested frequencies ($P < 0.01$). Gain values were as low as 0.04 ± 0.04 at 0.2 Hz and a maximum of 0.07 ± 0.06 at 3 Hz (Fig. 3*B1*). In contrast, while contralesional VORd gains were also significantly reduced at all tested frequencies ($P < 0.05$), the amount of attenuation was less than that observed for the VOR evoked by ipsilesional rotations ($P < 0.01$). Gain values were as low as 0.4 ± 0.07 at 0.2 Hz and reached a maximum of 0.69 ± 0.07 at 4 Hz. The phases of both the ipsi- and contralesional responses increased with

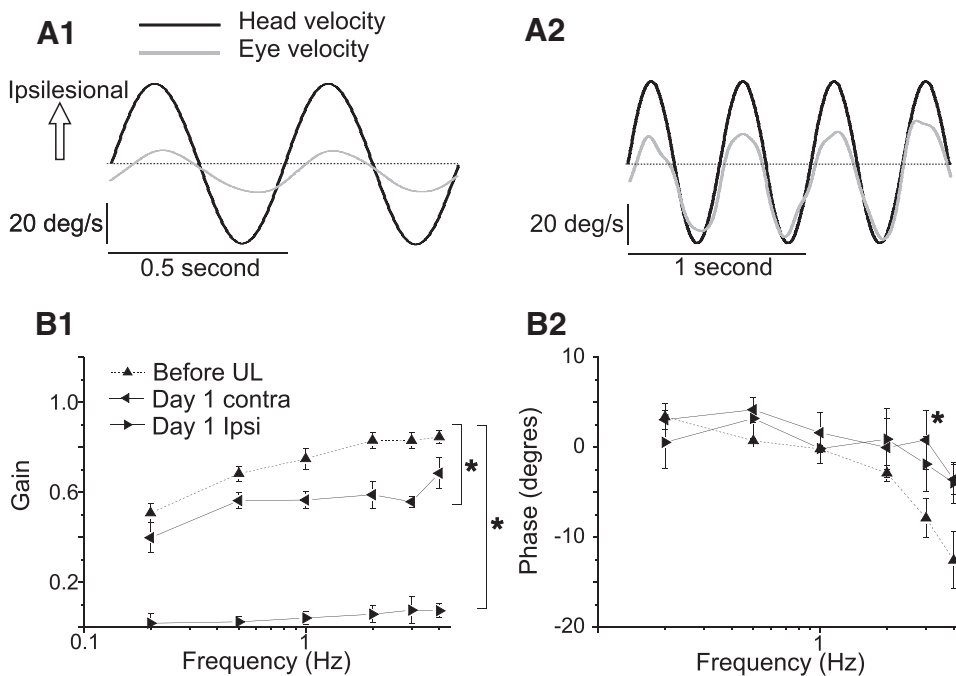


FIG. 3. VOR evoked by sinusoidal rotations in wild-type mice 1 day after unilateral labyrinthectomy. *A*: example eye and head velocity traces, during sinusoidal rotations of the head-on-body in the dark for a *WT* mouse 1 day after lesion. An asymmetry between ipsi- and contralesionally directed responses is more evident at higher frequencies of rotations [compare *A1* (0.5 Hz) and *A2* (2 Hz)]. *B*: gain (1) and phase (2) plots of responses to 0.2- to 4-Hz rotations averaged across the group of *WT* mice. Note that ipsilesional responses are virtually absent and that contralesional as well as ipsilesional gains were significantly reduced compared with control. *, values are significantly different from prelesion values ($P < 0.05$).

increasing frequencies and were generally not significantly different from those recorded prior to the lesion (Fig. 3*B2*). An exception was that the phase lags of the responses evoked by rotations at 3 and 4 Hz were less for both directions of rotation after labyrinthectomy as compared with before ($P = 0.041$ and $P = 0.043$, respectively).

Five days following lesion, the VOR evoked by ipsilesionally directed rotations in *WT* mice remained significantly impaired at all frequencies compared with control values ($P < 0.001$), improving to only 0.26 ± 0.06 at 0.2 Hz and 0.35 ± 0.08 at 4 Hz (Fig. 4*A1*). Response phase remained normal at all frequencies with one exception; there was a slight increase in lag at 0.5 Hz ($P < 0.05$). In contrast, the gain of the response evoked by contralesionally directed rotations (Fig. 4*A2*) returned to normal values for all frequencies of stimulation ($P > 0.1$). Response phase was also generally normal with the exception of small increases in lag that were seen at the highest frequencies tested (3 and 4 Hz, $P = 0.05$ and $P = 0.028$, respectively).

Ten days following lesion, the gain of the *WT* response to ipsilesionally directed rotations returned to prelesion values for all lower frequencies < 1 Hz ($P > 0.15$), but VORd gains were still abnormally reduced at higher frequencies (2–4 Hz, $P < 0.05$). Similarly, at day 20 (Fig. 4*B1*), ipsilesional response gains appeared slightly reduced; however, the difference relative to control values was significant only at 4 Hz ($P = 0.017$). In contrast, contralesionally directed movements produced a VORd response with normal gain for rotations at all frequencies by day 10, which remained stable up to day 20. Finally, response phase also returned to normal for both ipsi- and contralesionally directed rotations by day 10 ($P > 0.2$).

In summary, for *WT* animals the recovery of the reflex is achieved as soon as 5 days after the lesion for contralesionally directed movements. In contrast, responses for the higher frequencies of stimulation (> 1 Hz) still do not reach normal values by day 10 for ipsilesionally directed movements. However, 3 wk after the lesion, the recovery of VORd can be

considered to be complete for frequencies < 3 Hz regardless of the direction of the head movement.

Time course of compensation in *Lc/+* mice

Immediately following labyrinthectomy, both ipsi- and contralesional responses were comparable in *Lc/+* and *WT* mice. No significant differences were observed in response gains or phases for the range of frequencies that were tested ($P > 0.1$). Moreover, substantial recovery was observed in *Lc/+* mice at all frequencies within the first 5 days. Notably, these responses were also comparable to those of *WT* mice in the same recovery period ($P > 0.2$; Fig. 4*A*, 1 and 2, ipsi- and contralesional responses, respectively). In response to ipsilesionally directed rotations, VOR gain increased from 0.19 ± 0.02 on day 1 to 0.39 ± 0.02 on day 5 (Fig. 4*A1*). Similarly, for contralesionally directed rotations, VOR gain increased from 0.57 ± 0.02 on day 1 to 0.72 ± 0.03 on day 5 (Fig. 4*A2*). Response phases were also comparable in *Lc/+* and *WT* mice during the first 5 days following labyrinthectomy (data not shown).

After this initial recovery period, however, we observed marked differences in the time course of improvement for *WT* versus *Lc/+* mice. Figure 4, *A1* and *B1* and *A2* and *B2* show the difference in the course of the recovery that was seen for *Lc/+* mice compared with *WT* animals for ipsi- and contralesional rotations, respectively. In particular, *Lc/+* animals showed little improvement during the next 2 wk, such that responses observed at day 20 (Fig. 4, *A2* and *B2*) were comparable to those measured on day 5 (Fig. 4, *A1* and *B1*). For ipsilesionally directed rotations, no significant improvements were observed in response gains between days 5 and 10 (ranging from 0.3 ± 0.03 at 0.2 Hz and 0.49 ± 0.04 at 3 Hz; $P > 0.125$ at all frequencies). Between days 10 and 20, ipsilesional response gains still remained unchanged ($P > 0.2$) across the frequency range tested. Consequently, by day 10 response gains were significantly larger in *WT* than in *Lc/+* mice during ipsilesionally directed movements ($P < 0.05$ at all frequencies for days

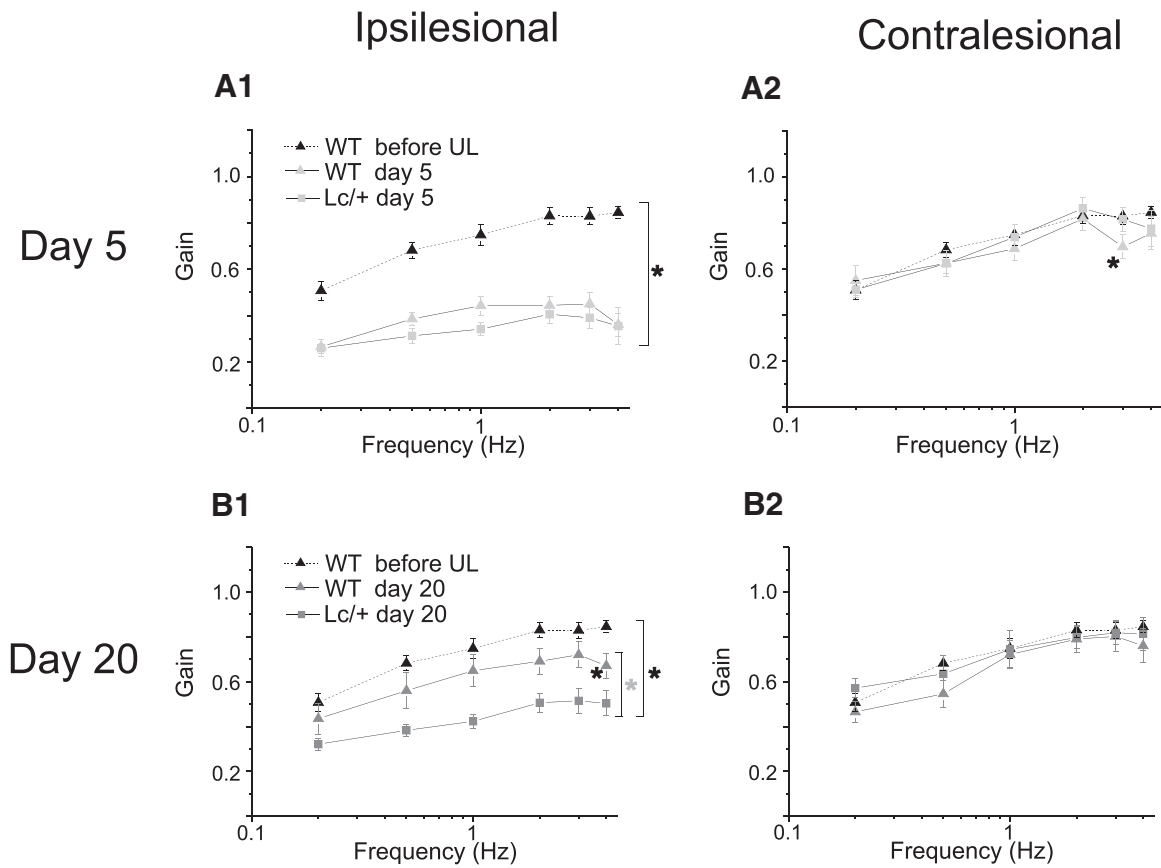


FIG. 4. Time course of VOR compensation for wild-type vs. lurcher mice: sinusoidal rotations. *A*: gain plots of the VOR response evoked 5 days after lesion by 0.2- to 4-Hz rotations. The response gains evoked by both ipsilesionally (*A1*) and contralesionally (*A2*) directed rotations are comparable for *WT* and *Lc/+* mice. Also note that in both strains, the gain of the VOR evoked by contralesionally directed movements is comparable to prelesion values. *B*: gain plots of the VOR response evoked 20 days after the lesion for ipsilesionally (*B1*) and contralesionally (*B2*) directed movements. While the response of *WT* animals showed additional recovery (relative to day 5), *Lc/+* gains showed no significant improvement. Significant differences compared with prelesion values (black asterisk) and between lesioned *WT* and *Lc/+* values (gray asterisk) are indicated.

10 and 20, Fig. 4*B1*). In contrast for contralesionally directed movements, because recovery in *Lc/+* mice followed the same course as in *WT* mice for the first 5 days and because in *WT* mice recovery was nearly complete in this period, there was no significant reduction in the contralesional response gains measured in *Lc/+* mice at day 10 or 20 following labyrinthectomy as compared with prelesion values ($P > 0.3$, Fig. 4*B2*).

Responses abrupt impulses after lesion in *WT* versus *Lc/+* mice

The gain of the VOR evoked in response to the transient head perturbation described in the preceding text (Fig. 2*C1*) was also measured following labyrinthectomy. Figure 5*A*, 1 and 2, shows examples of the VOR response of a wild-type mouse 1 day following labyrinthectomy for ipsi- and contralesionally directed rotations, respectively. Head movement stimuli were applied in the dark (black line represents inverted head velocity) and the evoked eye velocity (gray lines) was measured. While control animals produced compensatory eye movements with gains approaching unity in response to this stimulus (i.e., Fig. 2*C1*), ipsilesional responses of both *WT* and *Lc/+* mice never fully recovered after lesion (Fig. 5*B1*). Immediately (day 1–5) following labyrinthectomy, ipsilesional response gains showed dramatic reductions that were comparable for *WT* and *Lc/+* mice. Between days 5 and 20, however, response gains of *WT* mice showed continued im-

provement, reaching values of 0.72 ± 0.07 on day 20. In contrast, recovery of the response gain was limited in *Lc/+* mice; VOR recovery plateaued at a gain of ~ 0.4 (0.43 ± 0.05) and notably showed no improvement between days 5 and 20. As a result, response gains for ipsilesionally directed rotations were substantially greater for *WT* than *Lc/+* mice by day 20 ($P = 0.005$). Importantly, however, the VOR of *WT* mice did not show complete recovery; gains remained significantly lower than control values ($P = 0.013$). This result is in agreement with prior work showing that recovery of VOR gain is limited for more challenging stimuli even when well within the range of natural head movements.

In contrast to the results obtained for ipsilesionally directed rotations, we found that recovery was similar in both strains for contralesionally directed impulses. Moreover as we reported above for our analysis of contralesional sinusoidal stimuli, the recovery of responses evoked by contralesionally directed rotations followed a similar course for *WT* and *Lc/+* mice. Response gains were comparable to normal values within 5 and 10 days following the lesion for *Lc/+* and *WT* mice, respectively.

Summary of the vestibular compensation: *WT* versus *Lc/+* mice

To facilitate comparison of the relative recovery in both strains of mice across time, we normalized the VOR gain

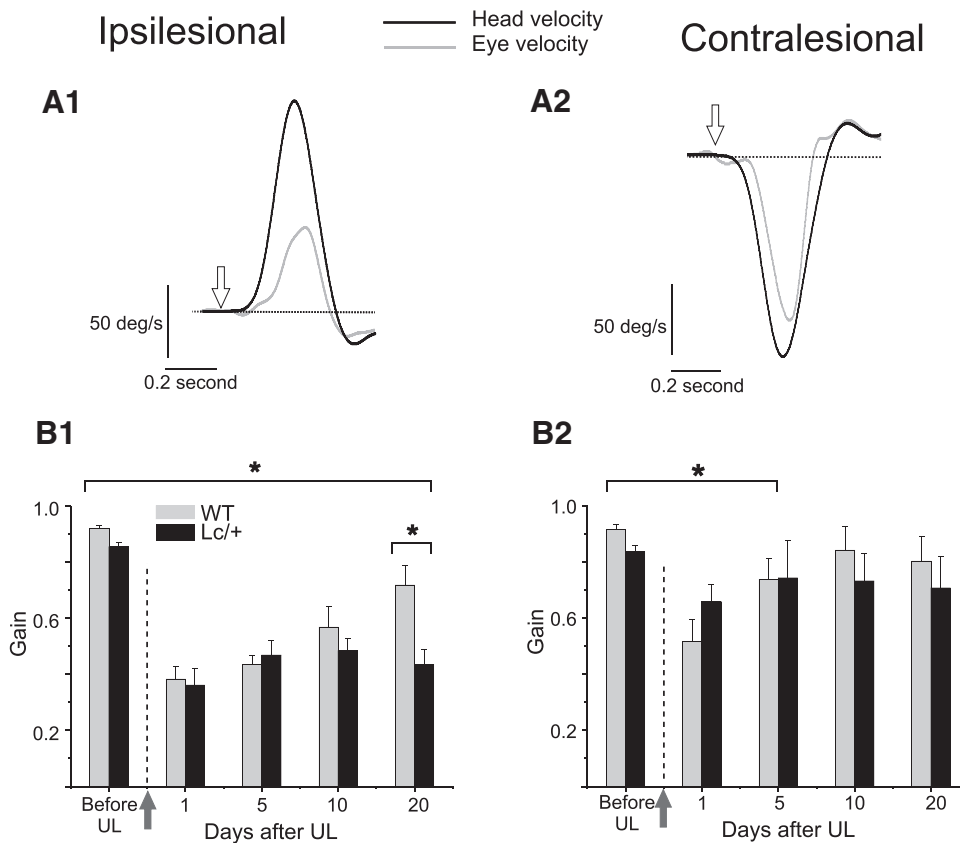


FIG. 5. Time course of VOR compensation for wild-type vs. lurcher mice: transient stimulation. *A*: example of a *WT* mouse's response to a transient rotation applied in the dark 1 day after lesion. *A*, 1 and 2: the VOR evoked by ipsi- and contralesionally directed rotations, respectively. *B*: time course of the mean VOR gain measured in *WT* vs. *Lc/+* mice before and after lesion. Gains are shown for ipsilesionally (*B1*) and contralesionally (*B2*) directed abrupt impulses. While response recovery in both strains was comparable for contralesionally directed rotations, responses to ipsilesionally directed rotations plateaued around day 5 for *Lc/+* mice. In contrast to responses evoked by sinusoidal stimulation, responses to ipsilesionally directed transients remained significantly reduced relative to prelesion values for both *WT* and *Lc/+* mice—even 3 wk after lesion. Significant differences ($P < 0.05$) are denoted by asterisk.

relative to prelesion values for sinusoidal rotations (at 0.5 and 4 Hz) and for impulses (Fig. 6). In *WT* mice, the time course of recovery was comparable for the different stimuli tested, and so an average estimate of percentage of VOR recovery was computed for each time point tested before and after lesion. Open symbols show the time course of recovery for ipsilesionally (Fig. 6A) versus (Fig. 6B) contralesionally directed move-

ments, respectively, in wild-type mice. Data for *Lc/+* mice following labyrinthectomy are superimposed (filled symbols). Note, the percentage recovery is shown for each stimulus (i.e., 0.5- and 4-Hz sinusoidal rotations and impulses).

Notably, in *WT* mice, most of the VOR recovery was achieved by day 10 such that ~80% of prelesion gain was restored for ipsilesionally directed movements and ~100% for

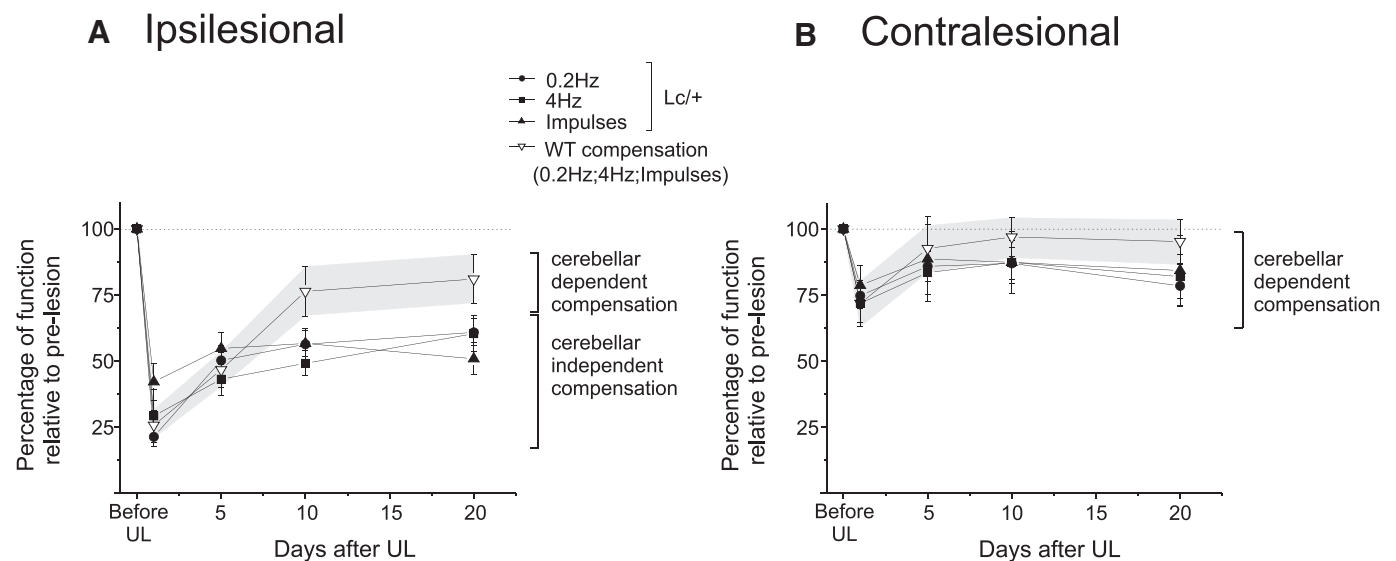


FIG. 6. Summary of the recovery: wild-type vs. Lurcher mice. Time course of percentage recovery of the VOR evoked by ipsilesionally (*A*) and contralesionally (*B*) directed rotations for *WT* (open symbols) vs. *Lc/+* mice (closed symbols). For *Lc/+* mice, average values are shown for testing using low (circles, 0.2 Hz) and higher (squares, 4 Hz) frequency sinusoidal stimulation as well as using transient impulses (triangles). Response gains were normalized to prelesion during each condition to compute the percentage recovery. For *WT* mice, mean response gains were computed across paradigms (see text). The shaded areas represent the SE across the values measured values at days 1, 5, 10 and 20.

contralesionally directed movements. As was the case for *WT* mice, the time course of recovery did not vary across stimuli. Moreover, recovery in *Lc/+* mice followed the same time course as that of *WT* for the 5 first days but then plateaued in response to ipsilesionally directed movements, remaining at <60% of prelesion values. In contrast, *Lc/+* responses to contralesionally directed rotations showed up to ~80% recovery such that relative improvement was comparable to that observed for *WT* mice. Overall, the similarity in the initial time course of recovery in both strains of mice suggests that cerebellar-independent mechanisms might support the initial recovery of VOR for ipsilesionally directed movements in *WT* as well as *Lc/+* mice.

DISCUSSION

In this study, we compared the vestibular compensation process in *WT* mice and a strain of mutant mice that completely lack cerebellar Purkinje cells (*Lc/+*). Sinusoidal and transient rotations were applied to characterize responses over the range of head movements made during natural exploratory behaviors. We found that while the VOR generated by intact *WT* and *Lc/+* mice was similar, recovery following labyrinthectomy was compromised in *Lc/+* mice. Notably, while cerebellar-deficient mice showed nearly normal improvement during the first week postlesion, their recovery was minimal after this interval. The initial recovery followed a similar course for *WT* and *Lc/+* groups during the first week postlesion; by day 5, VOR gains for ipsilesional rotations improved by 50%, and responses to contralesional rotations approached control values in both strains. However, while in *WT* animals VOR responses returned to almost normal values by day 20, recovery in *Lc/+*'s plateaued such that it remained significantly impaired for ipsilesional rotations. Our findings suggest that cerebellar pathways are critical for the long-term restoration of VOR during head movements directed toward the lesioned side, while noncerebellar pathways are sufficient to restore proper gaze stabilization during contralesionally directed head movements in cerebellar-deficient mice.

Compensation in normal WT mice: comparison with other species

Despite its growing importance as an animal model, there are still many open questions regarding the time course and dynamics of vestibular compensation process in the mouse. Here we characterized the VOR evoked by sinusoidal and transient stimuli in mice after unilateral labyrinthectomy. As in other vertebrates the disappearance of static signs largely took place during the first week after the lesion (for review, see Smith and Curthoys 1989). We found that the ocular nystagmus recovered to control levels by ~day 5 after lesion, whereas head tilt resolved within the first 10 days. We also quantified, for the first time, the asymmetry of the VOR evoked in mice after labyrinthectomy. VOR gains were bilaterally depressed immediately following the lesion, and this decrease was particularly marked for ipsilesionally directed movements. Notably, ipsilesional gains were reduced by nearly 75% on day 1, and never fully recovered (gerbil: Shinder et al. 2005; guinea pig: Vibert et al. 1993). Thus responses to ipsilaterally directed rotations in mice—as in other rodents (guinea pig: Vibert et al.

1993; Gilchrist et al. 1998; gerbil: Shinder et al. 2005)—are initially much lower when compared with nonrodent species (monkey: Fetter and Zee 1988; Lasker et al. 1999, 2000; Paige 1983; Sadeghi et al. 2006). In contrast, contralesional responses were far less affected (~20% reduction on day 1), and the recovery of VOR was almost complete ~1 wk after the lesion.

Over the longer term, we found that normal mice recover ~80% of their response gain for ipsilaterally directed rotations and show close-to-normal response gains for contralesionally directed movements across all paradigms. Furthermore, when we applied rapid impulses to test response to more dynamically challenging stimuli, we found that recovery was limited for both contra- and ipsilesionally directed rotations as has been described in other species (e.g., cat: Maioli et al. 1983; guinea pig: Gilchrist et al. 1998; Vibert et al. 1993; humans: Galiana et al. 2001; Paige 1989; macaque monkey: Sadeghi et al. 2006; squirrel monkey: Paige 1983; Lasker et al. 2000).

Notably, we found improved gain of ~0.7 for responses to ipsilesionally directed whole-body impulses. While similar recovery has been reported in monkey (Sadeghi et al. 2006), where gains of up to ~0.6 were measured in response to comparable high-velocity perturbations, average responses to similar stimulation protocols in guinea pig remained relatively more impaired over time (ipsilesional gains of ~0.3) (Gilchrist et al. 1998). It is important to note, however, that the level of asymmetry varied across subjects in each of these studies (i.e., present study; Gilchrist et al. 1998; Sadeghi et al. 2006), suggesting that unilateral labyrinthectomy (UL) recovery in animals like humans (e.g., Della Santina et al. 2002) shows considerable inter-individual variability both in term of gains and over time. Recent work by Weber and colleagues (2008) provides insights into why some human subjects compensate better than others. In response to manually delivered head impulses, unilateral vestibular patients generate an increased frequency of small catch-up saccades (termed covert saccades), which are synergistic to the slow-phase performance. The increase in eye velocity seen in Fig. 5A1 that is evident ~200 ms after ipsilesional head acceleration could result from a form of saccadic substitution similar to that reported in human patients or alternatively a long-latency component of VOR adaptation similar to that which has been previously described in cats (Khater et al. 1993).

Comparison with other studies of Lc/+ mice before lesion

In agreement with the recent study of Faulstich and colleagues (2006), we found no differences in the VOR of *WT* and *Lc/+* animals when tested in the dark. This contrasts with prior studies that reported higher gains of VORd at lower frequency of stimulation in *Lc/+* compared with *WT* animals (Katoh et al. 2005; Van Alphen et al. 2002). Moreover, we confirmed that the responses of *Lc/+* mice, like *WT* animals, are more robust in the light than dark and that this difference in performance is more striking at lower frequencies of rotation (Faulstich et al. 2006; Van Alphen et al. 2002). Additionally, while we found no consistent differences between the VOR in the light of both strains prior to lesion, gains of *Lc/+* showed a general tendency to be lower than *WT* at low frequencies of stimulation and then higher when tested >1 Hz. Previous studies have shown that the abnormal gain and/or timing of the VOR in light

in *Lc/+* mice are primarily a consequence of an impaired optokinetic reflex (OKR) (Faulstich et al. 2006; Koekkek et al. 1997; Van Alphen et al. 2002; but see also Katoh et al. 2005). Accordingly, because our goal was to quantify differences in the recovery in the two strains, we focused on the improvement of the VOR gain in the dark following labyrinthectomy.

Compensation in WT versus cerebellar-deficient mice: acute stage

The influence of the cerebellum in the vestibular compensation process has traditionally been studied using sequential lesions of the cerebellum and of vestibular organs (e.g., Courjon et al. 1982; Haddad et al. 1977; Kim et al. 1997a,b; Kitahara et al. 1997, 1998, 2000). More recently, the role of the cerebellum in both acute and long-term compensation process has been further studied using cerebellar-deficient mutant mice (Faulstich et al. 2006; Funabiki et al. 1995; Kitahara et al. 1998; Murai et al. 2004). In the following text, we consider how our findings compare with and extend the results of previous investigations of vestibular compensation conducted in cerebellar-deficient mice.

STATIC SIGNS. We found that UL initially triggers similar static symptoms (i.e., spontaneous nystagmus and head tilt) in both *WT* and *Lc/+*. However, while *WT* animals recovered in ~1 wk, we observed that despite an initial improvement static symptoms persist in *Lc/+* animals. These results differ from previous studies that reported that in cerebellar deficient mice the spontaneous nystagmus was transiently exaggerated compared with *WT* animals ($\delta 2^{-/-}$; Kitahara et al. 1998b; *Lc/+*; Faulstich et al. 2006) but similarly disappeared in the next days.

It is possible that the observed difference in the severity and recovery of the static symptoms across studies is the result of differences in experimental approach. First, the surgical approach that was used to induce lesions in *WT* and *Lc/+* mice differed in our study and that of Faulstich et al. (2006). Faulstich and colleagues mechanically disrupted the semi-circular canals sensory epithelia but did not remove the cristae. The authors propose that this unilateral vestibular damage (UVD) should eliminate the ability of the sensory periphery to encode head movement while not completely abolishing the spontaneous firing of vestibular afferents. On the other hand, the more standard labyrinthectomy approach that we used here produced a complete and permanent silencing of vestibular afferents (Jensen 1983; Sirkin et al. 1984), thereby resulting in a functional deafferentation of central vestibular neurons. Because static deficits are largely due to the imbalance in the spontaneous firing rate of vestibular nuclei neurons located on each side of the brain stem (for review, see Dieringer 1995; Smith and Curthoys 1989), the persistence of these symptoms in the *Lc/+* suggests that the cerebellum plays a role in rebalancing the spontaneous discharge through the vestibular complex (see cellular mechanisms in the following text). This proposal is in agreement with the results of previous studies of vestibular compensation following lesions of the cerebellum (cat: Courjon et al. 1982; human: Furman et al. 1997). Further, in their study of the $\delta 2^{-/-}$ mutant, Kitahara et al. (1998b) recorded spontaneous nystagmus in light (rather than darkness as in this study). The authors noted that specific synaptic

changes at the level of the Purkinje cells of $\delta 2^{-/-}$ mutant mice (see also in the following text) could underlie the initially compromised behavioral performance; it is furthermore likely that after this period visual inputs reduced and masked the persistent ocular nystagmus.

VOR RESPONSES. We did not observe marked differences in the recovery of VOR in the dark for *WT* as compared with *Lc/+* mice in the first 5 days after lesion (Figs. 3A and 6). Moreover, during this interval, responses recovered to near normal values for contralesionally directed movements in both strains. This contrasts with findings of Faulstich et al. (2006), who did not observe significant recovery in *Lc/+* VOR during the first days following the lesion. Thus our results are more similar to those of Murai et al. (2004), who similarly reported a comparable improvement of VORd gains in both *WT* and cerebellar deficient $\delta 2^{-/-}$ strain in the first week postlesion. Differences in the experimental design of the Faulstich's study including the lesion approach (see preceding text), as well as in the method for recording eye movements (i.e., scleral search coils vs. video-oculography) may have contributed to the observed differences. In particular, because search coils can reduce the apparent VOR gains as compared with video-oculography (Stahl et al. 2000), its use may have reduced the ability to track the time course of VOR gain improvement during this early period.

Compensation in WT versus cerebellar-deficient mice: chronic stage

The present study is the first to have compared vestibular compensation in *WT* and *Lc/+* over a ~3-wk period to characterize the chronic as well as acute compensation processes. We found that after the initial period of ~10 days, during which animals showed recovery, the performance of *Lc/+* mice—unlike *WT* animals—did not improve. As a result, the VOR gain of *Lc/+* plateaued at ~60% for ipsilesionally directed movements, while *WT* recovered $\leq 80\%$ of intact responses. On the other hand for rotation toward the contralesional side, *Lc/+* recovery paralleled that of *WT* animals and was close to normal values by day 10.

The question arises: how do our findings compare with those of other recent investigations that have studied the chronic stage of compensation in cerebellar-impaired mice? On the one hand, Funabiki et al. (1995) made the qualitative observation that even by 1 mo after UL, the vestibulo-spinal reflex of $\delta 2^{-/-}$ mutant mice does not recover to the same level as in *WT* mice. This result suggests that the plateau in recovery we described here for the VOR in *Lc/+* mice can be extended to other vestibularly driven reflexes. On the other hand, the recovery of VORd gain after UL in these same mice was reported to be normal 1 mo after the lesion, albeit the time course of recovery during this period was slower than in *WT* mice (Murai et al. 2004). Our results differ in that we do find at the chronic stage significant differences between *WT* and cerebellar-deficient mice. One possible explanation for this difference is that gains for rotations toward the contra- or the ipsilesional side were not distinguished (Murai et al. 2004); this could have contributed to reducing the apparent differences between the two strains. Another explanation is likely to lie in the difference in the mutations that tested in each study;

because $\delta 2^{-/-}$ mice have defects in Purkinje cell synapse formation, their cerebellar function is impaired (Kashiwabuchi et al. 1995) rather than eliminated as it is in $Lc/+$ (Doughty et al. 2000; Vogel et al. 2007; Wullner et al. 1995; Zuo et al. 1997). There is solid evidence that there are differences in the way each mutation alters gaze control (i.e., VORl, VORd, and OKR) (Katoh et al. 2005; Yoshida et al. 2004) that likely relate to underlying changes in the brain stem as well as cerebellum. As shown in other strains (Faulstich et al. 2006), the differential efficiency of these various reflexes and particularly that of OKR in $Lc/+$ and $\delta 2^{-/-}$ (Katoh et al. 2005; Yoshida et al. 2004) could underlie the saturation of the VOR recovery in $Lc/+$ versus the complete recovery in $\delta 2^{-/-}$.

Finally, this is the first study to report the asymmetric nature of recovery of VOR for ipsilaterally versus contralesionally directed movements in labyrinthectomized *WT* and cerebellar-deficient mice. In *WT* mice, this asymmetry is likely due to the absence of vestibular input from the suppressed vestibular organs. In $Lc/+$ mice, the absence of the cerebellum did partially impair the ability of the ipsilesional deafferented neurons to compensate for the absence of the vestibular inputs. It is noteworthy that we found no significant difference in the amplitude or in the timing of the recovery of VOR during contralesionally directed movements, suggesting that the cerebellum is not required for the restoration of the function of the vestibular neurons located on the contralesional side in *WT* animals (Beraneck et al. 2004; Ris and Godaux 1998; Smith and Curthoys 1988b).

Influence of the cerebellum on the intrinsic cellular plasticity mediating compensation

Our findings show that the absence of a functional cerebellum influences the recovery of both static and dynamic symptoms. Recent studies that have focused on the cellular mechanisms that underlie VOR motor leaning and compensation may provide insight into the processes involved in the formation of long-term synaptic and cellular changes.

Unilateral lesions of the vestibular end organs induce Fos expression throughout the vestibulo-olivo-cerebellar pathway in rodents (Cirelli et al. 1993, 1996; Kaufmann et al. 1992, 1993, 1999; Kim et al. 1997a; Kitahara et al. 1997a; Li et al. 2001; Sato et al. 1997; Shinder et al. 2005), which suggests that the activation of cerebellum-related pathways is an initial event of vestibular compensation. Furthermore, studies that used sequential lesions of the flocculus and vestibular organs to characterize the compensation process have shown that the flocculus plays a critical role in the resolution of static symptoms and particularly in eliminating the spontaneous nystagmus (Courjon et al. 1982; Kim et al. 1997; Kitahara et al. 2000). It has been proposed (Kitahara et al. 2000) that during the early stage of compensation, the flocculus could help to rebalance spontaneous discharge in the vestibular complex by preferentially inhibiting the contralesional medial vestibular nucleus (MVN) neurons, thereby reducing their commissural inhibition to the deafferented ipsilesional MVN cells after UL (McKabe and Ryu 1969; see for review Kitahara et al. 1998a). This idea is consistent with the early resolution of the static symptoms we observed in *WT* but not in $Lc/+$ mice. After this initial recovery period, Purkinje cell modulation could function to drive the formation of long-term synaptic changes at the

level of the vestibular nuclei; for example changes in the strength of *N*-methyl-D-aspartate receptor activation could contribute to the long-term modifications of pathway efficacy that mediate vestibular compensation (Kim et al. 1997b; Kitahara et al. 1998a, 2000).

Our data show that the absence of cerebellar inputs in $Lc/+$ mice impairs but does not completely abolish recovery. This finding suggests that other inputs influence the VOR and/or commissural pathways to mediate the cerebellar-independent recovery that we observed (Fig. 6). Prior work has shown substantial changes in the intrinsic membrane properties of central vestibular neurons (Beraneck et al. 2003; 2004; Cameron and Dutia 1997, 1999; Darlington et al. 2002; Him and Dutia 2001; Ris et al. 2002; see Straka et al. 2005 for a review), and synaptic reorganization of the brain stem vestibular pathways (Goto et al. 2000–2002; Johnston et al. 2001; Vibert et al. 2000; Yamanaka et al. 2000; see Dieringer 2003) following UL. Notably, Johnston and colleagues (2002) have suggested that while the increase in intrinsic excitability that develops in ipsilesional MVN neurons during vestibular compensation is cerebellar dependent and depends on glucocorticoid activation, the simultaneous downregulation of functional efficacy of GABA receptors that also occurs after UL is not. While substantial changes in intrinsic membrane properties occur during the first week following the labyrinthectomy (Him and Dutia 2001; Ris et al. 2002), this postlesional plasticity has a longer time course leading to even more drastic changes one month after the lesion (Beraneck et al. 2003; Vibert et al. 1999). Accordingly, the plateau we observed after the end of the first week in $Lc/+$ recovery during ipsilesionally directed movements could be related to the absence of floccular-mediated plastic effects on the intrinsic membrane properties of these neurons.

Overall, our results agree with the proposal that the vestibular compensation process consists of independent cellular plastic mechanisms, which display different dependencies on cerebellar inputs (Johnston et al. 2002; see Paterson et al. 2006 for a review).

Influence of the loss of cerebellar and/or vestibular inputs on central pathways

There is accumulating evidence to suggest that alterations of major inputs (such as vestibular afferent) influence in *WT* mice the membrane properties of central vestibular neurons during various types of plasticity (e.g., adaptation of the VOR: Serafin et al. 1999; firing rate potentiation: Nelson et al. 2003, 2005; unilateral labyrinthectomy: Beraneck et al. 2003, 2004; Ris et al. 1995; for review, see Gittis and Du Lac 2006). The growing use of mutant strains therefore raises the question of the alteration of the physiological and plastic properties of central vestibular neurons. A recent study (Eugene et al. 2007) was conducted on a transgenic mouse strain with a null mutation of the *KCNE1* gene, encoding the Isk channel protein, which causes a complete loss of sensory hair cells in the inner ears soon after birth (Vetter et al. 1996; Vidal et al. 2004). While the intrinsic membrane and firing properties of neurons in the MVN of the *KCNE1*^{-/-} juvenile mouse were affected by the absence of vestibular inputs, in the adult mutant these properties were similar to normal. Similarly, studies in the MVN of mice lacking cerebellar inputs [i.e., the Purkinje

cell degeneration (PCD) mutant mouse], have led to comparable conclusions (Baurle et al. 1997). Despite the lack of inhibitory inputs normally provided by the cerebellum, spontaneous activity and evoked firing rates of VN neurons during rotation were comparable, albeit slightly decreased, compared with those of *WT* mice. Further work in the same PCD strain (Killian and Baker 2002) demonstrated that while the neural circuits that exclude the cerebellar cortex are capable of the signal processing necessary for head angular velocity estimation, these circuits saturate for velocities $>150^\circ/\text{s}$. Interestingly, this result mirrors the significant difference we observed in VOR performance for intact *WT* versus *Lc/+* mice in response to high-velocity steps (Fig. 2C2).

In view of these behavioral and electrophysiological results, it is tempting to speculate that the central vestibular neurons of *Lc/+* mice likely show close-to-normal excitability and resting discharge properties, thus allowing normal functioning of the VORd. In this mutant as in others, it nevertheless remains to be determined whether the compensatory mechanisms which “rescue” the physiology of central neurons despite the permanent lack of inputs (e.g., vestibular afferent or cerebellar) early in development affect the plastic capacities of these cells when an additional pathophysiological situation such as a labyrinthectomy occurs. Comparison of the membrane properties of central vestibular neurons in *Lc/+* and others mutant strains as well as assessment of their responses during protocols that induce plasticity (for review, see Gittis and Du Lac 2006) will be required to further address these questions.

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