Long-term deficits in motion detection thresholds and spike count variability after unilateral vestibular lesion

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Abstract

The vestibular system operates in a push-pull fashion using signals from both labyrinths and an intricate bilateral organization. Unilateral vestibular lesions cause well-characterized motor deficits that are partially compensated over time and whose neural correlates have been traced in the mean response modulation of vestibular nuclei cells. Here we compare both response gains and neural detection thresholds of vestibular nuclei and semicircular canal afferent neurons in intact vs. unilateral-lesioned macaques using three-dimensional rotation and translation stimuli. We found increased stimulus-driven spike count variability and detection thresholds in semicircular canal afferents, although mean responses were unchanged, after contralateral labyrinth lesion. Analysis of trial-by-trial spike count correlations of a limited number of simultaneously recorded pairs of canal afferents suggests increased noise correlations after lesion. In addition, we also found persistent, chronic deficits in rotation detection thresholds of vestibular nuclei neurons, which were larger in the ipsilesional than the contralesional brainstem. These deficits, which persisted several months after lesion, were due to lower rotational response gains, whereas spike count variability was similar in intact and lesioned animals. In contrast to persistent deficits in rotation threshold, translation detection thresholds were not different from those in intact animals. These findings suggest that, after compensation, a single labyrinth is sufficient to recover motion sensitivity and normal thresholds for the otolith, but not the semicircular canal, system.
Introduction

Unilateral vestibular lesions cause well-characterized postural and motor deficits (reviewed in Curthoys 2000; Dieringer 1995; Vibert et al. 1997). Unilateral labyrinthectomy, in particular, results in large ‘static’ symptoms, including spontaneous nystagmus with slow phase toward the lesioned side and static head tilt, both of which recover within a few days depending on the species (Darlington et al. 2002; de Waele et al. 1989; Newlands et al. 2005; Precht et al. 1966; Sadeghi et al. 2006; Sirkin et al. 1984; Smith and Curthoys 1989). Despite this initial fast recovery, substantial asymmetries in the high frequency rotational vestibulo-ocular reflex (rVOR) persist on the long term, and are more pronounced during rotations towards the lesion side in many animal species (Beraneck et al. 2008; Broussard et al. 1999; Crane and Demer 1998; Fetter and Zee 1988; Gilchrist et al. 1998; Halmagyi et al. 1990; Lasker et al. 2000; Newlands et al. 2005; Paige 1983; Sadeghi et al. 2006; Shinder et al. 2005; Vibert et al. 1993). Large deficits in the translational VOR (tVOR) were also reported several months post-lesion in non-human primates (Angelaki et al. 2000).

Neural correlates of rVOR deficits and compensation have been found in the vestibular nuclei (VN), an area that receives direct vestibular afferent inputs and projects to both vestibulo-ocular and thalamo-cortical systems (Marlinski and McCrea 2008; Meng et al. 2007; Uchino and Kushiro 2011). In macaques, yaw rotation response gains of type I neurons (i.e., cells with firing rate increases during ipsilateral rotation) in the contralesional VN show nearly complete recovery one month post-lesion (Newlands and Wei 2013; Newlands et al. 2014; Sadeghi et al. 2011), much faster and more completely than in anesthetized or decerebrate animals (Newlands and Perachio 1990a; Smith and Curthoys 1988a; b).

Despite this wealth of interest in vestibular compensation from unilateral peripheral damage, our knowledge remains incomplete for multiple reasons. First, studies after unilateral labyrinthectomy have nearly exclusively used yaw rotations only. VN neurons, however, respond to rotations in three-dimensions (3D). Thus, there is currently no data on 3D rotational gain recovery. Second, neural compensation in the otolith system has typically been tested in anesthetized animals (Chan 1997; Chan et al. 1999; Hoshino and Pompeiano 1977; Lacour et al. 1985; Xerri et al. 1983), and little is currently known about central recovery of otolith pathways in alert animals (Newlands et al. 2014). Third, few previous studies quantified neuronal variability in addition to mean responses, and those that did only measured thresholds for a short time after labyrinthectomy (Liu et al. 2013b; Jamali et al. 2014; Newlands et al. 2014). As a result, no information is currently available on whether spike count variability and neuronal thresholds are compensated fully following long-term recovery from unilateral vestibular damage.

Bilateral interactions are not only limited to the vestibular nuclei. Communication between the two labyrinths through the efferent system has been clearly demonstrated in birds, where mechanical stimulation of the horizontal canal on one ear affected afferent activity on the other side (Dickman and Correia 1993) and a role of the vestibular efferent system in long-term modulation of afferent responses has also been suggested. Thus, it was perhaps surprising that semicircular canal afferents in the intact nerve showed no change in response gain, phase, resting discharge and dynamic
range, as well as other mean response properties following unilateral labyrinthectomy (Sadeghi et al. 2007b). The only significant change was an increase in the proportion of irregular afferents post-lesion, although lesion-induced changes in the spike count variability of vestibular afferent responses were not examined (Sadeghi et al. 2007b).

Here we have measured spike count variability and direction detection thresholds of horizontal, anterior and posterior semicircular canal afferents, as well as VN neurons, in both intact and compensated unilaterally labyrinthectomized macaques. We found higher afferent neural rotation thresholds in labyrinthectomized animals and this difference was traced down to increased trial-by-trial variability, whereas afferent mean response properties remained unchanged after contralateral vestibular lesion. In addition, we report persistent, chronic deficits in rotation detection thresholds of VN neurons during both ipsilesional and contralesional rotations. In contrast, translation thresholds of VN neurons recovered completely to normal values, suggesting that a single labyrinth is sufficient to generate highest sensitivity for the otolith, but not the semicircular canal, system.

Methods

Three-dimensional rotations were delivered using a six-degree-of-freedom motion platform (Moog 6DOF2000E) that was controlled using an Ethernet interface (60Hz). Data were collected from 5 labyrinth-intact male rhesus monkeys (Macaca mulatta), which were chronically implanted with a plastic head-restraint ring and a guide tube platform, as described in detail in previous publications (Gu et al. 2006; Meng et al. 2005; Dickman and Angelaki, 1999). One of these animals, plus a sixth macaque, were subjected to unilateral labyrinthectomy (animals C and W, right and left side, respectively; same animals as in Liu et al. 2013b). Additionally, a scleral search coil was implanted for monitoring eye movements (for details see: Gu et al. 2006; Meng et al. 2007). All surgical procedures were performed under sterile conditions and approved by the Institutional Animal Care and Use Committees at Washington University School of Medicine and Baylor College of Medicine in accordance with the National Institutes of Health and Institutional guidelines.

Canal afferent responses were collected over a period of 5 to 8 months after the vestibular lesion. We recorded extracellular neural activity from 238 canal afferents from labyrinth-intact monkeys (intact, IN; animal K: n=91; animal H: n=60; animal C: n=87) and 161 canal afferents from the contralateral nerve after unilateral labyrinthectomy (LB; animal C: n=56; animal W: n=105) using high impedance, epoxy-coated tungsten microelectrodes (FHC, Bowdoinham, ME). The vestibular nerve was isolated beneath the auditory meatus as it entered the brain, often in close proximity to the cochlear nucleus (see Haque et al. 2004; Yu et al. 2012).

The vestibular nuclei were identified using the abducens nuclei with their characteristic firing patterns during eye movements as a landmark (Klier et al. 2006). VN penetrations were then concentrated 1–5 mm posterior and 0–3 mm lateral to the abducens nucleus. Vestibular nuclei responses were collected over a period of 3 to 25 months after the labyrinthectomy (animal C: n=32 cells; animal W: n=34 cells). These responses are compared with data from 43 cells from the labyrinth-intact macaques (animal K: n=7; animal S: n=19; animal T: n=17).
Electrodes were inserted into 26-gauge transdural guide tubes and advanced by a remote-controlled microdrive (FHC, Bowdoinham, ME). Raw neural activity was amplified, filtered and passed through a dual time-amplitude window discriminator (BAK Electronics). The spike train of each recorded cell was analyzed off-line. Single units were identified based on waveform shape, latency, and amplitude. Only well isolated neurons were included for further analyses.

Each VN neuron was first tested for eye movement related activity. Responses during pursuit of a target moving in the four cardinal directions: up, down, left and right (Gaussian velocity profile, 9° amplitude and 2 sec duration) were used to determine if a cell had significant eye movement related tuning (P<0.05, one-way ANOVA). Only VN cells without eye movement related activity (“vestibular-only” cells) were used for further testing and analysis. All afferent and VN data were collected in darkness and animals were always sitting upright relative to the motion platform and gravity, with the horizontal stereotaxic plane earth-horizontal. In this position, yaw rotation activates primarily (but not exclusively; e.g., Fig. 1, top) the horizontal semicircular canals (Haque et al. 2004). Upon isolation, the following stimuli were delivered:

1. **Classification (CLA) protocol**: The spontaneous activity with the animal upright and stationary was recorded first. Next, cells were tested with a “classification protocol” to determine their preferred directions (PD): Sinusoidal stimuli (0.5 Hz, 9-10 cycles, lasting ~20s) were delivered in three directions of rotation roughly aligned with the three semicircular canal axes (yaw, right-anterior/left-posterior (RALP) and left-anterior/right posterior (LARP), 22º/s peak amplitude) and in the three orthogonal directions of translation: lateral (LR, 0.1 G), naso-occipital (NO; 0.1 G) and dorso-ventral (DV, 0.07 G). All 3 motion directions were successfully tested in 152 IN and 125 LB well-isolated canal afferent fibers and 42 IN and 64 LB (rotation) vs. 35 IN and 50 LB (translation) VN cells.

2. **Variable-magnitude (VMAG) rotations**: For canal-responsive cells (both canal afferents and VN neurons), the main experimental protocol consisted of 0.5 Hz sinusoidal rotations about the preferred direction of each canal afferent. A block of VMAG consisted of ~20s of spontaneous activity (0º/s amplitude) and 9 cycles of each of 6 different peak amplitudes (0.5º/s, 1º/s, 2º/s, 4º/s, 7.8º/s and 15.6º/s), randomly interleaved, lasting ~3 min in total. By comparing peak and trough responses to these different amplitude stimuli we could measure the smallest amplitude for which an ideal observer could discriminate the two rotation directions based on the firing rate of the particular neuron. All canal afferents included in the VMAG analysis (117 IN and 95 LB) were tested for at least 2 blocks (i.e., a minimum of 18 cycles for each rotation amplitude; lasting ~ 6 min), the majority of neurons (60.4%) had 4 blocks (~12 min) and 8.5% had 5 blocks (~16 min). In a small subgroup of these recordings (n=3), two semicircular canal afferents were simultaneously recorded for a minimum of 2 blocks.

For translation-responsive VN cells, translation detection thresholds were measured from responses to 0.005, 0.01, 0.02, 0.04, 0.08 and 0.16 G sinusoids (1 Hz) delivered along one or more of the same three directions as in the classification protocol. The order in which the 6 different sets of stimuli (3D rotation and 3D translation) were delivered for VN cells was based on the outcome of the classification protocol: the stimulus direction for which the cell was most responsive was tested first, the second-most responsive direction was recorded second, and so forth. If cell
isolation was lost before the end of the entire protocol, only some of the 6 cardinal
directions were included in the analysis. Note that we did not record from otolith
afferents after LB. Otolith afferent 3D thresholds in labyrinth-intact animals using an
identical experimental protocol have been presented in Yu et al. (2012).

(3) 3D tuning protocol: 11 pairs of canal afferents were also recorded
simultaneously during a 3D tuning protocol, which consisted of transient rotations about
26 axes (that included pitch, yaw and roll), evenly spaced on a sphere (Chen et al.
2010; Takahashi et al. 2007). The stimulus trajectory followed a Gaussian velocity
profile with a duration of 2s, peak rotation amplitude was 9° and peak angular velocity
was ~20°/s. Five repetitions of each stimulus direction was tested (lasting ~ 9 min). The
3D tuning data, along with the pair recordings during the VMAG protocol, was used to
measure interneuronal correlations (see below). Note that this analysis was not
performed for VN neurons because VN interneuronal correlations have been previously
measured and reported (Liu et al. 2013a).

Data analysis (canal afferents): To classify canal afferents based on discharge
regularity, the distribution of interspike intervals (ISIs) recorded during spontaneous
activity was used to compute the coefficient of variation (CV), CV=$\sigma_{\text{ISI}}/\mu_{\text{ISI}}$, where
$\sigma_{\text{ISI}}$ and $\mu_{\text{ISI}}$ were the SD and mean of the ISI distribution, respectively. Because CV varies
with the mean ISI, we used a normalized CV* to classify vestibular afferents (Goldberg
et al. 1990a; b; Goldberg et al. 1984). In line with previous studies, neurons with
CV*<0.10 were classified as ‘regular’ firing, whereas those with a CV*>0.10 were
classified as ‘irregular’ canal afferents.

Sinusoidal responses during the 0.5 Hz oscillations about the yaw, LARP and
RALP axes (CLA protocol) were first quantified using instantaneous firing rate (IFR),
computed as the inverse of the interspike interval and assigned to the middle of the
interspike interval (Fig. 1; each dot corresponds to one IFR value). We then stacked
responses to repeated stimulus cycles into a single IFR cycle. Gain and phase were
then calculated by fitting both neural response (clipped off at zero firing rate) and
stimulus with a sine function (first and second harmonics and DC offset) using a
nonlinear least-squares algorithm (Levenberg-Marquardt method). Response amplitude
was then measured to be half the peak-to-trough first harmonic modulation of the
sinusoidal fit. Neural gain was computed as the ratio of response modulation amplitude
over the stimulus velocity amplitude (in units of spikes/s/°/s). These gain values along
the 3 orthogonal directions were subsequently used to compute the 3D preferred
direction (PD) and the response gain along the PD based on a cosine-model for
response tuning (Fernandez and Goldberg 1971; Goldberg and Fernandez 1971b).

To measure direction detection thresholds (i.e., the sensitivity of individual
neurons to detect the direction of sinusoidal rotation), we compared distributions of firing
rate (across multiple cycles of the VMAG protocol) for each trough and peak of
response modulation about the preferred direction of each cell; that is, yaw, RALP and
LARP axis for horizontal, right anterior or left posterior and left anterior or right posterior
canal afferents, respectively. The timing of response peak and trough (as response
phase is generally non-zero) was computed by shifting the time of each zero-crossing of
the stimulus according to the phase of the measured neural response using the phase
estimated from the sinusoidal fit. Thus, for each cycle, we computed firing rate (spike
count) within two temporal windows of 500 ms, each centered on trough and peak, that
corresponded to opposite stimulus directions. Distributions of peaks and troughs for each stimulus amplitude were then subjected to ROC analysis to compute discriminability and construct neurometric functions (Gu et al. 2008; Gu et al. 2007; Yu et al. 2012). These neurometric functions were then fit with cumulative Gaussian functions, and neural threshold was defined as the standard deviation of the Gaussian (corresponding to 84% correct performance). These same data were also used to measure amplitude tuning slope and response (spike count) variability.

To illustrate that the actual threshold and variance measured depend on how neural firing rates are computed, we varied the width of the temporal window during which spike counts were measured at peak and trough. In addition, for comparison with a previous study (Sadeghi et al. 2007a), we also computed thresholds and variance after firing rate was converted into a continuous function using a low-pass filter with a Kaiser window and cutoff frequency greater than the stimulus frequency by 0.1 Hz (Sadeghi et al. 2007b; Fig. 1, gray lines). Using the Kaiser-filtered data, we also computed response variance using the smaller number of cycles of the CLA experimental protocol. Because only a single rotation amplitude was used for CLA, we computed firing rate distributions by binning each response cycle into bins of 1°/s, after shifting the time of each zero-crossing of the stimulus according to the phase of the measured neural response. These distributions were then used to compute response variability (defined as ‘CLA variance’), which was subsequently compared on a cell-by-cell basis with the VMAG variance for 97 IN and 82 LB canal afferents for which both data sets were available. Notice that, whereas response variance from the VMAG protocol was computed from data collected in a time frame of several minutes (6-18 min), CLA variance was measured using data collected within the time frame of no more than 20s.

Data analysis (VN neurons): For the VN data, detection thresholds were only measured for stimulus directions for which the cell showed significant modulation. This was determined using a permutation analysis, which was thus applied to firing rates during each of the 6 cardinal stimulus directions tested under the CLA protocol. For this, IFR responses were binned into 40 bins per cycle and a Fourier ratio (FR) was defined as the fundamental frequency divided by the maximum of any of the first 20 harmonics. Then the 40 bins were shuffled randomly to remove any modulation and a FR was calculated again. This randomization process was repeated 1000 times and if the original FR was higher than the FRs of the 99% of the permuted data, the modulation was considered to be significant (P < 0.01). If a cell responded significantly to one or more directions of rotation or one or more directions of translation (but not to eye pursuit), the cell was used for further analysis. To calculate the cell’s rotational and translational preferred directions (PD), responses during the classification protocol were quantified by measuring the gain and phase for each of the three rotational directions and each of the three translational directions, as long as at least one of the 3 cardinal directions passed the permutation significance test. Gain and phase were computed by superimposing the instantaneous firing rates of each cycle (similarly as for vestibular afferents), and fitting the stacked IFR data with a sinusoidal function (Meng et al. 2005; Yu et al. 2012). We then used a spatiotemporal cosine-like model to compute 3D PD and gain (Angelaki, 1991, 1992; Schor and Angelaki, 1992). Direction detection thresholds for rotation were measured in VN neurons using the VMAG protocol in an
identical analysis as the canal afferents. However, direction detection thresholds for translation were analyzed using 250 ms windows to ensure the window size was kept constant relative to the cycle duration (¼ of a cycle).

Interneuronal ('noise') correlation analysis: To analyze trial-by-trial correlations between firing rates of simultaneously recorded canal afferents, we searched for pairs of well isolated single units from the same electrode during the VMAG and/or 3D tuning protocol using spike sorting software. Such canal-canal cell pairs could be extracted from 5 recordings from intact animals and from 9 recordings from labyrinthectomized animals. Interneuronal correlation was computed as the Pearson correlation coefficient (ranging between -1 and 1) of the normalized trial-by-trial responses from the spike counts during the 400ms centered around peak and trough (sinusoidal protocols) or the middle 400ms of the stimulus duration (3D tuning protocol) (Bair et al. 2001; Gu et al. 2011; Zohary et al. 1994). Because rotation direction and/or stimulus amplitude was varied across trials, spike counts from individual trials were z-scored to remove the stimulus effect and to allow pooling of data across different stimuli. Thus, the measured correlation reflected only trial-to-trial variability. We then pooled data across different stimuli to compute one correlation value; the corresponding p-value was used to assess the significance of correlation for each pair of neurons.

Results

Semicircular canal afferents: Basic response characteristics and comparison of mean responses

We recorded from 238 canal afferents bilaterally in intact (IN) animals and 161 canal afferents from the contralateral nerve in animals with one labyrinth surgically ablated (LB). Each fiber was first characterized in terms of its spontaneous activity and its modulation during 0.5 Hz oscillations along three axes: Yaw, LARP, RALP (Fig. 1). The basic response properties of IN semicircular canal afferents were similar to those described in previous studies (Bronte-Stewart and Lisberger 1994; Goldberg and Fernandez 1971a; b; Haque et al. 2004; Ramachandran and Lisberger 2006; Sadeghi et al. 2007a; Sadeghi et al. 2006; 2007b). The average resting firing rate was 96.0±35.2 spikes/s and the yaw response gain of horizontal canal afferents averaged 0.40±0.19 spikes/s/º/s and 1.21±0.54 spikes/s/º/s for regular and irregular afferents, respectively. The preferred direction (PD) gain and phase were computed for both IN and LB canal afferents, with response properties summarized in Fig. 2 and 3. Both response gain and phase showed a strong dependence on discharge regularity, quantified by the normalized coefficient of variation, CV* (Goldberg et al. 1990a; b). The more irregular the fiber's firing rate, the higher its PD gain (Fig. 2A) and the larger the phase lead relative to rotational velocity (Fig. 2B). Both of these relationships were significant (PD gain vs. CV*: r=0.77, p<0.001; phase vs. CV*: r=0.84, p<0.001, type II regressions). At 0.5 Hz, the mean canal afferent PD gain was (geometric means and SD) 0.42±1.75 spikes/s/º/s and 1.35±1.51 spikes/s/º/s for regular and irregular fibers, respectively (Fig. 2A, black symbols and bars). The average phase leads for regular and irregular afferents were 10.0±6.1º and 27.2±9.2º, respectively (Fig. 2B, black symbols and bars). There was no significant difference in either response gain or phase based on canal
There was also no significant difference in PD gain for IN versus LB afferents (regular: p=0.6; irregular: p=0.08; Fig. 2A, marginal histograms) or phase (p=0.6 for both regular and irregular afferents; Fig. 2B, marginal histograms). In addition, we found no difference between IN and LB data sets in how PD gain and phase varied with frequency or canal type (ANCOVA, p>0.3). Note that we did not encounter many cells with high CV* and low response gains, which have been shown to correspond to canal afferents forming calyx endings in the central striola region in rodents (C-irregular; Baird et al. 1988). The absence of such units in our sample is also shown by the absence of a clear second peak in the CV* distribution (Fig. 2C) (Baird et al. 1988; Fernandez and Goldberg 1971). In Fig. 2A,B we have marked with filled symbols the few canal afferents with CV*>0.2 and gain <1; equivalent to the criterion used by Sadeghi et al. (2007a) to distinguish putative calyx-type from dimorph-type irregular canal afferents.

In addition to no change in mean gain and phase, we also found no significant difference in spontaneous firing rate for IN (94.6±30.8 (SD) spikes/s) versus LB (98.9±31.1 spikes/s) afferents (p=0.23, Wilcoxon rank test). However, the percentage of irregular afferents increased after labyrinthectomy (30% vs. 24%). The geometric mean of the corresponding CV* distributions (± geometric SD): 0.05±2.34 (IN) vs. 0.06±2.78 (LB) were different after labyrinthectomy (p=0.04, Wilcoxon rank test; Fig. 2C, compare red and black distributions). Such difference in CV* can be further illustrated by comparing the cumulative distributions (Fig. 2D, IN: black, LB: red). A similar finding was reported by Sadeghi et al. (2007a).

Preferred directions are shown as unit vector projections onto the three cardinal planes in Fig. 3 (IN: black lines; LB: gray lines). Note that PDs do not exactly coincide with the stimulus axes because animals were positioned in stereotaxic coordinates, i.e., the yaw rotation plane was the stereotaxic horizontal rather than the plane of the horizontal semicircular canals (Fig. 3, dashed lines; see also Haque et al. 2004). Nevertheless, as the difference is small (and identical for IN and LB afferents), the remaining analyses have used the maximum response direction (yaw for horizontal canal afferents, RALP for right anterior and left posterior afferents and LARP for left anterior and right posterior afferents) to quantify neural threshold and variance.

**Semicircular canal afferents: Direction detection thresholds**

The computation of the direction detection threshold for an example left anterior canal afferent (CV*=0.3) is shown in Fig. 4. We also illustrate the smooth, continuous function generated using the Kaiser filter (Fig. 4A, gray curve superimposed on instantaneous firing rate; see also Fig. 1). From spike count distributions created by quantifying peak and trough firing rates (500 ms temporal window), the sensitivity of each cell for discriminating oppositely directed rotations was quantified using signal detection theory (see Methods). The firing rates were first converted into a two-alternative forced choice (2AFC) format using 500 ms bins centered around the peak and trough of each response cycle (Fig. 4A). We then grouped together all firing rates within each peak (filled bars) and trough (open bars), for all stimulus magnitudes (0.5-15.6º/s; Fig. 4B). For the example cell shown, distributions are far apart for 15.6º/s and 7.8º/s, have a very small overlap at 2º/s and completely overlap at 0.5º/s (Fig. 4B). As a
result, an ideal observer would be able to distinguish whether a given firing rate came from one or the other distribution with a high degree of certainty for rotations larger than 2º/s, but not for 0.5º/s. Thus, the neuron’s direction detection threshold should be between 0.5º/s and 2º/s. Indeed, as illustrated by the afferent’s neurometric function (Fig. 4C), this neuron had a direction detection threshold of \( \sigma = 1.37 \text{o/s} \).

Direction detection thresholds for the entire macaque canal afferent population are summarized in Fig. 5. When all cells were considered together, there was only a weak dependence of neural threshold on CV* (ANCOVA, \( p=0.05 \); geometric mean±SD: 2.83±1.42º/s (regular, IN), 2.00±1.48º/s (irregular, IN)). However, when putative calyx afferents were excluded, this dependence became stronger (\( p<<0.001 \); irregular: 1.85±1.37º/s). A similar conclusion was also reached for otolith afferents (Yu et al. 2012). We found no difference in neural threshold for horizontal versus vertical canal afferents (ANCOVA main effect, \( p=0.74 \); Fig. 5, different symbols; see also Table 1), so data from all 3 canal afferent types have been pooled together for subsequent analyses.

Even though there was no difference in mean response gain and phase, we found that LB canal afferent thresholds were significantly higher than IN afferent thresholds (geometric mean±SD: 3.25±1.78º/s vs. 2.57±1.48º/s, i.e., a 27% increase; Wilcoxon test, \( p<0.001 \); Table 1). This difference reached significance even when comparing the thresholds for the one animal tested both before and after labyrinthectomy (IN: 2.74±1.46º/s (n=51) versus LB: 3.48±1.82º/s (n=42); Wilcoxon test, \( p=0.02 \)). Note that the few putative calyx-type afferents had high thresholds and likely large differences between IN and LB animals (4.06±1.38º/s vs. 7.23±1.24º/s, compared to 2.83±1.42º/s vs. 3.55±1.59º/s for regular afferents and 1.85±1.37º/s vs. 1.94±1.67º/s for irregular-dimorph afferents), although the small number of putative calyx units encountered prevented further quantification.

**Semicircular canal afferents: Increased variability in LB versus IN canal afferents**

Neural thresholds depend on two properties that determine how much the two spike count distributions overlap (Fig. 4B): the difference in their means and their width (variance) (ANCOVA main effects, \( p<<0.001 \)). The difference in the distribution means is directly related to the slope (steepness) of the magnitude tuning curve, a parameter that is similar to response gain (because all magnitude tuning curves were linear, with a mean correlation coefficient of \( r^2=0.97±0.003 \) (SD, IN) and \( r^2=0.95±0.008 \) (LB)). The dependence of neural threshold on the magnitude slope and variance (computed for each cell as the median for all tested velocities) was identical in LB and IN data sets (ANCOVA, \( p>0.14 \); Fig. 6A, B). Furthermore, there was no difference in magnitude slope between IN and LB afferents (geometric mean±SD: 0.58±2.08 spikes/sºº/s versus 0.57±2.37 spikes/sºº/s, respectively; Wilcoxon rank test, \( p=0.86 \); Fig. 6A, red vs. black histograms), in line with the fact that response gains were also unchanged (Fig. 2). Instead, the threshold difference between IN and LB afferents was due to differences in the spike count variance, which was significantly larger in LB (geometric mean±SD: 6.78±3.50 spikes²/s²) than in IN (4.46±2.99 spikes²/s²) animals (Wilcoxon rank test, \( p=0.01 \); Fig. 6B, red vs. black histograms).

When plotted as a function of CV*, both magnitude slope and variance scaled with CV* (Fig. 6C,D; type II regression, \( p<<0.001 \) for both IN and LB data). That is, irregular afferents had both higher gain and higher variance than regular afferents, such
that irregular afferents had similar or even smaller thresholds compared to regular canal afferents. A similar property was also a notable characteristic of otolith afferents (see Fig. 5 of Yu et al. 2012): magnitude slope and variance both increased similarly, if not more, with increasing CV*, such that irregular afferents were generally as or more sensitive than regular afferents. Note though that putative calyx canal fibers (Fig. 6, filled symbols) might not share this property, as their gains do not follow the monotonic dependence on CV* (see Discussion). Due to the small number, putative calyx canal afferents have not been distinguished in subsequent plots.

The difference in spike count variance between LB and IN afferents has been further illustrated in Fig. 7, where the data are plotted as a function of magnitude slope. For IN afferents, there was a strong correlation between the two parameters (r=0.78, p<0.001, type II regression). Thus, the higher the magnitude slope (i.e., gain), the larger the cell’s variance, thus resulting in thresholds that do not show a strong dependence on CV* (Fig. 5). This relationship was weaker, but still significant in LB afferents (r=0.43, p<0.001). Notably, the relationship between spike count variance and magnitude slope was significantly altered after lesion of the contralateral labyrinth, as illustrated in Fig. 7 (red versus black type II regression: slope 95% CI: [19.7, 32.6] vs. [36.8, 138.1]; intercept 95% CI: [-15.3, -7.3] vs. [-97.9, -17.4]). Thus, for the same magnitude slope (i.e., response gain), spike count variance was higher in LB than in IN animals. The difference in spike count variance between LB and IN afferents was also significant when afferents were separated into regular (p=0.014, Wilcoxon rank test) and irregular (p=0.015) groups (Fig. 7, left marginal histograms). In contrast, there was no difference in magnitude slope for LB vs. IN data (p>0.38; Fig. 7, bottom marginal histograms).

As we have previously reported (Yu et al. 2012), the exact threshold (Fig. 8A) and spike count variance (Fig. 8B) measured depends on the filtering method (e.g., Kaiser filter versus spike count) and window size used to compute the opposite direction response distributions (Fig. 4B, filled versus open bars). In contrast, magnitude slope was largely independent of both filtering method and window size (Fig. 8C). Thus, one cannot compare neural thresholds from different studies using different firing rate measures. Also, it is inappropriate to directly compare neural thresholds in macaques with behavioral thresholds in humans (see Discussion); so we have not attempted such comparisons here. Importantly, differences between IN and LB threshold (Fig. 8A) and variance (Fig. 8B) persisted regardless of the filtering method used to quantify the firing rate distributions. Thus, although the exact magnitude of measured neural threshold should be interpreted with caution, the measured differences between IN and LB afferents hold independently of the analysis method used.

The variable-magnitude protocol (VMAG) used here to compute neural threshold took several minutes (6-18 min) to complete (see Methods). Thus, it is possible that the observed increase in cycle-by-cycle variability might not be present when the variance is computed for shorter time intervals. To investigate the time scale of increased variability, we compared response variance computed from the VMAG (6-18 min) and CLA (20s) protocols (see Methods). For the latter, following the analysis of Sadeghi et al. (2007b), head velocity was binned into 1º/s steps and the analysis illustrated in Fig. 4 was performed on distributions centered on those bins.
The median firing rate variability computed from the short CLA protocol also increased in LB as compared to IN afferents (geometric mean±SD, averaged over all velocity bins: 3.50±4.90 spikes²/s² vs. 2.51±3.72 spikes²/s²; p<0.001, Wilcoxon rank test). However, the VMAG variance was larger than the CLA variance, as illustrated by most data points falling above the unity-slope dotted line in the scatter plot of Fig. 9A,B (p<<0.001, Wilcoxon sign rank test). In addition, the difference between these two variability measures, computed as a 'VMAG/CLA variance ratio', increased after LB (1.37±1.17 vs. 2.73±1.27, geometric mean and SD; p<0.001, ANOVA; Fig. 9C). Thus, although LB vs. IN variability differences were significant for both CLA and VMAG datasets, the difference was larger when variance was computed over the time scale of minutes (VMAG protocol) than seconds (CLA protocol).

**Semicircular canal afferents: Interneuronal correlations**

The observed increase in firing rate variability in LB versus IN semicircular canal afferents could reflect changes in interneuronal trial-by-trial (i.e., cycle-by-cycle) correlations. Multi-electrode recordings from the vestibular nerve were not possible, but we could spike-sort off-line a limited number of semicircular canal afferent pairs recorded from the same electrode. Thus, to investigate whether the observed increase in variance for LB afferents reflects correlated variability, we measured interneuronal correlations (i.e., the trial-by-trial correlations between the spike counts of two simultaneously recorded afferents) by spike-sorting records for which two single fibers could be distinctly discriminated off-line.

Interneuronal correlations were computed as the Pearson correlation coefficient of the normalized trial-by-trial spike counts between two simultaneously recorded cells (see Methods). Interneuronal correlations were measured for 5 (IN) and 5 (LB) pairs of afferents from the same canal and 4 (LB) afferents from different canals. Despite the limited data set, correlations were larger in LB than IN afferents (0.17±0.08 vs. -0.05±0.10, mean±SD; p=0.002, Wilcoxon rank test) and this result did not appear to depend on CV* (Fig. 10). Thus, the increased spike count variance observed in the intact vestibular nerve after LB could reflect correlated variability, although a larger number of afferent pairs would be needed to verify this suggested finding.

**Vestibular nuclei neurons: Basic response characteristics and comparison of mean responses**

We also analyzed responses from 109 VN neurons, of which 43 cells were recorded from three intact animals and 66 cells from the same two labyrinthectomized animals (35 LB-ipsi, i.e., cells recorded from the side ipsilateral to the lesion and 31 LB-contra, i.e., cells from the contralesional side). The majority of cells (82/109, 75%) showed significant modulation for at least one of the three cardinal directions during both rotation and translation (permutation test, p<0.01, see Methods). The remaining cells were significantly modulated during rotation only (24/109, 22%) or translation only (3/109, 3%). This ratio was consistent across the three groups of cells (intact: 34/43, 79%; 8/43, 19%; 1/43, 2%; LB-ipsi: 26/35, 74%; 8/35, 23%; 1/35, 3%; LB-contra: 22/31, 71%; 8/31, 26%; 1/31, 3%). None of the recorded cells showed any slow eye movement modulation, as determined during pursuit eye movements (see Methods).
VN neurons were tested during 3 directions of rotation (yaw, LARP, RALP) and 3 directions of translation: lateral (LR), naso-occipital (NO) and dorso-ventral (DV), as illustrated with an example cell in Fig. 11A, B. From these responses, 3D preferred direction (PD), gain and phase were computed using a spatio-temporal convergence model (see Methods and Angelaki 1992; Schor and Angelaki 1992; data not shown). The distributions of spontaneous activity, as well as 3D rotation and translation response gains are summarized in Fig. 12A-C. There was no difference in spontaneous activity for intact, LB-ipsi and LB-contra responses (35.7±21.3 (SD), 35.9±20.7, 41.6±23.4 spikes/s; 3-way ANOVA, p = 0.45). For cells that modulated significantly during rotation, response gains along the preferred direction in 3D were lower after labyrinthectomy (3-way ANOVA, p = 0.002). Non-parametric comparisons revealed significant differences between LB-ipsi and both intact and LB-contra data (Wilcoxon’s test, p<0.001 and p=0.001, respectively, see ** and * in Fig. 12B).

In contrast, there was no difference in translation response gain computed along the 3D preferred direction (intact: 213.7±1.8, LB-contra: 190.9±1.9, LB-ipsi: 182.1±2.1 spikes/s/G; 3-way ANOVA, p = 0.82). Since VN responses before and after unilateral vestibular lesion have never before been tested in 3D, no direct comparisons with previous studies are possible. However, considering only yaw rotation responses, we found significant gain differences between intact and labyrinthectomized animals for type I cells but not for type II cells (3-way ANOVA, type I: p=0.04, n=44; type II: p=0.10, n=45).

Vestibular nuclei neurons: Direction detection thresholds for rotation and translation

VN neurons were further characterized with stimuli consisting of sinusoidal rotations (0.5 Hz) or translations (1 Hz) along the cardinal axes at six different amplitudes (VMAG experimental protocol). Each cell was first tested in the cardinal direction with the largest response, followed by the other directions (see Methods). Distributions of spike counts (Fig. 11C-E) then underwent ROC analysis to generate neurometric functions and measure neuronal threshold (Fig. 11F).

**Rotation thresholds:** Yaw rotation thresholds were measured in 35/109 (32%) cells, LARP rotation thresholds in 44/109 (40%) cells and RALP rotation thresholds in 40/109 (37%) cells. For neurons recorded in intact animals, rotation thresholds averaged 6.9 ±2.9 º/s (geometric mean ± SD). Thresholds in chronically labyrinthectomized animals were significantly higher, 10.4 ± 2.2 º/s (LB-contra) and 16.2 ± 2.3 º/s (LB-ipsi) (Fig. 13A; ANOVA, p = 0.011). Post hoc analysis showed this significant difference was driven by the comparison between LB-ipsi and intact groups (p = 0.02, Tukey’s HSD test for unequal sizes). Non-parametric comparisons revealed significant differences between intact and both LB-ipsi and LB-contra data (Wilcoxon’s test, p<0.001 and p=0.03, respectively, see * and ** in Fig. 13A, marginal histograms). When only yaw responses were considered, significant differences were found only for LB-ipsi vs. intact response thresholds (type I: p=0.008; type II: p=0.04). In contrast, LB-contra yaw thresholds were not significantly different from those in intact animals (type I: p=0.28; type II: p=0.25).

As illustrated in the scatter plot of Fig. 13A, neuronal thresholds depended on the direction of the stimulus relative to the preferred direction of maximal response, Δ(3D-
PD), for each cell. The lowest thresholds were observed for rotation axes parallel to the
preferred direction ($\Delta(3D-PD) = 0^\circ$ or $180^\circ$) and the largest thresholds were observed
perpendicular ($90^\circ$) to the preferred direction (dashed vertical line in Fig. 13A). Thus, to
estimate thresholds for stimulation along the cell’s PD, data were folded along the
dashed vertical line, such that the relationship was monotonic. Thresholds were
significantly different (Fig. 13B; 3-way ANCOVA, $p<0.001$), with larger deficits for LB-ipsi
($p<0.001$, Post hoc Tukey’s HSD test for unequal sizes) than LB-contra neurons
($p=0.04$, comparison with intact group) as compared to intact animals. Furthermore, LB-
ipsi and LB-contra neurons were significantly different ($p=0.04$). This relationship was
also quantified using a type II regression (Fig. 13B), whose intercept provided an
estimate of the PD population threshold (Table 2). Preferred direction thresholds ($\pm 95$
CI) were $2.5 (1.5-4.3)$, $3.4 (2.0-5.5)$ and $6.8 (4.9-10.3) \, ^\circ$s for intact, LB-contra and LB-
ipsi groups, respectively. Note that inverse cosine fits gave slightly larger PD thresholds
for all 3 groups, although fits were not better than those of a type II regression (Table 2).

Neuronal thresholds depended on both the slope of the response amplitude
tuning curve (e.g., Fig. 11E) and response variance (two-covariate ANCOVA, $p<0.001$).
Furthermore, the relationship between threshold and variance was consistent in intact
and labyrinthectomized animals as well as the relationship between threshold and
response amplitude tuning curve (interaction term, $p=0.60$ and $p=65$, respectively).

Translation thresholds: LR stimulation was tested in 43/109 (39%) cells, NO
stimulation was tested in 48/109 (44%) cells and DV stimulation was tested in 32/109
(29%) cells. In intact animals, translation thresholds averaged (geometric mean ± SD):
$42.1 \pm 3.4 \, \text{cm/s}^2 (0.043 \, \text{G})$, which is not significantly different than otolith afferent
thresholds ($57.3 \pm 2.8$, $p=0.09$, $n=97$; Yu et al. 2012). Chronically labyrinthectomized
animals had similar translation thresholds (LB-contra: $39.4 \pm 3.1 \, \text{cm/s}^2$; LB-ipsi: $56.8 \pm
2.9 \, \text{cm/s}^2$) as controls (3-way ANOVA, $p=0.82$; Fig. 14, marginal histograms). Similar
conclusions (i.e., no significant difference between intact and lesioned thresholds) were
reached when accounting for the threshold dependence on the difference of the
stimulus direction with the 3D-PD (ANCOVA, $p=0.27$). Based on a type II regression,
PD thresholds averaged ($\pm 95$ CI) $13.8 (3.7-39.1)$, $18.7 (7.3-36.6)$ and $14.8 (6.4-34.2)$
$\, \text{cm/s}^2$ for intact, LB-contra and LB-ipsi, respectively. Slightly higher PD thresholds were
estimated using inverse cosine fits (Table 3). For comparison, otolith afferent thresholds
along the 3D PD were $11.6 (6.8-18.1)$ and $22.7 (18.4-28.3) \, \text{cm/s}^2$, for linear and
inverse cosine fits, respectively (considering regular and irregular afferents together; Yu
et al. 2012). Regardless of the interpolation method, 95% CIs overlap, demonstrating
that there is no difference in translation detection thresholds for either otolith afferents
and VN neurons or intact and lesioned responses.

Finally, translation thresholds depended on both the amplitude tuning curve slope
and variance (two-covariate ANCOVA, $p=0.002$ and $p=0.03$, respectively), and these
relationships were not different in intact vs. labyrinthectomized animals (interaction
terms: $p=0.62$ and 0.54, respectively). Thus, both response gain and variance, as well
as translation detection thresholds appeared fully recovered after destruction of one
labyrinth. Consequently, the remaining labyrinth is sufficient after compensation to
maintain translation detection thresholds at the low values of labyrinth-intact animals.

Discussion
We have characterized neural variability and direction detection thresholds of semicircular canal afferents and central VN neurons in intact macaques and animals whose contralateral labyrinth was surgically ablated. Unlike past studies that quantified mean responses only (Sadeghi et al. 2007b), here we show that spike count variance, and thus detection thresholds, of canal afferents were both significantly increased after contralateral labyrinth lesion. In agreement with Sadeghi et al. (2007a), we found no difference in resting discharge, as well as mean response gain and phase (Fig. 2). Sadeghi et al. (2007a) did report a decrease in the proportion of regular afferents (45 vs. 38%) after LB, similar to findings in the present study (76% vs. 70%). We also found a small (27%) but significant increase in the detection threshold of vestibular afferents after lesion of the contralateral labyrinth. Such increase in neural threshold was not due to differences in mean response gain, which remained unchanged, but rather due to a significant increase in spike count variability. Analysis of trial-by-trial spike count correlations of a small number of simultaneously recorded pairs of afferents revealed increased interneuronal correlations after labyrinthectomy. Although the number of simultaneously recorded canal afferents was low to support firm conclusions, increases in the measured correlations support the hypothesis that LB might increase correlated variability. The observed increase in variability could also be related to the higher mean CV* after labyrinthectomy (Fig. 2C, D).

Importantly and for the first time after vestibular damage, VN neurons were tested using 3D rotations and translations. We note that VN thresholds interpolated along the cell’s preferred direction were similar, and maybe slightly higher, than vestibular afferent thresholds (Tables 1-3). Because many VN cells responded during both rotation and translation, and because we tested cells during both yaw and vertical plane oscillations, VN rotation thresholds do not necessarily reflect activation of semicircular canals exclusively. For this reason, we made no attempt to compare VN and semicircular canal afferent thresholds for rotation, although we did compare VN and otolith afferent thresholds for translation (Fig. 14, data from Yu et al. 2012). In general, our analysis has shown much lower thresholds for both afferents and VN neurons than those reported previously by Cullen and colleagues (Jamali et al. 2013; Jamali et al. 2014; Massot et al. 2011; Sadeghi et al. 2007a). One major difference is the fact that Massot et al. (2011), Sadeghi et al. (2007a) and Jamali et al. (2014) used stimuli limited to yaw rotations. Similarly, Jamali et al. (2013) use linear accelerations limited to the horizontal plane. In contrast, we have tested rotation and translation responses in 3D, which could at least partly explain the lower thresholds. However, we note that, as illustrated in Fig. 8, neural threshold depends on filtering and analyses used. Furthermore, comparisons between regular and irregular afferent thresholds can be skewed because of sampling biases and arbitrary cut-offs (e.g., CV*=0.1). Thus, comparisons between different labs using different motion platforms and different analyses might not be useful and justifiable.

Regardless, comparison among areas using identical stimuli and analyses, as done here, is extremely valuable. Remarkably, although convergence between the two labyrinths improved the modulation gain of central vestibular neurons in the VN (at least compared to regular afferents; compare Fig. 11 and 2), it does not improve detection thresholds, and this is true for both rotation and translation stimuli (Tables 1-3). This
likely occurs because of increased response variability in VN versus vestibular
afferents. Thus, it is unclear whether there are any benefits of commissural
convergence in sensory detection and discrimination of vestibular motion signals and
this hypothesis should be explored in future experiments.

We note that the present conclusions, which were based on comparisons
between thresholds for 3D rotation and 3D translation stimuli several months (up to two
years) following unilateral labyrinthectomy, are not directly comparable to previous
studies. We found persistent deficits in rotation detection thresholds, which were due to
lower response gains, while response variance was unaltered. This result differs from
the higher variability reported by Jamali et al., (2014), who tested yaw responses
approximately a month after labyrinthectomy. The present results show that response
variability completely recovers in the long-term after LB (and when evaluated in 3D). On
the other hand, we found no difference in translation detection thresholds or 3D gains
for VN neurons in intact vs. labyrinthectomized animals. Thus, deficits in gain and
threshold reported by Newlands et al. (2014) and Liu et al. (2013b) appear to recover in
steady-state.

Finally, it is important to note that the relationship between the observed
persistent increases in canal afferent variability and the recovered variability of central
neurons chronically after labyrinthectomy is presently unknown. This is because of
current limitations in understanding how input variability influences output variability.
Such relationships would depend both on individual neuron properties, as well as on the
correlated variability and information transfer among multiple neurons in the network.
Future studies that simultaneously measure stimulus-driven responses across a large
number of neurons, combined with theory, would be necessary to understand these
relationships.

Next we briefly summarize the most relevant prior findings on vestibular afferent
properties, vestibular compensation following unilateral labyrinth loss, as well as
differences in the organization of the semicircular canals and otolith pathways. In
addition, we also discuss the challenges associated with comparison of neuronal with
behavioral thresholds when they were not measured simultaneously.

Basic properties of semicircular canal afferents and efferents

Semicircular canal afferents were characterized by similar mean response
properties as in previous studies (Haque et al. 2004; Ramachandran and Lisberger
2006; Sadeghi et al. 2007a; Sadeghi et al. 2007b). The only difference between the
present sample and previous reports is that we did not encounter many cells with high
CV* and low response gains, which have been shown to correspond to canal afferents
forming calyx endings in the central striola region of the chinchilla (Baird et al. 1988).
Compared to dimorphic-irregular afferents, which are characterized by the highest gain
across all canal afferents, calyx-irregular afferents have much lower gains than what
would be expected by the typical monotonic relationship between response gain and
CV* (Baird et al. 1988; Ramachandran and Lisberger 2006; Sadeghi et al. 2006). Such
a group of irregular afferents (CV* > 0.35 & gain at 0.5 Hz < 0.5) was previously identified
in the macaque by Ramachandran and Lisberger (2006), although other macaque
studies also did not encounter them readily (Haque et al. 2004; Sadeghi et al. 2007a;
Sadeghi et al. 2007b). The reason for this difference is not known, but may reflect
differences in recording methodologies; e.g., use of metal electrodes in the present study. Thus, the conclusions reached here should be considered applicable to only regular and dimorphic irregular canal afferents.

The low yield of calyx-like canal afferents could also explain the two differences between the present IN results and those of Sadeghi et al. (2007b): First, we encountered a higher proportion of regular afferents (70-76% versus 38-45%). Second, we found a small dependence of neural threshold on $CV^*$, and this dependence was in the opposite direction to that reported by Sadeghi et al. (2007b). That irregular afferents are as sensitive (i.e., have lower threshold), or more sensitive, than regular afferents has also been reported for otolith afferents (Jamali et al. 2013; Yu et al. 2012), and is due to the fact that spike count variability is directly proportional to response gain (Fig. 7). Thus, for the majority of regular and irregular afferents, a strong positive correlation between response gain and spike count variance results in neuronal thresholds that show either no dependence on $CV^*$ (Jamali et al., 2013) or small improvement with increasing $CV^*$ (Fig 5; Yu et al., 2012). This finding is common to both canal and otolith afferents. However, a separate population of low-gain putative calyx type canal afferents exists and these fibers do not follow the same gain vs. variance relationship (Fig. 6, filled symbols). Thus, the detection thresholds for putative calyx canal afferents may be the highest of all afferents due to low response gains and high spike count variance. In addition, it is possible that low gain, calyx-type, irregular afferents might exhibit the largest increases in firing rate variability after labyrinthectomy (Fig. 5, filled red/black symbols).

Although we cannot exclude that the observed increase in spike count variability after labyrinthectomy is due to retrograde changes due to altered properties in vestibular nuclei neurons that receive inputs from both labyrinths, it is tempting to speculate that the observed changes in spike count variability might be mediated by the vestibular efferent system. Efferent fibers (from ~300-400 brainstem cells in primates) make contacts presynaptically onto type II hair cells and postsynaptically onto afferent calyces (Klinke and Galley 1974; Lindeman 1969; Lysakowski and Goldberg 1997; Sans and Highstein 1984). Efferent-mediated effects on vestibular afferents are heterogeneous (Bernard et al. 1985; Boyle and Highstein 1990; Brichta and Goldberg 2000; Goldberg and Fernandez 1980; Highstein and Baker 1985; Holt et al. 2006; Marlinski et al. 2004; McCue and Guinan 1994; Rossi and Martini 1991; Rossi et al. 1980; Sugai et al. 1991; reviewed by Lysakowski and Goldberg 2004). Effects of efferent electrical stimulation are the largest in irregular afferents, consisting of both fast (10-100 ms time constant) and slow (5-20 s) components. In contrast, efferent effects on regular afferents are small and predominantly slow (Goldberg and Fernandez 1980; Marlinski et al. 2004; McCue and Guinan 1994).

Over the years multiple functions have been suggested for the vestibular efferent system (see review by Goldberg 2000) and each has been systematically rejected. Vestibular afferent activity is similar during active vs. passive head movements and does not modulate during proprioceptive or visual stimulation (Cullen and Minor 2002; Miles and Braitman 1980). Similarly, the hypothesis that the vestibular efferent system could be used to balance activity between the two labyrinths and/or extend the dynamic range of the intact labyrinth after contralateral vestibular damage has also been refuted.
Sadeghi et al. 2007b). Our results are completely consistent with these findings, showing no difference in mean response gain, phase and preferred direction.

**VOR deficits after unilateral labyrinthectomy**

It has been well-established that loss of unilateral vestibular function results in both postural and VOR deficits, including a pronounced head tilt towards the lesion (Angelaki et al. 2000; Fetter and Zee 1988; Smith and Curthoys 1989). However, in contrast to incomplete passive VOR recovery, counter-rotation gains during combined eye-head gaze shifts (i.e., the compensatory eye counter-rotation that stabilizes gaze as the head movement continues during an eye-head gaze shift) recovered within a week after unilateral labyrinthectomy, likely using extra-vestibular cues (Newlands et al. 2001).

Previous investigations have described two phases in compensation from unilateral loss (Curthoys and Halmagyi 1995; Fetter and Zee 1988; Lasker et al. 2000; 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 spontaneous firing rate in central neurons. VOR gain recovery is also fast during this period, likely due to the restoration of spontaneous activity in central pathways. The second compensation phase is slower and takes place within several weeks or months after unilateral loss. The goal of the present study was not to characterize the early deficits, but rather those after the process of compensation from vestibular imbalance had been completed.

The higher the peak acceleration of rotation, the smaller the recovery of the rVOR and the larger the asymmetry between responses to ipsilesional and contralesional rotation (Crane and Demer 1998; Gilchrist et al. 1998; Halmagyi et al. 1990; Sadeghi et al. 2006; Tabak et al. 1997; Vibert et al. 1993). In contrast, low acceleration rotations elicit a nearly complete recovery of the yaw rVOR 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). Because here we measured detection thresholds, stimuli were exclusively in the low magnitude range.

**Changes in neuronal response gain during rotation**

Commissural inhibition is fundamental to the central organization of semicircular canal signals (Kasahara and Uchino 1974; Precht and Shimazu 1965; Precht et al. 1966; Shimazu and Precht 1966). For example, VN neuron responses are driven by excitatory inputs from the ipsilateral horizontal semicircular canal and disinhibition from the contralateral horizontal canal. As a result of this push-pull arrangement, facilitation from the ipsilateral side and disinhibition from the contralateral side ensures higher gains in VN neurons than canal afferents. The significance of this bilateral organization was demonstrated long ago, by showing only partial gain recovery after unilateral labyrinthectomy (Newlands and Perachio 1990a; b; Ris and Godaux 1998; Smith and Curthoys 1988a; b). More recent studies in alert macaques have shown small but persistent gain deficits for type I VN neurons post-lesion (Newlands and Wei 2013; Sadeghi et al. 2011; 2010). Our results are in general agreement with these findings. We found that 3D preferred direction gains after compensation remain lower than those in intact animals, even after several months post-lesion.

Changes in neuronal responses during translation

Unlike the semicircular canals, the otolith receptors have a wide representation of preferred directions of linear acceleration within a single macula, including opposite-directed responses across an imaginary line known as the striola (Flock 1964; Lindeman 1969). Indeed, in addition to the commissural system (Bai et al. 2002; Uchino et al. 1999; Uchino et al. 2001), another mechanism, known as ‘cross-striolar inhibition, was shown to exist and be stronger for the sacculus than the utricle (Ogawa et al. 2000; Uchino et al. 1997): VN neurons were excited monosynaptically by ipsilateral otolith afferents from one side of the striola and inhibited disynaptically by afferents from the other side of the striola of the same end organ. Thus, appropriate push-pull afferent convergence in the VN could arise either from both labyrinths (as in the canal system) or from the same otolith macula through cross-striolar inhibition (Uchino et al. 1999).

Despite this redundancy, which could allow the otolith system to maintain the push-pull organization with just a single functional labyrinth, dramatic changes in the translational VOR have been reported even after 3 months of recovery following unilateral vestibular damage, particularly during transient displacements (Angelaki et al. 2000). Such asymmetric tVOR responses during ipsilesional and contralesional translation are very strong within the first week following lesion (Angelaki et al. 2000; Lempert et al. 1998; Tian et al. 2007). How much tVOR has recovered in chronic patients with unilaterally vestibular damage remains controversial (Bronstein et al. 1991; Tian et al. 2007). Asymmetric response gains have been traced down to VN neurons in anesthetized animals (Chan 1997; Chan et al. 1999; Hoshino and Pompeiano 1977; Lacour et al. 1985; Xerri et al. 1983). How signals from the remaining intact otolith organs reach the motoneurons through reorganization of ipsilesional and/or contralesional pathways (Angelaki et al. 2001; Green et al. 2001; Rohregger and Dieringer 2003) requires further study.

In summary, the present findings, showing complete recovery of translation response gains and detection thresholds, demonstrate that otolith afferent signals from a single labyrinth are sufficient after compensation to maintain the sensitivity and direction discriminability of linear acceleration responses in VN neurons. In contrast, recovery was incomplete during 3D rotations, where both response gains and rotation...
detection thresholds were lower than normal, particularly in the VN ipsilateral to the
lesion.

It is important to highlight that direct comparisons with behavioral performance
are not possible because behavioral thresholds have never been measured either in
labyrinth-intact (but see Garcia-Johnston et al. 2013) or in labyrinthectomized
macaques (but see Cousins et al. 2013; Cutfield et al. 2011; Grabherr et al. 2008;
Haburcakova et al. 2012; Priesol et al. 2014; Valko et al. 2012 for human perceptual
thresholds). We are only aware of Liu et al. (2013b) who showed persistent heading
discrimination deficits for up to 3 months post-labyrinthectomy. We note that, in the
absence of simultaneous behavioral recordings, we have made no attempt to estimate
population thresholds. This is because, as summarized next, we consider flawed any
ttempt to calculate population thresholds and pool size in the absence of
simultaneously measured behavior because of many potentially erroneous
assumptions.

How can neural thresholds be compared with behavioral thresholds?

Several recent studies have measured neural thresholds in the vestibular
periphery (canal afferents: Sadeghi et al. 2007a; otolith afferents: Jamali et al. 2013; Yu
et al. 2012) and the vestibular brainstem (translation: Liu et al. 2013a; Liu et al. 2013b;
the exception of Liu et al. (2013a;b) in the vestibular nuclei (but see also Chen et al.
2013; Gu et al. 2007; Gu et al. 2011 for cortical areas), none of these studies actually
measured neuronal thresholds simultaneously with behavioral thresholds. There are
multiple reasons that direct comparisons between neural and behavioral thresholds
should not be made unless measured simultaneously in the same animals using the
same motion platform. First, behavioral thresholds vary from subject to subject (e.g.,
see Suppl. Fig. 2 of Liu et al. 2013a). Second, macaque and human thresholds are not
necessarily similar; thus, quantitative comparisons between macaque neurons and
human behavior (as previously done by Massot et al. 2011 and Jamali et al. 2013) may
lead to inappropriate conclusions. Third, the exact value measured for the neural
threshold depends critically on the filtering and averaging used to compute trial-by-trial
firing rates (Fig. 8; see also Fig. 9, Yu et al. 2012). Fourth, the inherent stimulus-driven
vibrations in different motion systems might also result in different thresholds in different
labs.

A few recent studies characterizing neuronal thresholds without simultaneously
measuring perceptual thresholds have also computed population thresholds and
characterized the extent of further convergence necessary to convert macaque
neuronal thresholds into human perceptual thresholds (Jamali et al. 2013; Massot et al.
2011). In addition to the multiple problems associated with this approach summarized in
the previous paragraph, an additional, serious caveat emerges when considering the
fact that trial-by-trial firing rates show robust interneuronal correlations in the VN (Liu et
al. 2013a). Such interneuronal correlations can affect both the information carried by the
population, but also the decoding efficiency (see Liu et al. 2013a,b for more details).
Furthermore, when interneuronal correlations are present, population thresholds might
not increase in proportion to the number of neurons in the pool and, for the same
neuronal pool size, different population thresholds will result depending on whether the
decoder has full knowledge of these correlations or not (Haefner et al. 2013; Pitkow et al. 2013). Furthermore, it is now well established that, to connect the dots between neural activity and perception, one must consider both (1) the decoder (optimal vs. suboptimal and there are multiple levels of suboptimality) and (2) interneuronal correlations. Some types of correlations can be removed with optimal decoding (by 'reading' out the neural activity along the best axis, which always exists when correlations are in a different format from the signal). But other types of correlations (those which are identical to the signal) cannot be 'removed' by any decoder, optimal or suboptimal (Beck et al., 2012). The only way to realistically tackle this challenge is by simultaneously measuring neural activity and perception. Recent theory has provided ways of inferring read-out weights, but one needs to know, not only neural thresholds, but also correlations among neurons and choice-probabilities (correlations between neuron and behavior) (Haefner et al. 2013).

We note that in the present study we have measured neural thresholds without simultaneously measuring perception. Thus, we have made no attempt to compute population thresholds and to compare the present results with perception. Future studies employing simultaneously recorded neural and perceptual thresholds, which is an important requirement for quantitative simulations and predictions at the population level, are necessary to understand both the peripheral and central processing of vestibular signals.
Figure Legends

**Figure 1.** Example anterior semicircular canal afferent response during the classification protocol. A cell's modulation during three cycles of sinusoidal rotation about the yaw, left-anterior-right-posterior (LARP) and right-anterior-left-posterior (RALP) axes are shown as instantaneous firing rate (IFR). Each dot corresponds to an IFR value. Stimuli (0.5 Hz) are shown below the IFR. Gray lines illustrate Kaiser filtered data (see Methods) superimposed on top of the IFR.

**Figure 2.** Summary of mean response properties of semicircular canal afferents in intact (IN, black) and lesioned (LB, red) animals. (A) Response gain (along the 3D preferred direction) is plotted as a function of CV* for n=152 (IN) and n=125 (LB) cells. The marginal histograms on the right show gain distributions (arrows illustrate geometric means) for regular (IN: 122, LB: 85) and irregular (IN: 30, LB: 40) afferents. (B) Response phase as a function of CV* for n=238 (IN) and n=161 (LB) canal afferents. Marginal histograms on the right show phase distributions (arrows illustrate geometric means) for regular (IN: 180, LB: 112) and irregular (IN: 58, LB: 49) afferents. Different symbols in the scatter plots illustrate different canal types; circles: horizontal (H) canals, squares: anterior (A) canals, and diamonds: posterior (P) canals. The difference in the number of cells between A and B is due to loss of cell isolation before the CLA protocol was completed (thus, a PD gain could not be measured). (C) Distributions of CV* (arrows illustrate geometric means). (D) Cumulative distributions of CV* for IN (black) and LB (red) afferents (IN: 238 and LB: 161).

**Figure 3.** Summary of preferred directions (PD). Each unit vector is shown in stereotaxic coordinates (front, top, left side views; see drawing) according to the right-hand rule. Red circles, green triangles, and blue diamonds represent horizontal, anterior, and posterior afferent vectors, respectively. LAC: left anterior canal; LHC: left horizontal canal; LPC: left posterior canal; RAC: right anterior canal; RHC: right horizontal canal; RPC: right posterior canal. Black lines: IN afferents (n=152); Gray lines: LB afferents (n=125). Dotted lines illustrated the 3 axes used to test canal afferents during the classification protocol.

**Figure 4.** Computation of direction detection threshold for an anterior canal afferent. (A) Instantaneous firing rate (IFR) of the same afferent as in Fig. 1 with superimposed gray line illustrating the Kaiser filter response (see Methods), as well as corresponding raster plots for different trials during rotation about the cell's maximum response direction. Bars mark 500ms intervals used to compute mean firing rate for peak (filled bar) and trough (open bar) response, analyzed cycle-by-cycle. (B) Firing rate distributions for 4 pairs of stimulus magnitudes (15.6º/s, 7.8º/s, 2.0º/s, and 0.5º/s), with filled bars corresponding to peak and open bars corresponding to trough spike counts. (C) Example neurometric function, with circles showing proportion direction decisions of an ideal observer as a function of peak velocity magnitude, computed from distributions like those shown in (B). Solid lines show cumulative Gaussian fit to the neurometric function.
Figure 5. Summary of direction detection thresholds. Neural threshold is plotted as a function of CV* on a cell by cell basis, shape-coded according to canal type (H: circle, A: square, P: diamond) and color-coded according to intact (IN, black) versus labyrinthectomized (LB, red) type. Marginal histograms on the right show threshold distributions, separately for IN (black, n=117) and LB (red, n=95) data (arrows illustrate geometric means). Filled symbols: putative C-irregular neurons.

Figure 6. Parameters influencing neural threshold. (A), (B) Dependence of threshold on magnitude tuning curve slope (A, in units of spikes/s per °/s) and median variance (B, in units of (spikes/s)^2). Median variance is computed from multiple response amplitude distributions, like those in Fig. 4B. Histograms on the top show the corresponding distributions of magnitude tuning curve slope and median variance (arrows illustrate geometric means). (C) Magnitude tuning curve slope and (D) median variance plotted as a function of CV*. Black symbols: IN (n=117). Red symbols: LB (n=95). Solid lines show type II linear regression (plotted only whenever correlation was significant). Filled symbols: putative C-irregular neurons.

Figure 7. Dependence of median variance on magnitude tuning curve slope. Median variance is computed for each direction from multiple response amplitude distributions, like those in Fig. 4B. IN: n=117 (black); LB: n=95 (red). Solid lines: type II linear regression. Marginal histograms show slope distributions (bottom) and median variance distributions (left) for regular (IN: 85, LB: 66) and irregular (IN: 32, LB: 29) afferents separately (arrows illustrate geometric means).

Figure 8. Effects of filtering method used for firing rate computation. (A) Average detection threshold, (B) median variance, and (C) magnitude tuning curve slope plotted as a function of window size for two different filtering methods: spike count (solid lines) and Kaiser filter (dotted lines). Black: IN, Red: LB. Error bars represent standard error.

Figure 9. Relationship between firing rate variability computed from the classification (CLA) and variable magnitude (VMAG) protocols. (A), (B) Scatter plots for IN (A) and LB (B) afferents, where each data point represents to variability computed for one velocity bin for each neuron (13 data points per cell; note results are independent of the velocity bin; p=0.16, ANOVA). Data are color-coded for IN (black, n=97) versus LB (red, n=82) animals. Solid line: type II linear regression. (C) Distributions of VMAG/CLA variance ratios (arrows illustrate geometric means). To exclude the possibility that the observed difference could arise due to the different trial numbers, we also measured variance separately for each of 13 stimulus amplitudes (0°/s, ±0.5°/s, ±1°/s, ±2°/s, ±4°/s, ±7.8°/s and ±15.6°/s) by randomly drawing 10 sample cycles from the VMAG protocol, and the results were similar.

Figure 10. Interneuronal correlations from IN (black, n=5) and LB (red, n=9) afferents are plotted versus the CV* of the recorded pair of afferents (connected by line). Circles: same canal pairs; Squares: different canal pairs. Filled symbols denote significant correlations (p<0.05), whereas open symbols illustrate non-significant correlations. Each data set consisted of a minimum of 87 (and up to 540) trials.
**Figure 11.** Example vestibular nucleus neuron (intact animal). (A), (B) Classification responses (instantaneous firing rate, IFR) using 0.5 Hz stimulation around three axes of rotation (yaw, LARP and RALP) and three directions of translation (LR, NO, DV). The solid gray lines show sinusoidal fits. This cell showed significant responses for yaw and RALP rotation (p<0.001), but not for translation. (C)-(F) Computation of rotation thresholds using different amplitude sinusoids (0.5 Hz). Responses (only 3 of 6 amplitudes are shown in C, D) are shown as spike count distributions centered on peak (D, black bars) and trough (D, open bars), velocity tuning curve (E) and neurometric function (F), from which direction detection threshold was computed as the standard deviation of a cumulative Gaussian function fit.

**Figure 12.** Basic response properties of rotation- and translation-modulating cells. (A) Distribution of spontaneous firing rates, with arrows illustrating mean values (n = 109 cells). (B), (C) Distributions of rotation and translation response gains along the preferred direction in 3D. Arrows illustrate geometric means for data from intact (black, n = 42 for rotation and n = 35 for translation), LB-contra (striped, n = 30 for rotation and n = 23 for translation) and LB-ipsi (striped, n = 34 for rotation and n = 27 for translation) animals. Asterisks illustrate statistically significant mean differences (*: p<0.01; **: p<0.001, Wilcoxon's test).

**Figure 13.** Direction detection thresholds for rotation. (A) Neuronal thresholds as a function of the absolute difference between the tested direction and the preferred 3D direction of the cell, Δ(3D-PD), with data from each cell shown for 1-3 motion directions. Vertical dashed line marks Δ(3D-PD) = 90° (i.e., tested direction perpendicular to the cell’s preferred direction). Marginal histograms on the right show threshold distributions, separately for intact (black, n = 43), LB-contra (green, n = 41) and LB-ipsi (red, n = 35) animals (arrows illustrate geometric means). (B) Data in (A) folded around 90°, such that type II linear regression (solid) and inverse cosine function (dashed) lines are fit to the data, separately for the three groups of animals (values in Table 2). (C) Dependence of neuronal threshold on rotation magnitude tuning curve slope, with data from each cell shown for 1-3 motion directions. Different symbols are used for different animals (triangles: animal S; circles: animal T; squares: animal K; stars: animal C; diamonds: animal W).

**Figure 14.** Direction detection thresholds for translation. Neuronal thresholds as a function of the absolute difference between the tested direction and the preferred 3D direction of the cell, Δ(3D-PD), folded around 90°, such that type II linear regression (solid color) and inverse cosine function (dashed) lines are fit to the data, separately for the three groups of animals (data from each cell shown for 1-3 motion directions). Gray solid/dashed lines show corresponding fits for otolith afferents (data from Yu et al. 2012). Marginal histograms on the right show threshold distributions, separately for intact (black, n = 43), LB-contra (green, n = 31) and LB-ipsi (red, n = 49) animals (triangles: animal S; circles: animal T; squares: animal K; stars: animal C; diamonds: animal W).
### Table 1. Rotation detection thresholds for semicircular canal afferents.

Data are shown as population geometric means ± SD separated by canal type (rows) and intact vs. LB (columns).

<table>
<thead>
<tr>
<th></th>
<th>Intact</th>
<th>LB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Regular</td>
</tr>
<tr>
<td>Horizontal semicircular canals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2.81±1.49 (n=36)</td>
<td>3.34±1.37 (n=21)</td>
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<tr>
<td>Anterior semicircular canals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2.40±1.50 (n=36)</td>
<td>2.59±1.45 (n=30)</td>
</tr>
<tr>
<td>Posterior semicircular canals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2.54±1.44 (n=45)</td>
<td>2.77±1.37 (n=34)</td>
</tr>
<tr>
<td>All</td>
<td>2.57 ±1.48 (117)</td>
<td>2.83± 1.42 (85)</td>
</tr>
</tbody>
</table>

### Table 2. VN detection thresholds for rotation.

Top and middle rows: Neuronal thresholds in deg/s with 95% confidence intervals (in parentheses), interpolated along the preferred direction from linear fits (top row) or cosine fits (middle row). Bottom row: Geometric means and standard deviation of thresholds along all tested directions (from distributions in Fig. 13A).

<table>
<thead>
<tr>
<th></th>
<th>VN-Intact</th>
<th>VN-LB-contra</th>
<th>VN-LB-ipsi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear fit</td>
<td>2.5 (1.5–4.3)</td>
<td>3.4 (2.0–5.5)</td>
<td>6.8 (4.9–10.3)</td>
</tr>
<tr>
<td></td>
<td>r²=0.30, p&lt;0.001</td>
<td>r²=0.43, p&lt;0.001</td>
<td>r²=0.39, p&lt;0.001</td>
</tr>
<tr>
<td>Inverse Cosine fit</td>
<td>4.2 (3.2–6.1)</td>
<td>5.8 (4.6–7.4)</td>
<td>9.6 (7.0–14.4)</td>
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<tr>
<td></td>
<td>r²=0.26, p=0.001</td>
<td>r²=0.49, p&lt;0.001</td>
<td>r²=0.34, p&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.9 ± 2.9</td>
<td>10.4 ± 2.2</td>
<td>16.2 ± 2.3</td>
</tr>
</tbody>
</table>

### Table 3. VN detection thresholds for translation and comparison with otolith afferents.

Top and middle rows: Neuronal thresholds in cm/s² with 95% confidence intervals (in parentheses), interpolated along the preferred direction from linear fits (top row) or cosine fits (middle row). Bottom row: Geometric means and standard deviation of thresholds along all tested directions (from distributions in Fig. 14A).

<table>
<thead>
<tr>
<th></th>
<th>Otolith afferents</th>
<th>VN-Intact</th>
<th>VN-LB-contra</th>
<th>VN-LB-ipsi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear fit</td>
<td>11.6 (6.8–18.1)</td>
<td>13.8 (3.7–39.1)</td>
<td>18.7 (7.3–36.6)</td>
<td>14.8 (6.4–34.2)</td>
</tr>
<tr>
<td></td>
<td>r²=0.41, p&lt;0.001</td>
<td>r²=0.13, p=0.019</td>
<td>r²=0.06, p=0.19</td>
<td>r²=0.23, p&lt;0.001</td>
</tr>
<tr>
<td>Inverse Cosine fit</td>
<td>22.7 (18.4–28.3)</td>
<td>20.0 (11.6–38.4)</td>
<td>27.4 (16.6–47.2)</td>
<td>25.9 (17.7–41.2)</td>
</tr>
<tr>
<td></td>
<td>r²=0.48, p&lt;0.001</td>
<td>r²=0.18, p=0.005</td>
<td>r²=0.05, p=0.10</td>
<td>r²=0.28, p&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>57.3 ± 2.8</td>
<td>42.1 ± 3.4</td>
<td>39.4 ± 3.1</td>
<td>56.8 ± 2.9</td>
</tr>
</tbody>
</table>
References


Fernandez C, and Goldberg JM. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. II. Response to sinusoidal stimulation and dynamics of peripheral vestibular system. *J Neurophysiol* 34: 661-675, 1971.


Interneuronal correlation vs. CV*
A Rotation
IFR
Stim Yaw
22 °/s
IFR
Stim LARP
22 °/s
IFR
Stim RALP
50 spikes/s
500 ms

B Translation
IFR
Stim LR
0.1 G
IFR
Stim NO
0.1 G
IFR
Stim DV
0.07 G
500 ms

C Positive window
16 °/s
IFR
2 °/s
IFR
0.5 °/s
50 spikes/s
500 ms

D
Number of cycles
0 50 100 150 200
16 °/s

E
Mean firing rate (sp/s)
0 50 100 150 200
-16 -12 -8 -4 0 4 8 12 16
Velocity (°/s)

F
Proportion of downward choices
0 0.2 0.4 0.6 0.8 1
-16 -12 -8 -4 0 4 8 12 16
Velocity (°/s)
Spontaneous firing rate (spikes/s) vs. Neuron count

3D-PD Rotation gain (spikes/s/°/s) vs. Neuron count

3D-PD Translation gain (spikes/s/G) vs. Neuron count

Key:
- LB-ipsilateral
- LB-contralateral
- Intact

Significance levels:
- ***
- **
- *
Direction detection threshold (cm/s²)

Δ(3D-PD) - Neuron count

Intact

LB-ipsilateral

LB-contralateral