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Behavioral/Systems/Cognitive

Relationship between Complex and Simple Spike Activity in Macaque Caudal Vermis during Three-Dimensional Vestibular Stimulation

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Lobules 10 and 9 in the caudal posterior vermis [also known as nodulus and uvula (NU)] are thought important for spatial orientation and balance. Here, we characterize complex spike (CS) and simple spike (SS) activity in response to three-dimensional vestibular stimulation. The strongest modulation was seen during translation (CS: 12.8 ± 1.5, SS: 287.0 ± 23.2 spikes/s/G, 0.5 Hz). Preferred directions tended to cluster along the cardinal axes (lateral, fore-aft, vertical) for CSs and along the semicircular canal axes for SSs. Most notably, the preferred directions for CS/SS pairs arising from the same Purkinje cells were rarely aligned. During 0.5 Hz pitch/roll tilt, only about a third of CSs had significant modulation. Thus, most CSs correlated best with inertial rather than net linear acceleration. By comparison, all SSs were selective for translation and ignored changes in spatial orientation relative to gravity. Like SSs, tilt modulation of CSs increased at lower frequencies. CSs and SSs had similar response dynamics, responding to linear velocity during translation and angular position during tilt. The most salient finding is that CSs did not always modulate out-of-phase with SSs. The CS/SS phase difference varied broadly among Purkinje cells, yet for each cell it was precisely matched for the otolith-driven and canal-driven components of the response. These findings illustrate a spatiotemporal mismatch between CS/SS pairs and provide the first comprehensive description of the macaque NU, an important step toward understanding how CSs and SSs interact during complex movements and spatial disorientation.

Introduction

The vestibulo-cerebellum (flocculus, ventral paraflocculus, nodulus, and uvula) is phylogenetically old and thus potentially important in providing insights into its highly conserved, exquisite circuitry (Eccles et al., 1966; Eccles, 1967; Fox et al., 1967). Historically, much attention has focused on the role of the flocculus and ventral paraflocculus in motor learning (for review, see du Lac et al., 1995; Raymond et al., 1996; Blazquez et al., 2004; Boyden et al., 2004), whereas the functions of lobules 10 (nodulus) and 9 (uvula) of the caudal vermis, areas thought to be important in spatial orientation, are less well characterized.

Vestibular mossy fibers to the primate nodulus/uvula (NU) arise from primary afferents ipsilaterally (Newlands et al., 2003), and all but the lateral vestibular nucleus (VN) and the nucleus prepositus hypoglossi bilaterally (Rubertone and Haines, 1981; Brodal and Brodal, 1983, 1985; Carleton and Carpenter, 1983; Belknap and McCrea, 1988). Climbing fibers originate mostly from the contralateral inferior olive, primarily the caudal subgroups c (also known as β-nucleus) and d of the medial accessory olive and dorsomedial cell column (Brodal and Kawamura, 1980; Brodal and Brodal, 1981, 1982; Whitworth et al., 1983). Efferents from the primate NU project back to the ipsilateral vestibular and fastigial nuclei (Dow, 1938; Haines, 1977; Carleton and Carpenter, 1983).

Until very recently, the best stimulus for simple spike (SS) and complex spike (CS) responses of NU Purkinje cells was thought to be low-frequency tilt, based on studies in anesthetized rabbits (Barmack and Shojaku, 1995; Fushiki and Barmack, 1997), mice (Yakhnitsa and Barmack, 2006), and cats (Marini et al., 1976). Using for the first time three-dimensional (3D) translation and rotation stimuli at multiple frequencies, Yakusheva et al. (2007, 2008) have recently shown that the strongest and most likely functionally relevant SS modulation is observed during translation. At mid/high frequencies, SSs selectively respond to 3D translation and ignore changes in spatial orientation relative to gravity. Thus, their activity reflects a solution to the otolith afferent ambiguity (Angelaki et al., 1999, 2004; Merfeld et al., 1999), which was shown to arise through convergence of spatially and temporally matched signals from otoliths and semicircular canals, such that they cancel each other out during tilt. However, at low frequencies (less than ~0.1 Hz), the convergent otolith signals are no longer temporally matched and thus SSs cease to be selective for translation and respond to tilt as well (Yakusheva et al., 2008).

Here, we characterize CS activity in response to 3D vestibular stimulation. Special care was taken to simultaneously record both CS and SS activity for a direct comparison of their response properties. We show that CS and SS responses share many similarities, including a strong modulation during 3D translation and low-frequency tilt. However, they also show important differences, including distinct but remarkably consistent spatial and temporal...
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Fastigial nuclei; IntA, interpositus anterior; IntP, interpositus posterior, Dent, dentate. Anatomical structures and lobules were identified according to Madigan and Carpenter (1971) and Paxinos et al. (2000). FN, only a subpopulation of cells was tested during vertical translation). Finally, black-filled circles illustrate CSs with significant modulation during fore-aft motion (largest response modulation. Red fill: CSs with maximum modulation during lateral motion (circular canal contribution to Purkinje cell firing rates (Angelaki et al., 2004; Yakusheva et al., 2007). Note that because during combined tilt minus translation stimuli net linear acceleration is zero, otolith afferents are not activated. Thus, tilt minus translation can be used to isolate and characterize the properties of the vertical semicircular canal contribution to Purkinje cell firing rates (Angelaki et al., 2004; Yakusheva et al., 2007, 2008). These protocols were delivered either during lateral motion and roll tilt and/or fore-aft motion and pitch tilt, whichever gave the largest response modulation. Note that the tilt plus translation protocol was delivered last, and thus responses were only available for a small number of cells.

**Protocol 5.** Finally, a subpopulation of Purkinje cells was tested during 3D motion, using 0.5 Hz translation (±10 cm, 0.1 G) delivered along the three cardinal directions: lateral (left-right), fore-aft, and vertical (up-down). Note that we recorded from all well isolated SSs or CSs; thus, the percentage of translation-responding NU Purkinje cells could be determined.

Protocols 1–4 were delivered using the Acutronic three-axis rotator/sled. Protocol 5 was delivered in the Moog motion platform. Note that no attempt was made to systematically characterize spontaneous activity. This is because most (in not all) NU Purkinje cells are sensitive to static tilt, so really “spontaneous” activity is not easily defined.

**Histology**

For two of the animals (D and F) we pressure injected 0.2 μl of 2% horseradish peroxidase (HRP) as well as 0.1% wheat germ agglutinin or 0.3 μl of 100% biotinylated dextran amine into the deep cerebellar nuclei. After a postinjection survival time of 48 h, the animals were killed under sodium pentobarbital (50 mg/kg, i.v.) and perfused through the heart with a buffered saline prewash followed by a solution containing 1.0% paraformaldehyde and 1.25% glutaraldehyde in 0.1 M phosphate buffer (PB), pH 7.2. The brain was blocked in the frontal plane and removed. It

![Figure 2](image-url)
was cryoprotected in 30% sucrose PB before being frozen and sectioned at a thickness of 80 µm on a sliding microtome. For the recorded neurons of the animals with histology, each cell location was reconstructed according to the relationship between its recorded position (based on the predrilled recording grid hole and micromanipulator depth reading) and the location of the bilateral abducens and deep cerebellar nuclei (which also allowed estimation of distance from midline). For the remaining two animals, where histology is not yet available, we followed the same procedure to place the recorded cells into the sections drawn from animal F (Fig. 2).

Data analysis and statistics
CS activity was isolated off-line using spike sorting (Spike2 software, Cambridge Electronics Design). Subsequently, data were imported into Matlab (MathWorks) and analyzed similarly as done previously for SSs (Yakusheva et al., 2007, 2008). First, responses were binned (40 bins per cycle) and subjected to a permutation analysis to characterize the statistical significance of the response modulation (p < 0.01) (for details, see Yakusheva et al., 2008). Briefly, the 40 response bins were shuffled randomly, thus destroying the systematic modulation in the data but maintaining the inherent variability of the responses. A “Fourier ratio” (FR) was then defined as the ratio of the fundamental over the maximum of the first 20 harmonics as the randomization process was repeated 1000 times. If the FR for the original data exceeded that for 99% of the permuted datasets, the temporal modulation was considered to be statistically significant (p < 0.01).

Subsequently, neural activity was converted into instantaneous firing rate (IFR), computed as the inverse of interspike interval. We then stacked responses to repeated stimulus cycles into a single IFR cycle. Gain and phase were then calculated by fitting both neural response and stimulus with a sine function (first and second harmonics and DC offset) using a nonlinear least-squares algorithm (Levenberg–Marquardt methods). Modulation amplitude was then measured to be half the peak-to-trough sinusoidal fit. Neuronal gain for translation was computed as the ratio of the neural response and stimulus with a sine function (gray lines). Peak modulation amplitudes for CSs were as follows: A: 3.3 spikes/s (cell 1), 0.19 spikes/s (cell 2), and 1.9 spikes/s (cell 3); B: 0.1 spikes/s (cell 1), 1.5 spikes/s (cell 2), and 2.2 spikes/s (cell 3). Note that multiple dots appear on these IFR plots despite low CS firing rates (see spikes for the unfolded data on the left). CS modulate during lateral motion for cell 1, during fore-aft motion for cell 2, and during both motion directions for cell 3. SSs modulate significantly during both lateral and fore-aft translation in all three Purkinje cells. Hacc is linear acceleration stimulus.

Figure 3. A, B. Examples of CS and SS responses from three NI Purkinje cells during lateral (A) and fore-aft (B) translation. Data are shown either as raw spikes (left, bottom traces), isolated CSs (left, top traces), or instantaneous firing rate for SSs (left, middle traces). Right: Responses were analyzed by stacked instantaneous firing rates from multiple cycles and fitting with a sinusoidal function (gray lines). Peak modulation amplitudes for CSs were as follows: A: 3.3 spikes/s (cell 1), 0.19 spikes/s (cell 2), and 1.9 spikes/s (cell 3); B: 0.1 spikes/s (cell 1), 1.5 spikes/s (cell 2), and 2.2 spikes/s (cell 3). Note that multiple dots appear on these IFR plots despite low CS firing rates (see spikes for the unfolded data on the left). CS modulate during lateral motion for cell 1, during fore-aft motion for cell 2, and during both motion directions for cell 3. SSs modulate significantly during both lateral and fore-aft translation in all three Purkinje cells. Hacc is linear acceleration stimulus.

Table 1. Percentage of significant CS modulation encountered for each stimulus condition

<table>
<thead>
<tr>
<th>Experimental protocol</th>
<th>Lateral motion/Roll tilt rotation</th>
<th>Fore-aft motion/Pitch tilt rotation</th>
<th>Vertical motion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Translation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 Hz</td>
<td>52/115 (45%)</td>
<td>55/115 (48%)</td>
<td>21/57 (37%)</td>
</tr>
<tr>
<td>Tilt rotation</td>
<td>13/39 (33%)</td>
<td>17/50 (34%)</td>
<td></td>
</tr>
<tr>
<td>0.05 Hz</td>
<td>10/23 (43%)</td>
<td>14/23 (61%)</td>
<td></td>
</tr>
<tr>
<td>Tilt-translation</td>
<td>12/36 (33%)</td>
<td>17/40 (42%)</td>
<td></td>
</tr>
</tbody>
</table>

The neuronal gain and phase during translation and tilt from two directions (i.e., lateral and/or fore-aft motion or pitch and roll tilt) were fitted with a two-dimensional (2D) spatiotemporal model (Angelaki, 1991, 1992), which computes the preferred direction in the horizontal plane together with the response gain and phase along that direction. For the subpopulation of cells tested with 3D translation, preferred direction was defined in spherical coordinates as follows. First, the preferred direction was computed in the horizontal plane (thus defining the azimuth of the 3D vector). Subsequently, the vertical gain and phase, along with the preferred direction in the horizontal plane, were used to calculate the elevation of the 3D preferred direction (for details, see Yakusheva et al., 2008; Liu and Angelaki, 2009).

We quantified whether a measured distribution was significantly different from a uniform distribution by performing a resampling analysis as follows: (1) we calculated the sum-squared error (across bins) between the measured distribution and an ideal uniform distribution containing the same number of observations; (2) we also calculated the sum-squared error between a random distribution that was created by drawing the same number of data points from a uniform distribution and the ideal uniform distribution; (3) this second step was repeated 1000 times to generate a distribution of sum-squared error values that represent random deviations from an ideal uniform distribution; (4) if the sum-squared error for the experimentally measured distribution lay outside the 95% confidence interval of values from the randomized distributions, then the measured distribution was considered to be significantly different from uniform (p < 0.05). For nonuniform distributions, a modality test was also performed to further test whether they are unimodal or bimodal (for details, see Takahashi et al., 2007). The test generated two p values, with the first one (puni) for the test of unimodality and the second one (pbi) for the test of bimodality.

Finally, to determine whether the CS of each Purkinje cell correlated best with translation or net linear acceleration, linear regression analysis...
was used to simultaneously fit the cumulative cycles of cell modulation during each of the translation, tilt, and combined stimuli with net acceleration- and translation-coding models (for details, see Angelaki et al., 2004; Green et al., 2005). Briefly, these models assume that neural firing rate modulation is due either to the net acceleration or to the translational acceleration component. How well each of these two models fitted the data was evaluated using a partial correlation analysis. To remove the influence of correlations between the predictions themselves, we calculated partial correlation coefficients, which were subsequently converted to z-scores using Fisher’s r-to-z transform to facilitate the interpretation of statistical significance independently of the number of data points (for further details of this analysis, see Angelaki et al., 2004; Green et al., 2005; Yakusheva et al., 2007). The advantage of this comparison is that when z-scores for one model are plotted versus the respective z-scores for the other model, the plot can be easily separated into regions in which data points can be distinguished as being better correlated with one model as compared with the other at a particular level of significance. Only CS responses obtained for all four stimulus combinations (translation, tilt, tilt minus translation, and tilt plus translation) were used for this analysis.

Results

We recorded complex spike activity from 115 Purkinje cells in the cerebellar nodulus and uvula (lobules 10 and 9, respectively) of four monkeys (animal V: 63 cells; animal W: 28 cells; animal F: 10 cells; and animal D: 14 cells). Of these, both SSs and CSs were recorded from all but three cells for which only CSs (but not SSs) were isolated. Among these 112 simultaneously recorded CS/SSs, 81 pairs were confirmed to arise from the same Purkinje cell, by observing a pause of 10–20 ms in SS activity following each CS (Fig. 1B) (Granit and Phillips, 1956); only this group of cells for which CS-triggered silencing of the simultaneously recorded SS could be confirmed were used in CS/SS comparisons. Note that although the SS response properties of a smaller population of Purkinje cells have been presented by Yakusheva et al. (2007, 2008), basic findings are replotted in Figures 4, 5, and 12 whenever relevant for comparisons with CS responses.

Recording tracks were later confirmed histologically in animals F and D (Yakusheva et al. 2007, their supplemental Figs. 1, 2). Figure 2 plots all recorded CSs projected onto coronal sections through the cerebellar nodulus and uvula of animal F. Note that recordings extended into lobules 9 and 10, including the ventral (folia 9d and 9c) and dorsal (folia 9a and 9b) uvula (Fig. 2). The properties of CSs described here were characteristic of both nodulus and ventral/dorsal uvula, and we found little difference in vestibular responses within folia 9a, 9b, 9c, 9d, and 10 (see Discussion). There was no evidence of topography for either response type or translation preferred direction within the nodulus and uvula. We started by comparing the properties of CS and SS responses during translation, which is the stimulus we tested first upon isolation of a complex spike.

CS responses during translation: 2D spatial properties

Of 115 well isolated CSs tested during 0.5 Hz translation in the horizontal plane, 52 (45%) and 55 (48%) modulated significantly during lateral and/or fore-aft motion, respectively (Table 1). Examples of simultaneously recorded CS and SS responses during lateral and fore-aft translation are shown for three Purkinje cells in Figure 3, A and B. Responses from four cycles of 0.5 Hz trans-
luation are illustrated as raw CSs and SSs (left column, bottom traces), as well as separately as discriminated CSs (Fig. 3 A,B, left columns, top traces marked “CS”) and instantaneous firing rate for SSs (Fig. 3 A,B, left columns, middle traces marked “SS”).

Instantaneous firing rates from multiple cycles were overlaid and fitted with a sinusoidal function (Fig. 3 A,B, right columns, top: CSs, bottom: SSs). Please note that because IFRs from multiple cycles were stacked, many data points appear on each of these single-cycle IFRs. As reported previously (Bauswein et al., 1983; Kano et al., 1991; Barmack and Shoja, 1995; Yakhnitsa and Barmack, 2006), CSs had low spontaneous firing rates and were typically driven to modulation amplitudes of 0.23–6.7 spikes/s (mean ± SEM: 1.85 ± 0.15, n = 85) as illustrated in Figure 4 A, which plots the distribution of CS response amplitudes along the maximum response direction from sinusoidal fits such as those shown in Figure 3 (gray lines). This range is comparable to the modulation previously reported during low-frequency tilt in anesthetized rabbits (Barmack, 2003). The modulation amplitude for SSs was larger (Fig. 4 B), ranging from 10 to 183 spikes/s, with an average of 54.1 ± 2.4 (± SEM; n = 269).

In addition to response modulation amplitude, other differences between CSs and SSs can already be seen in these representative examples. SSs typically modulated during both lateral and fore-aft translation; in contrast, most CSs (63/115) responded only to translation along one of the two motion directions (e.g., cell 1: lateral motion; cell 2: fore-aft motion). Only a few (22/115) CSs had significant modulation during both lateral and fore-aft translation (e.g., cell 3). As shown later, these representative examples reflect an overall tendency of CS responses to prefer cardinal (i.e., lateral, fore-aft, or vertical) movement directions.

For 85 (74%) CSs that modulated significantly along either lateral or/and fore-aft translation at 0.5 Hz, the preferred direction in the horizontal plane was computed using a spatiotemporal model (Angelaki, 1991, 1992; Angelaki and Dickman, 2000) (see Materials and Methods). The resulting polar plot showing both maximum response gain and preferred direction is shown in Figure 4C. Here, each dot corresponds to a cell’s CS response, with the distance to the origin illustrating response gain (in units of spikes/s/G), and its angular location illustrating the preferred direction (Fig. 4C, drawing, upper left). Translation response gains along the horizontal plane (2D) preferred direction averaged 9.8 ± 0.8 spikes/s/G (± SE).

The preferred directions of CSs were not lateralized, such that both leftward and rightward preferred directions were encountered in the right and left NU (Fig. 4C, filled vs open circles). There was, however, a tendency for CS preferred directions to cluster along the cardinal axes. This was quantified in Figure 4D (filled bars), which plots the histogram of preferred directions in the range [0°, 180°], where 0°/180° and 90° correspond to forward/backward and lateral motion directions, respectively. The distribution was not uniform (uniformity test, p = 0.016) and appeared to have peaks around the cardinal axes, 0°/180° and 90°, although the distribution was not significantly bimodal (modality test, puni = 0.09, pbis = 0.95). The distribution of the preferred directions for CSs contrasts that for SSs (Fig. 4D, hatched bars), which were clustered along oblique axes (45°/135°) (Yakusheva et al., 2008).

To further emphasize the difference in preferred translation direction for CSs and SSs, the histogram of the absolute direction difference between simultaneously recorded SSs and CSs (confirmed to be from the same Purkinje cell, as in Fig. 1B) is illustrated in Figure 4E. At the level of individual Purkinje cells, the preferred direction difference between CS and SS responses to translation tend to cluster around 45° and 135° (n = 61; due to the small sample size, the distribution was not different from uniform; p = 0.08). For both CSs and SSs, the distribution of translation response phase (expressed relative to linear acceleration) was broad (Fig. 4F) (Yakusheva et al., 2007, 2008). We will compare other properties of CSs and SSs (e.g., gain and phase) later in this section. First, we will quantify the relationship between CS and SS preferred directions during 3D translation.
CS responses during translation: 3D spatial properties
A subpopulation (57) of well isolated CSs was tested during 3D translation. CS and SS responses from an example Purkinje cell that preferred vertical over horizontal translation are shown in Figure 5A. Twenty-one (37%) CSs had significant modulation (p < 0.01, permutation test; see Materials and Methods) during vertical translation (Table 1), and 48 (84%) CSs showed significant modulation along at least one of the lateral, fore-aff, or vertical motion directions. Most (31/48, 65%) responding CSs modulated during translation along only one of the three cardinal directions. Importantly, only nine (16%) CSs were unresponsive to translation when tested in 3D.

From a total of 48 CS/SS pairs (verified to arise from the same Purkinje cell) (Fig. 1B), 38 (79%) CSs and 46 (96%) SSs modulated significantly for at least one translation direction. For 36 (75%) pairs, there was a significant modulation of both SSs and CSs, whereas only SS modulation was seen in 10 cells and only CS modulation was seen in 2 Purkinje cells. Thus, 0.5 Hz translation stimuli were very effective in eliciting both SS and CS modulation.

For cells with significant modulation along at least one stimulus direction, the 3D preferred direction gain, phase, and orientation were computed using a spatiotemporal model (Angelaki et al., 1992; Liu and Angelaki, 2009) (see Materials and Methods). Translation response gains along the 3D preferred direction (at 0.5 Hz and computed only for responsive cells) averaged 12.8 ± 1.5 (±SE) spikes/s/G (CS) and 287.0 ± 23.2 spikes/s/G (SS). The orientation of the 3D preferred direction was defined using spherical coordinates, i.e., each preferred direction was described by two angles, azimuth and elevation. These angles are illustrated in Figure 5B (CS) and 5C (SS), both as scatter plots (elevation vs azimuth) and as marginal distributions. Each data point in the plot corresponds to the preferred direction of one Purkinje cell, defined by a set of two angles, azimuth and elevation. For example, when [azimuth, elevation] = [0°,0°], the preferred direction points forward, [90°,0°] is leftward, whereas elevation angles of 90° and −90° illustrate upward and downward preferring directions.

For CS preferred directions, the distribution of elevation angles was not uniform (uniformity test, p = 0.003), with some Purkinje cells preferring vertical directions and others preferring horizontal directions (Fig. 5B). A similar but less dramatic organization also characterized the distribution of elevation angles for SSs (Fig. 5C) (uniformity test, p = 0.027). For illustrative purposes, cells with |elevation| >45° have been labeled red (CS) or blue (SS) to distinguish them from horizontally tuned cells (black dots) in subsequent figures.

For the 36 CS/SS pairs with significant 3D translation responses of both CSs and SSs, the absolute angular difference in 3D preferred directions (|Δ(CS-SS)|, 3D preferred direction) has been compared with the corresponding preferred direction difference in 2D (i.e., the horizontal plane, |Δ(CS-SS)|, 2D preferred direction) in the scatter plot of Figure 6A. For Purkinje cells whose SS and CS preferred directions both lie within 45° of the horizontal plane, data points fall along the unity-slope diagonal (Fig. 6A, black dots). This is not surprising, since for horizontally tuned cells, |Δ(CS-SS)|, 3D preferred direction| ≈ |Δ(CS-SS)|, 2D preferred direction|. As illustrated in Figure 6A (black bars), marginal distributions tended to cluster around 45° and 135° (see also Fig. 6E).

However, when only one of the preferred directions has |elevation| >45° and the other has |elevation| <45° (i.e., when one preferred direction is near vertical but the other is near horizontal), the |Δ(CS-SS)|, 3D preferred direction| is ~90° (Fig. 6A, right, red and blue marginal histograms), whereas the difference in the vectors’ projection onto the horizontal plane, |Δ(CS-SS)|, 2D preferred direction, remains clustered around 45° and 135° (Fig. 6A, top, red and blue marginal histograms). This occurs because the preferred directions for CSs and SSs appear to cluster along 3D orthogonal axes, of which the vertical axis is common, but the horizontal axes are rotated relative to each other by 45° (Fig. 6B).

Thus, in summary, CSs respond to 3D translation, as do SSs. However, CS preferred directions tend to be organized in the cardinal 3D coordinate system (i.e., vertical, lateral, fore-aff) (Fig. 6B, magenta arrows), whereas SS preferred directions use the semicircular canal coordinate system (i.e., vertical and oblique directions in the horizontal plane) (Fig. 6B, green arrows). Note also that preferred directions for CS and SS responses from a single Purkinje cell are rarely aligned in 3D. For approximately half of Purkinje cells (19/36), one (either CS or SS) prefers vertical
translation and the other horizontal translation (Fig. 6A, red and black symbols/bars). For another 13/36 cells, both CSs and SSs have preferred directions close to the horizontal plane, 45/135° apart from each other (Fig. 6A, black symbols/bars). Finally, only four Purkinje cells have [elevation] >45° for both SSs and CSs (Fig. 6A, mixed red/blue dots and bars). This spatial misalignment (by either 45° or 90°) of CS/SS pairs is striking (see Discussion).

CS responses during translation: dynamics

How CS modulation changes as a function of frequency is illustrated with an example cell in Figure 7A. Note that responses were characterized during either lateral or fore- aft motion, to whichever stimulus the cell responded best. For both CSs and SSs, modulation decreased as frequency was increased (Fig. 7A). CS gain and phase, plotted as a function of frequency, have been summarized for 13 Purkinje cells in Figure 7B and C, respectively. CS gains decreased with increasing frequency (ANCOVA, \( F_{(2,35)} = 12.4, p < 0.001 \)), but phase was independent of frequency (ANCOVA, \( F_{(2,35)} = 1.5, p = 0.18 \)).

To directly compare the dynamics of CSs and SSs during translation, we first normalized gains to 1 at 0.5 Hz and then computed averages as a function of frequency (Fig. 7D). Gain versus frequency slopes were larger for CSs (−1.24, CI = [−1.68, −0.81]) than for SSs (−0.70, CI = [−0.98, −0.41]) (where CI is confidence interval), although the difference was not significant (overlapping 95% confidence intervals). These near-unity slopes in log-log frequency plots suggest a temporal integration (Ogata, 1970), i.e., responses appear to follow linear velocity rather than linear acceleration. Indeed, when we recalculated gains relative to linear velocity, CS gains were independent of frequency (ANCOVA, \( F_{(2,35)} = 0.14, p = 0.86 \)) and the slope was not significantly different from zero (−0.20, CI = [−0.68, 0.19]). By comparison, the velocity gains of SSs show a significant increase with frequency (ANCOVA, \( F_{(2,35)} = 5.3, p = 0.009 \)), with a slope of 0.56 (CI = [0.23, 0.78]) (Yakusheva et al., 2008). Thus, although similar, CS/SS response dynamics may not be identical because CSs follow linear velocity, whereas SSs respond to combinations of linear velocity and linear acceleration.

CS responses during pitch/roll rotation (tilt)

After the translation stimuli, and as long as isolation was maintained, Purkinje cells were also tested during pitch and/or roll tilt, first at 0.5 Hz, then at 0.05 Hz, and subsequently at additional frequencies (see Materials and Methods). Example SS/CS responses during pitch and roll tilt at 0.5 and 0.05 Hz are illustrated in Figure 8A. Note that preferred directions are again not aligned. This particular cell preferred roll with its CS response and pitch with its SS response. Also note that the modulation magnitude of both SSs and CSs increased at 0.05 Hz as compared with 0.5 Hz.

A third of CSs modulated significantly during 0.5 Hz tilt, and this percentage nearly doubled at 0.05 Hz (Table 1); of 23 CSs tested with 0.05 Hz roll/pitch rotations, 17 (74%) modulated significantly for either pitch and/or roll. The increase in gain with decreasing frequency was a consistent finding for all Purkinje cells, as illustrated in Figure 8B, which summarize CS gain as a function of frequency. The dependence of gain on frequency was significant (ANCOVA, \( F_{(4,89)} = 8.7, p < 0.001 \)), whereas, as evident in Figure 8C, phase was independent of frequency (ANCOVA, \( F_{(4,89)} = 0.4, p = 0.8 \)).

Average CS and SS dynamics during tilt were similar (Fig. 8D), with slopes of −1.09 (CI = [−1.30, −0.87]) and −0.82 (CI = [−0.94, −0.70]) for both CSs and SSs, respectively. For a given peak velocity, the monkey moved much more during 0.05 Hz tilt than during 0.5 Hz tilt. Thus, when expressed relative to tilt position, gains became independent of frequency (CS: ANCOVA, \( F_{(4,100)} = 0.21, p = 0.88 \)) and SS: \( F_{(4,132)} = 0.45, p = 0.76 \) (data not shown) (but see Yakusheva et al., 2008). Thus, both CS and SS responses follow head position during tilt.

CS preferred directions during 0.5 Hz, 0.05 Hz, and 0.02 Hz tilt (computed using the spatiotemporal model; see Materials and Methods) are shown as polar plots in Figure 9A and as histogram distributions in Figure 9B, C (0.05 Hz) and D (0.02 Hz). Although the data sample of tilt-responding cells is too small for statistical comparisons, there is some trend for 0.5 Hz preferred directions to cluster around roll (90°/270°) and low frequency (0.05 and 0.02 Hz) preferred directions to cluster around pitch (0°/180°). Such potential change in tilt preferred direction needs to be scrutinized in future studies.

CS responses during combinations of tilt and translation

Using combinations of 0.5 Hz tilt and translation stimuli, we have previously shown that SS responses correlate best with translation rather than with net linear acceleration (i.e., the sum of tilt-related gravitational and translational accelerations, which is the stimulus activating otolith afferents) (Yakusheva et al., 2007, 2008). To test whether CS responses also selectively correlate with translation and ignore changes in the orientation of the head

Figure 7. CS response dynamics during translation. A, Examples of CS and SS responses during lateral translation at 0.16, 0.5, and 1 Hz. B, C, Neuronal gain (\( B \)) and phase (\( C \)) (expressed relative to linear acceleration) are plotted as a function of frequency for individual CS responses (\( n = 13 \)). D, Normalized average gains are shown for both CSs (black solid line) and SSs (gray dashed line). Gains have been normalized by dividing each gain value by the cell’s 0.5 Hz gain before the calculation of the average.
relative to gravity during tilt, we recorded CS responses during tilt, translation, and combined tilt/translation at 0.5 Hz (tilt minus translation and tilt plus translation; see Materials and Methods) (Angelaki et al., 2004), as shown with the schematics of Figure 9 (top). Because peak tilt amplitude is such that the horizontal linear acceleration due to gravity is the same as that during translation, when both translation and tilt are presented together, the net horizontal acceleration is either zeroed (tilt minus translation) or doubled (0.4 G, tilt plus translation, see Materials and Methods).

Representative examples of simultaneously recorded SS and CS responses are shown in Figure 10 for two Purkinje cells. Although net acceleration was the same during translation and tilt, both CS and SS responses of Purkinje cell 1 modulated more strongly during translation than during tilt (compare peak-to-trough sinusoidal modulation of firing rate). When translation and tilt were presented simultaneously, such that net horizontal linear acceleration was either zero (tilt minus translation) or double (tilt plus translation), CS/SS responses for cell 1 appeared similar to those during translation.
Thus, cell 1, typical of all SS responses in the NU (Yakusheva et al., 2007), had both CS and SS responses following translation rather than net linear acceleration. Results differed for the CS responses of cell 2. Unlike the SS modulation, which was selective for translation, the CS responses of cell 2 followed net acceleration; i.e., responses were similar (although small) for translation and tilt, negligible during tilt minus translation and twice as big during tilt plus translation.

Results are summarized in Figure 11, where CS response amplitude and phase during tilt, tilt minus translation, and tilt plus translation have been plotted versus the respective responses during translation. If responses follow net acceleration, data should fall along the gray dashed lines. In contrast, if responses follow translation, data should fall along the solid black lines. Data are mixed, with a few CSs falling along the gray dashed lines (indicating net acceleration-like responses) and others along the solid black lines (indicating translation-coding responses). Importantly, most CS responses modulated during tilt minus translation, although primary otolith afferents do not respond to this stimulus (because the net horizontal plane linear acceleration is zero). Across the population, CS responses to both tilt and tilt minus translation were significantly smaller compared with those during translation [Wilcoxon rank test: p < 0.001 (Fig. 11A), p = 0.002 (Fig. 11B)] but similar during tilt plus translation and translation [Wilcoxon rank test, p = 0.53 (Fig. 11C)]. Similarly for the response phase, some data points fell along the predictions of net acceleration (gray dashed lines), but others fell along the predictions of translation coding (Fig. 11 D–F, solid black lines).

To quantify these observations, multiple linear regression analysis was used in n = 15 cells that were tested under all four stimulus conditions to compute partial correlation coefficients of how well each CS response to translation, tilt, tilt minus translation, and tilt plus translation could be predicted by net acceleration or translation-coding models, e.g., how well the modulation of the cells in Figure 10 could be described by the pattern of modulation of Hacc (head translational acceleration), illustrating the translation model, and Net acc, illustrating the net gravitational acceleration model (for details, see Green et al., 2005; Yakusheva et al., 2007). To simplify plotting and visual interpretation, the variances of these partial correlation coefficients were normalized using Fisher’s r-to-z transform (Angelaki et al., 2004). Figure 12 shows the resulting scatter plot, where dashed lines mark the 0.01 level.
of significance (which is a straight line because of the z-transform). Data points that fall above the top dashed line illustrate Purkinje cells whose responses fit better with the translation model, whereas data points below the lower dashed line illustrate responses that fit better with the net acceleration model (data points between the two dashed lines correspond to responses for which a best-fit model could not be distinguished at a significance level of \( p = 0.01 \).

In addition to CS data (black circles), Fig. 12 also plots SS data from Yakusheva et al. (2007) for comparison (gray circles). The majority (11/15, 2 cells in the nodulus, 6 cells in the ventral uvula, and 3 cells in the dorsal uvula) fall in the upper-left quadrant, illustrating that their firing rates were better correlated with translation; the remaining 4/15 CS responses (2 in the ventral uvula and 2 in the dorsal uvula) were better correlated with net acceleration (Fig. 12, lower-right quadrant). Thus, the distribution of CS responses is similar to that of SS responses in that most correlate best with translation than with net linear acceleration. Still, CS responses are distinct from SS responses in that about a quarter of them correlate best with net linear acceleration. In contrast, none of the SS responses we encountered correlated best with net linear acceleration. Importantly, even for those four CS responses that correlated best with net linear acceleration, responses were generally weak and modulation to tilt was not significant (permutation test, see Materials and Methods). Because the correlation analysis uses the responses to all four stimuli simultaneously, the highest correlation with net linear acceleration came about because of the following: (1) smaller responses during tilt minus translation than translation; and (2) larger responses during tilt plus translation than tilt and translation (as with the example cell 2 in Fig. 10).

**CS responses during yaw rotation**

Yaw responsiveness (0.5 Hz) was also tested in a subpopulation \((n = 15)\) of cells, as illustrated with an example in Figure 13A. None of the SSs showed a significant modulation during yaw rotation (see also Yakusheva et al., 2007, 2008). In contrast to SSs, CS yaw modulation was significant in 4/15 (27%) Purkinje cells, as illustrated with the example of Figure 13A, and with the summary data of Figure 13B. One of those yaw-responding cells was located in the ventral uvula, whereas the remaining three cells with significant yaw responses were encountered in the dorsal uvula. The yaw-responding cell in the ventral uvula was one of the cells in Figure 12 correlating better with translation than with net linear acceleration. Among the yaw-responding cells in the dorsal uvula, one responded to neither tilt nor translation, another responded to translation but not tilt, and the third responded to tilt and vertical (but not horizontal plane) translation.

**Gain and phase relationship between SSs and CSs during vestibular stimulation**

We now return to the relationship between response properties of CS and SS, identified as simultaneously recorded pairs (as in Fig. 1). How response gains for simultaneously recorded CS/SS pairs relate to each other has been illustrated in Figure 14, A (translation) and B (tilt). This analysis only included CS/SS pairs for which data were collected for both lateral/fore-aft (translation) and roll/pitch (tilt) stimuli and were applied to the gain of the preferred direction (horizontal plane) of both CSs and SSs. This is important, because preferred directions for CS/SS responses did not match; thus, any attempt to correlate CS/SS
translation or tilt modulation gain along a single axis could be misleading. There was a significant correlation between the CS/SS gain during tilt (Fig. 14B) (Spearman rank correlation, \( p < 0.001 \)), but not during translation (Fig. 14A) (Spearman rank correlation, \( p = 0.63 \)). Note, however, that these comparisons were based on 0.5 Hz data for translation and mainly lower frequency data for tilt. Thus, they could reflect either translation/tilt or high-/low-frequency differences; for example, it is possible that a better CS/SS gain correlation might also exist for low-frequency translation. At present, these data do not allow a firm conclusion.

Perhaps the most conspicuous observation is that the CS modulation during vestibular stimulation was not always out of phase with the SS modulation, a finding that contrasts with what was previously reported in rabbits (Fushiki and Barmack, 1997). This observation is readily seen in the raw waveforms and discriminated spikes in Figures 3, 5, 7, 8, and 10. On a cell-by-cell basis (note that this comparison was only done for identified SS/CS pairs) (Fig. 1), the (SS-CS) phase difference was similar for lateral/fore-aft translation (Fig. 14C) (Wilcoxon rank test, \( p = 0.51 \)) or pitch/roll tilt (Fig. 14D) (Wilcoxon rank test, \( p = 0.027 \)), but varied broadly from cell to cell. The (SS-CS) phase difference distributions were uniform (uniformity test, \( p > 0.05 \); marginal distributions) (Fig. 14C, D).

Remarkably, for individual Purkinje cells the (SS-CS) phase difference during translation was identical to that during tilt minus translation (Wilcoxon rank test, \( p = 0.16 \)) (Fig. 15A) and tilt plus translation (Wilcoxon rank test, \( p = 0.9 \)) (Fig. 15B), with slopes that were not significantly different from unity: 95% confidence interval, [0.7, 1.2] and [0.92, 1.62], \( p < 0.001 \). There was also no difference with the (SS-CS) phase difference during translation and tilt (Wilcoxon rank test, \( p = 0.9 \)).

Thus, in summary, CSs did not always modulate out of phase with SSs. Yet, although the phase difference between the modulation of CSs and SSs was broadly distributed across the population of Purkinje cells, that difference was matched on a cell-by-cell basis such that it was exactly the same for translation, tilt minus translation, tilt plus translation, and tilt. Such matching of the (SS-CS) phase difference is of particular relevance for translation versus tilt minus translation. Recall that translation activates otolith afferents only, and thus translation responses reflect the otolith-driven component of Purkinje cell responses. In addition, during the tilt minus translation stimulus otolith afferents do not respond at all (because the net horizontal plane linear acceleration is zero) (Angelaki et al., 2004); thus, tilt minus translation responses reflect the contribution of semicircular canal activation to Purkinje cell responses (Shaikh et al., 2005; Yakusheva et al., 2007). Thus, the findings of Figure 15 show that the (SS-CS) phase difference is precisely matched for the otolith-driven and canal-driven components of the Purkinje cell response (see Discussion).

**Discussion**

We have quantified the properties of the complex spike responses of NU Purkinje cells during 3D vestibular stimulation and have compared them with the properties of SS responses (Yakusheva et al., 2007, 2008). Our main findings are discussed below.

First, the strongest SS/CS modulation was seen during translation. CS preferred directions tended to cluster along the three cardinal (vertical, lateral, and fore-aft) axes, whereas SS preferred directions clustered along the semicircular canal axes (vertical and the two 45° oblique horizontal axes) (Fig. 6B) (Yakusheva et
al., 2008). Most notably, the preferred directions for CS/SS pairs arising from the same Purkinje cells were rarely aligned.

Second, both CSs and SSs modulated little during 0.5 Hz pitch/roll tilt, but gains increased with decreasing frequency. However, unlike SS responses, none of which followed net linear acceleration at 0.5 Hz (Yakusheva et al., 2007, 2008), CS responses were mixed, most correlating best with translation (while ignoring changes in spatial orientation relative to gravity) and about a third correlating best with net linear acceleration.

Third, CSs and SSs had similar response dynamics. During tilt, both CSs and SSs responded to angular position. During translation, CSs followed linear velocity, whereas SSs encoded combinations of linear velocity and linear acceleration (Yakusheva et al., 2008).

Fourth, a small percent of CSs in the uvula were modulated during 0.5 yaw rotation. This finding contrasts with SSs, which never modulated during earth-vertical axis rotations (e.g., yaw from an upright orientation) (Yakusheva et al., 2007, 2008).

Fifth, CSs did not always modulate out of phase with SSs. Simple and complex spikes could respond to vestibular stimulation either in phase or out of phase and the distribution of CS/SS phase difference was broad and uniform. For each individual Purkinje cell, however, the CS/SS phase difference was precisely matched for the otolith-driven and canal-driven components of the response.

**CS and SS modulation during vestibular stimulation**

Clustering of preferred directions has been reported previously for visually driven CSs in the vestibulo-cerebellum. For example, optokinetic preferred directions for CS/SSs in the rabbit flocculus were clustered along the semicircular canal axes (i.e., along two oblique $45^\circ$ directions in the horizontal plane and the vertical axis) (Graf et al., 1988). In birds, preferred directions of NU CS responses to translational optic flow were also organized along the semicircular canal axes (Wylie and Frost, 1999). To our knowledge, vestibular responses in the NU were previously tested only during static and dynamic tilt (Marini et al., 1976; Barmack and Shojaku, 1995; Fushiki and Barmack, 1997; Yakhnitsa and Barmack, 2006), thus providing an incomplete picture of their properties. All vestibularly responsive CSs were sensitive to static tilt in mice (Yakhnitsa and Barmack, 2006), but only about half were static tilt sensitive in rabbits (Fushiki and Barmack, 1997). Although we have not tested macaque Purkinje cells with static and Barmack (1997), has been found in neither mice (Yakhnitsa and Barmack, 2006) nor macaques (present study).

Neither we (Yakusheva et al., 2007, 2008) nor others (Barmack and Shojaku, 1995; Yakhnitsa and Barmack, 2006) observed SS modulation during yaw rotation despite strong horizontal canal afferent inputs to the NU (Keveketter and Perachio, 1986; Purcell and Perachio, 2001; Maklad and Fritsch, 2003; Keveketter et al., 2004). In fact, $\sim27\%$ of mossy fibers in the rabbit NU responded to yaw rotation (Barmack and Shojaku, 1995). We (Green et al., 2005; Green and Angelaki, 2007; Yakusheva et al., 2007) have proposed that horizontal canal inputs are gated by a signal reflecting orientation relative to gravity. According to this framework, NU Purkinje cells would respond to yaw rotations that change orientation relative to gravity (e.g., yaw while laying on our side or back) (Green and Angelaki, 2004, 2007). In support of this hypothesis, rotations about pitch/roll axes activate SSs when they reflect tilt relative to gravity (i.e., delivered while upright) but are ineffective when they do not change orientation relative to gravity (i.e., in ear-down or prone/supine positions) (Yakusheva et al., 2007).

Unlike SSs, a few CSs, one in the ventral uvula and three in the dorsal uvula, modulated significantly during yaw from an upright orientation (Fig. 13). CS modulation during yaw was also reported in cats (Precht et al., 1976; Robinson et al., 1988), but not in rabbits and mice (Barmack and Shojaku, 1995; Yakhnitsa and Barmack, 2006).

**Nodulus versus uvula: neuroanatomical versus physiological findings**

We found few differences in the vestibular properties of CS/SSs based on their location within the nodulus, ventral uvula, and dorsal uvula. This might be surprising given the different behavioral effects observed with electrical stimulation (Heinen et al., 1992; Solomon and Cohen, 1994) or lesions (Angelaki and Hess, 1995; Heinen and Keller, 1996; Wearne et al., 1998), as well as the known differences in afferent and efferent projections. For example, vestibular primary afferents reach the nodulus and ventral (but not dorsal) uvula (Newlands et al., 2003). In addition, VN mossy fiber inputs become progressively fewer from nodulus to ventral uvula to dorsal uvula (Rubertone and Haines, 1981; Sato et al., 1989; Thunnissen et al., 1989). The dorsal uvula instead receives major mossy fiber inputs from the pontine nuclei (Sato et al., 1989; see also review by Voogd et al., 1996). However, such differences might not exist for CSs; the termi-

![Figure 15. Summary of the (SS-CS) phase difference during tilt minus translation ($|\Delta(\text{SS-CS})|$) plotted versus the corresponding (SS-CS) phase difference during translation. The corresponding marginal distributions for tilt minus translation and tilt plus translation are also shown on the right. Data are shown for either lateral motion/roll tilt and/or fore-aft motion/pitch tilt, whichever direction produced largest responses.](image-url)
nation of vestibular-responding climbing fibers is organized into longitudinal zones extending throughout the nodulus and dorsal and ventral uvula (Whitworth et al., 1983; Kanda et al., 1989; Voogd et al., 1996).

Unlike mossy fiber projections from both vestibular afferents and VNs that terminate diffusely and not in sagittal zones, there is a strict topology and modular organization in the climbing fiber, cerebellar output, and nucleo-olivary projections (Akaogi et al., 1994; Voogd et al., 1996; Wearn et al., 1998; Wylie et al., 2003; for review, see Voogd et al., 1996). Such zonal organization has been observed physiologically in the preferred directions of canal and visual CS activity in the vestibulo-cerebellum (Fushiki and Barmack, 1997; Graf et al., 1988; Wylie and Frost, 1999). We did not observe such an organization based on the CS preferred directions to translation (Fig. 2). Thus, in agreement with the lack of any obvious sagittal plane organization of CS preferred directions during static tilt (Fushiki and Barmack, 1997; Yakhnitsa and Barmack, 2006), it is likely that otolith-driven climbing fiber inputs to the NU might not adhere to the zonal organization followed by canal-driven and visually driven signals.

CS and SS interactions

The most salient finding is that NU CSs/SSs are misaligned, both spatially and temporally. Spatially, because CS/SS translation preferred directions differ by 45° (horizontal plane) or 90° (in 3D). Temporally, because CSs do not always modulate out of phase with SSs. The CS/SS phase difference varied broadly among Purkinje cells, yet for each cell it was precisely matched for the otolithic-driven and canal-driven components of the response (Fig. 15). We have shown previously that spatially and temporally matched otolith-driven and canal-driven SS response components represent a hallmark signature of their ability to compute translation. It is likely that the two findings are related, i.e., the precise spatiotemporal CS/SS mismatch across NU Purkinje cells (while maintaining a precise CS/SS matching for otolith/canal responses on a cell-by-cell basis) might be functionally linked to the reported precise canal/otolith spatiotemporal matching on a cell-by-cell basis while maintaining an across-Purkinje cell mismatch on preferred direction and phase (Green and Angelaki, 2004).

In-phase SS and CS modulation has also been recently described in the flocculus of awake rabbits during rotation in darkness (Simpson et al., 2002), a finding that contrasts the reciprocal relationship between SSs and CSs during visual stimulation (Graf et al., 1988; Stone and Lisberger, 1990; Kobayashi et al., 1998; Kitama et al., 1999). In the NU, Fushiki and Barmack (1997) reported out-of-phase CS/SS modulation during tilt in darkness. At present, the reasons for these differences remain unclear.

It is important to emphasize that even Purkinje cells with in-phase CS/SS modulation exhibited the characterizing SS pause following a CS (Fig. 1). These two properties operate in different time scales (tens of milliseconds versus several seconds for 0.1–1 Hz stimuli) and are not necessarily related, as suggested previously (Fushiki and Barmack, 1997). In addition, unlike Barmack and Shojaku (1995), we found either SS/CS relationship: SS modulation in the absence of CS modulation, or CS modulation in the absence of SS modulation. Yet, in agreement with Fushiki and Barmack (1997), we also found a significant correlation between CS/SS gain during low-frequency tilt (Fig. 14B). However, there was no CS/SS gain correlation for mid-/high-frequency translation (Fig. 14A).

Despite years of debate, there is little consensus about the role of SSs and CSs in cerebellar function (Lou and Bloedel, 1992; Welsh and Llinas, 1997; Gibson et al., 2004; Manzoni, 2005; Bengtsson and Hesslow, 2006; Jacobson et al., 2008; D’Angelo et al., 2009). The exquisitely elegant circuitry of the cerebellar cortex has been described often as ideal for precise spatial and temporal computations (Yarom and Cohen, 2002; Ohyama et al., 2003; Ito, 2006; Jacobson et al., 2008). In the macaque NU, we have started gaining some basic understanding of CS/SS responses under simple vestibular stimulation. Future studies examining how NU Purkinje cells change their activity under conditions of sensory conflict and spatial disorientation might provide fundamental insight into their function. Equally important is the understanding of how visual cues drive and/or modify SS/CS activity. Characterization of the role of the caudal vermis in these spatiotemporal multisensory computations might provide new functional insights into the role of the cerebellar cortex and its circuitry.

References


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