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Vestibular responses in the macaque pedunculo pontine nucleus and central mesencephalic reticular formation

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Abstract

The pedunculo pontine nucleus (PPN) and central mesencephalic reticular formation (cMRF) both send projections and receive input from areas with known vestibular responses. Noting their connections with the basal ganglia, the locomotor disturbances that occur following lesions of the PPN or cMRF, and the encouraging results of PPN deep brain stimulation in Parkinson's disease patients, both the PPN and cMRF have been linked to motor control. In order to determine the existence of and characterize vestibular responses in the PPN and cMRF, we recorded single neurons from both structures during vertical and horizontal rotation, translation, and visual pursuit stimuli. The majority of PPN cells (72.5%) were vestibular-only cells that responded exclusively to rotation and translation stimuli but not visual pursuit. Visual pursuit responses were much more prevalent in the cMRF (57.1%) though close to half of cMRF cells were vestibular-only cells (41.1%). Directional preferences also differed between the PPN, which was preferentially modulated during nose-down pitch, and cMRF, which was preferentially modulated during ipsilateral yaw rotation. Finally, amplitude responses were similar between the PPN and cMRF during rotation and pursuit stimuli, but PPN responses to translation were of higher amplitude than cMRF responses. Taken together with their connections to the vestibular circuit, these results implicate the PPN and cMRF in the processing of vestibular stimuli and suggest important roles for both in responding to motion perturbations like falls and turns.

Keywords

pedunculo pontine nucleus; central mesencephalic reticular formation; vestibular system

Introduction

The pedunculo pontine nucleus (PPN) has connections to and from multiple areas with demonstrated motor and/or vestibular responses. Direct projections to the PPN from the vestibular nuclei (Woolf and Butcher, 1989, Hazrati and Parent, 1992, Horowitz et al., 2005), deep cerebellar nuclei (Hazrati and Parent, 1992, Teune et al., 2000), premotor and motor cortices (Matsumura et al., 2000, Aravamuthan et al., 2007), and frontal eye fields

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(Stanton et al., 1988b, Matsumura et al., 2000) have been shown in primates or rodents. The PPN also projects to multiple thalamic nuclei including the ventral posterior thalamus (Smith et al., 1988, Steriade et al., 1988, Lavoie and Parent, 1994b, Newman and Ginsberg, 1994, Erro et al., 1999) and is reciprocally connected with multiple basal ganglia nuclei (Parent and Smith, 1987, Lavoie and Parent, 1994b, a, Charara et al., 1996). Descending projections include primarily non-cholinergic efferents to the cervical and thoracic spinal cord (Goldsmith and van der Kooy, 1988, Rye et al., 1988, Spann and Grofova, 1989, Skinner et al., 1990a, Aravamuthan et al., 2007) and primarily cholinergic efferents to the pontine and medullary reticular formations (Garcia-Rill and Skinner, 1987, Skinner et al., 1990b, Takakusaki et al., 1996, Whelan, 1996, Jordan, 1998, Garcia-Rill et al., 2001) including projections to a large portion of medullary reticulospinal neurons (Garcia-Rill and Skinner, 1987). It is these reticulospinal connections that are thought to mediate the induction of locomotion (Grillner and Shik, 1973, Steeves and Jordan, 1980, Noga et al., 1991, Whelan, 1996, Jordan, 1998, Noga et al., 2003, Dai et al., 2005) and the changes in postural and limb tone (Takakusaki et al., 1994, Takakusaki et al., 2003, Takakusaki et al., 2004a, Takakusaki et al., 2004b) noted with PPN chemical or electrical stimulation. These connections allow the PPN to play a key role in the relay and regulation of motor and vestibular information.

Clinically, PPN degeneration has been associated with Parkinsonism (Hirsch et al., 1987, Zweig et al., 1987, Zweig et al., 1989, Rinne et al., 2008) and the degree of degeneration correlates with severity of Parkinsonian symptoms (Hirsch et al., 1987). Recently, deep brain stimulation of the pedunculopontine nucleus (PPN) has been shown to decrease falls, decrease gait freezing, and improve postural instability in patients with Parkinson's disease (Ferraye et al., 2010, Moro et al., 2010, Hamani et al., 2011, Khan et al., 2011, Thevathasan et al., 2011). Despite this association with falls and balance, PPN neuronal responses to vestibular stimuli have not yet been demonstrated.

Like the PPN, the central mesencephalic reticular formation (cMRF, variably known as the deep mesencephalic nucleus and the midbrain reticular formation) receives inhibitory input from the substantia nigra pars reticulata and internal segment of the globus pallidus (Veazey and Severin, 1982, Hay-Schmidt and Mikkelsen, 1992, Rodriguez et al., 2001), sends GABAergic projections to the ventral thalamus (Bowsher, 1975, Veazey and Severin, 1980a, Newman and Ginsberg, 1994, Rodriguez et al., 2001), and sends descending projections to the cervical spinal cord (Veazey and Severin, 1980b, Warren et al., 2008). In addition, the cMRF directly projects to the PPN (Rodriguez et al., 2001). These connections have led some to suggest that the cMRF, like the PPN (Mena-Segovia et al., 2004), can function as an auxiliary basal ganglia output nucleus important for motor control (Rodriguez et al., 2001).

The cMRF has been most frequently linked to space-time coordination of saccades (Cohen et al., 1985, Cohen et al., 1986, Moschovakis et al., 1988, Scudder et al., 1996, Waitzman et al., 1996, Handel and Glimcher, 1997, Chen and May, 2000, Cromer and Waitzman, 2006, Graf and Ugolini, 2006, Luque et al., 2006, Pathmanathan et al., 2006a, Pathmanathan et al., 2006b, Cromer and Waitzman, 2007). In addition, similar to substantia nigra lesions, cMRF lesions have been shown to result in repetitive ipsilateral turning behaviors that can be potentiated with dopamine agonists (Imperato and Di Chiara, 1981, Imperato et al., 1981, Morelli et al., 1981, Di Chiara et al., 1982, Vaccarino et al., 1985). Head turning has also been shown to modulate cMRF firing rates (Pathmanathan et al., 2006a, Pathmanathan et al., 2006b). However, cMRF responses to locomotion, limb movement, or whole body rotation or translation stimuli have not yet been characterized.

In order to determine whether neural activity in these two structures is modulated by vestibular stimuli, we recorded single neurons in the PPN and cMRF. Of note, saccade-related activity has been demonstrated in both the PPN (Kobayashi et al., 2001, Kobayashi et al., 2002, Kobayashi et al., 2004, Okada and Kobayashi, 2009) and cMRF (Cohen et al., 1985, Cohen et al., 1986, Moschovakis et al., 1988, Scudder et al., 1996, Waitzman et al., 1996, Handel and Glimcher, 1997, Chen and May, 2000, Cromer and Waitzman, 2006, Graf and Ugolini, 2006, Luque et al., 2006, Pathmanathan et al., 2006a, Pathmanathan et al., 2006b, Cromer and Waitzman, 2007) and was thus not investigated here. In contrast to saccades, responses to smooth visual pursuit have not been as extensively characterized in either structure. Therefore, we searched for responses to both vestibular and visual pursuit stimuli in order to compare PPN and cMRF response properties to those previously characterized in the vestibular nuclei (Miles, 1974, Fuchs and Kimm, 1975, Keller and Daniels, 1975, Keller and Kamath, 1975, King et al., 1976, Chubb et al., 1984, Tomlinson and Robinson, 1984, McFarland and Fuchs, 1992, Scudder and Fuchs, 1992, Cullen et al., 1993, Cullen and McCrea, 1993, Angelaki et al., 2001, Roy and Cullen, 2003, Meng et al., 2005), cerebellar nuclei (Gardner and Fuchs, 1975, Buttner et al., 1991, Siebold et al., 1997, Siebold et al., 1999, Zhou et al., 2001, Shaikh et al., 2004, Shaikh et al., 2005), and vestibular thalamus (Meng et al., 2007, Meng and Angelaki, 2010). This work will provide insight into the roles of the PPN and cMRF in motor control and increase our understanding of the neural pathways involved in the processing of vestibular stimuli.

Methods

Animals and experimental setup

All recordings were done in two alert juvenile *Macacca mulatta* monkeys. The animals were chronically implanted with a delrin ring to restrain head movement during experiments. A neural recording platform with predrilled holes spaced 0.8 mm apart was secured within the head-restraining ring and allowed electrode penetrations to cover areas of the PPN and cMRF bilaterally. Search coils were also chronically implanted for measuring eye movements (Angelaki et al., 2000, Angelaki et al., 2001, Meng et al., 2005, Meng et al., 2007). The surgical and experimental procedures conformed to the National Institutes of Health guidelines and were approved by the Animal Care and Use Committee at Washington University.

Animals were seated comfortably in a primate chair that was mounted inside a vestibular turntable (Acutronics, Pittsburgh, PA). The turntable delivered rotations in three dimensions (yaw, pitch, and roll) and horizontal plane translations. The position of the animal inside the primate chair was adjusted such that (1) the rotation axes passed through the center of the head, along the interaural line and (2) the horizontal stereotaxic plane was parallel with the earth-horizontal during experiments. Visual targets for pursuit eye movements were delivered using a laser/x-y mirror galvanometer system (GSI Lumonics, Moorpark, CA), with the laser beam back projected onto a screen placed 33 cm away. We monitored the animal's motion using the output of a three-dimensional accelerometer that was mounted on the inner frame of the turntable, as well as velocity and position feedback signals from the rotators. These signals, as well as eye coil voltages, were filtered (200 Hz, 6 pole Bessel), digitized at a rate of 833.33 Hz, and stored for off-line analysis. Stimulus delivery and data acquisition were controlled with custom-written scripts for the Spike2 software environment by use of a Cambridge Electronics Design (Cambridge, UK) data acquisition interface (model power 1401, 16 bit resolution). Eye movement calibration procedures were similar to those in previous studies (Meng et al., 2005, Meng et al., 2007).

Neural recordings and localization

Extracellular recordings from isolated single neurons were obtained with epoxy-coated tungsten microelectrodes (2 to 4 M Ω impedance; FHC, Bowdoinham, ME). Each electrode reached the brainstem through a 26 gauge cannula (0.46 mm outer diameter, placed perpendicular to the recording platform) and was manipulated with a remote-controlled microdrive (FHC). Neural activity was amplified and filtered (300 Hz–6 kHz). The action potentials were discriminated using spike sorting functionality in Spike2.

In initial experiments performed in each monkey, the trochlear nucleus and the rostral interstitial nucleus of medial longitudinal fasciculus (riMLF) were identified based on their characteristic firing patterns during pursuit, saccade, and fixation eye movements. These two structures were then used as landmarks for guiding electrode penetrations into the PPN and cMRF. The trochlear nucleus, a small area <1 mm across, characteristically demonstrates increased activity selectively during downward eye movement (concordant with superior oblique extra-ocular muscular activity). The trochlear nucleus is located 1–3 mm medial to the PPN, at the same depth and antero-posterior level. The riMLF is also a small area (<2 mm across) whose cells burst selectively during vertical and torsional saccadic eye movements (Suzuki et al., 1995). The PPN extend approximately 1 mm posterior and 3 mm anterior to the trochlear nucleus. The cMRF is located immediately superior to the PPN and extends anteriorly to the riMLF.

The cMRF is a large brainstem region that has been variably defined in the literature. The anterior portion of our recordings appear to include the deep mesencephalic nucleus as defined by Rodriguez et al. (Rodriguez et al., 2001), an area which is delimited by the superior colliculus superiorly, the substantia nigra inferiorly, and the red nucleus medially. The red nucleus is at the same anteroposterior level as the riMLF (Paxinos et al., 2000), the structure we used to delineate the anterior extent of the cMRF. Our cMRF recordings also encompass the recording sites frequently used to characterize cMRF saccade metrics, noted to be 2–4 mm lateral to the oculomotor nuclei (Waitzman et al., 1996, Cromer and Waitzman, 2006, Pathmanathan et al., 2006a, Pathmanathan et al., 2006b, Cromer and Waitzman, 2007). The cuneiform nucleus delimits the posterior extent of the cMRF and was not included in our recordings as we did not record more than 0.8 mm posterior to the largest aspect of the trochlear nucleus (Paxinos et al., 2000).

As has been done previously to localize the PPN in the awake macaque, auditory responses in the inferior colliculus were used to differentiate between the PPN and cMRF based on depth (Kobayashi et al., 2001). The PPN is located 3 to 7 mm deep to the inferior border of the inferior colliculus (Paxinos et al., 2000). Since the PPN is located immediately superior and lateral to the superior cerebellar peduncle and its decussation, tonic fiber activity (>20 Hz baseline firing rate with brief <1ms spike discharges including a prominent positive potential component) was noted frequently during all recordings in the PPN vicinity and served as a further indicator of appropriate depth and medio-lateral location for PPN recordings (Paxinos et al., 2000, Kobayashi et al., 2001).

As the electrode entered the cMRF and subsequently the PPN, our search stimulus consisted of yaw/pitch rotation or lateral translation at a single frequency (0.5 Hz). Once a cell was satisfactorily isolated, it was tested with 0.5 Hz sinusoidal rotation (yaw, pitch, and roll, 0.5 Hz $\pm$ 10°) and translational movement (lateral and fore-aft, 0.5 Hz $\pm$ 0.2 G, G = 9.8 m/s²), as well as with targets for horizontal/vertical pursuit eye movements. Yaw and pitch rotation were tested while the monkey (1) tracked a target fixed in space (SF), thus engaging the vestibulo-ocular reflex (VOR), (2) tracked a target fixed relative to the head (HF), thus cancelling the VOR, and/or (3) was reflexively generating random eye movements in complete darkness (Dark). Roll rotation was tested during the HF and Dark conditions only.

Translation was tested only in darkness. Only well isolated cells tested during pursuit and at least the HF rotation conditions were included in this study.

Data analyses

Data analyses were performed off-line using Matlab (MathWorks, Natick, MA). Neural firing rate was calculated as the inverse of interspike interval. At least 10 response cycles, with periods of saccadic eye movements excluded, were folded into a single cycle, and fitted by a sine function to determine response amplitude and phase (for details, see Meng et al., 2005; Meng and Angelaki 2006). Response amplitude refers to half the peak-to-trough modulation. Neural response gain for rotation was computed as the ratio of response amplitude and peak stimulus velocity (in units of spikes per second per degrees per second). Response phase for rotation was calculated as the difference between peak response and peak head velocity. For quantification of the frequency responses of neurons during translation, response gain in units of spikes per second per G ($G=9.81 \text{ m/s}^2$) and phase were expressed relative to linear acceleration. The neural gain and phase during translation and rotation were fitted by a two-dimensional spatiotemporal model (Angelaki, 1991, 1992; Schor and Angelaki 1992) to compute the preferred (maximum response) direction of the neuron and its phase.

To assign a statistical significance in the response gain for each neuron, we also computed average binned histograms (40 bins per 2 second cycle) and a 'Fourier Ratio (FR)', defined as the ratio of the fundamental over the maximum of the first 20 harmonics. The statistical significance of FR was then based on a permutation analysis. Briefly, the 40 response bins were shuffled randomly, thus destroying the systematic modulation in the data but maintaining the inherent variability of the responses. The FR was then computed from those randomly permuted histograms, and the randomization process was repeated 1,000 times. If the FR for the original data exceeded that for 99% of the permuted data sets, we considered the temporal modulation to be statistically significant.

In order to determine whether the measured distribution of rotation and translation preferred directions was significantly different from uniform, we performed a resampling analysis. First, we calculated the sum squared error (across bins) between the measured distribution and an ideal uniform distribution containing the same number of observations. Next, we generated a random distribution by drawing the same number of data points from a uniform distribution using the "unifrnd" function in Matlab. The sum squared error was again calculated between this random distribution and the ideal uniform distribution. 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. If the sum squared error for the experimentally measured distribution lay outside the 95% confidence interval (CI) of values from the randomized distributions, then the measured distribution was considered to be significantly different from uniform ($p < 0.05$) (Takahashi et al., 2007, Meng and Angelaki, 2010).

To draw comparisons between vestibular responses in the PPN and cMRF and those in the vestibular nuclei, cells were classified into 5 groups based on responses to rotation and pursuit (Scudder and Fuchs, 1992, Meng et al., 2005):

1. Position-Vestibular (PV) where the sinusoidal modulation of firing rate during horizontal/vertical pursuit is in-phase (i.e., within $\pm 90^\circ$) with the modulation during yaw/pitch HF rotation, respectively. Classically, in PV neurons in the cerebellar and vestibular nuclei, these signals superimpose during SF rotation.

2. Eye-Head (EH) where modulation during pursuit is anti-phase to modulation during rotation. EH cells in the cerebellar and vestibular nuclei, demonstrate opposition of these signals during SF rotation.
3. Vestibular-Eye (VE) where modulation during pursuit is in phase with modulation during rotation in one plane (eg. horizontal pursuit modulation is in-phase with modulation during yaw rotation as would be seen for a PV cell) but out of phase in the other plane (eg. vertical pursuit modulation is anti-phase with modulation during pitch rotation as would be seen for an EH cell).
4. Vestibular-Only (VO) where neuronal activity was significantly modulated during rotation but not modulated during pursuit.
5. Eye-Only (EO) where activity was significantly modulated only during pursuit eye movements.

Cells responsive to rotation or translation were further differentiated as those that responded to ipsilaterally-directed (ipsi) vs. contralaterally-directed (contra) head motion during HF rotation.

Results

PPN cells are often exclusively modulated by vestibular stimuli while cMRF cells are often concurrently modulated by vestibular stimuli and visual pursuit

Sixty-two cells were recorded in the PPN (47 in the left PPN and 15 in the right PPN). Forty of these cells were tested with the full protocol described above (rotation, translation, and pursuit, Figs. 1 and 2) and an additional 2 cells were tested during HF rotation and pursuit before losing cell isolation. Eighty-eight cells were recorded in the cMRF (55 in the left cMRF and 33 in the right cMRF) of which 52 were tested with the full protocol and 6 were tested during HF rotation and pursuit (Table 1).

Responses to vestibular stimuli (rotation and translation) and to visual pursuit were observed in both the PPN and cMRF. Most PPN and cMRF cells demonstrated activity modulation during rotation or translation. Examples of cells characterizing the PPN (a VO cell) and cMRF (a VE cell) are shown in Fig. 1 and Fig. 2. The PPN VO cell was modulated during fore-aft and lateral translation in complete darkness and during yaw, pitch, and roll rotation during HF, SF, and in Dark conditions. The cell was not modulated during horizontal or vertical pursuit and was thus characterized as a Vestibular-Only (VO) cell. Similarly modulated cells, which respond to rotation and/or translation but not to pursuit, comprise 50.0% ($n=20/40$) of PPN cells. The cMRF VE cell was modulated during all tested directions of rotation, translation, and visual pursuit, similar to 34.5% ($n=19/55$) of all cMRF cells (Table 1). The cMRF cell was classified as Vestibular-Eye movement (VE) because modulation during HF yaw rotation is in-phase with modulation during horizontal pursuit (peak modulation during HF rotation is within 90 degrees from peak modulation during pursuit) while modulation during HF pitch rotation is out of phase with modulation during vertical pursuit.

The majority of neurons in both regions responded to rotation or translation stimuli. Though a significant number of cells in the PPN and cMRF responded to only rotation and not translation, very few cells responded to only translation without also showing modulation during rotation stimuli. Approximately 3 out of every 4 cells in the PPN ($n=31/42$, 73.8%) or cMRF ($n=43/58$, 74.1%) were modulated during rotation with similar response amplitudes between yaw, pitch, and roll rotational stimuli (mean $\pm$ SD of 0.5 ± 0.3 , 0.7 ± 0.4 and 0.5 ± 0.4 spikes/s/ $^{\circ}$ /s, respectively, for PPN, and mean $\pm$ SD of 0.7 ± 0.4 , 0.5 ± 0.4 and 0.6 ± 0.3 spikes/s/ $^{\circ}$ /s, respectively, for cMRF) and between the PPN and cMRF. Of these

cells, 29.0% (n=9/31) of PPN cells and 37.2% (n=16/43) of cMRF cells were modulated during rotation and not translation. Similarly large proportions of PPN cells (n=30/40, 70%) and cMRF cells (n=38/55, 69.1%) were modulated during translation though PPN response amplitudes were larger than cMRF response amplitudes during lateral and fore-aft translation (with mean $\pm$ SD of 114 $\pm$ 12 and 115 $\pm$ 10 spikes/s/G, respectively, for PPN, and mean $\pm$ SD of 58 $\pm$ 8 and 51 $\pm$ 7 and, respectively, for cMRF). Only 2 PPN cells (5.0%) and 1 cMRF cell (1.8%) were modulated during translation and not rotation. For ease of comparison to cell classes in the vestibular nuclei which are differentiated based on responses to rotation and visual pursuit stimuli, these 3 cells that were responsive only to translation were excluded from further analysis.

Though the prevalence of cells responsive to vestibular stimuli was similar between the two structures, visual pursuit responses were less frequent in the PPN than in the cMRF. Only 22.5% of PPN cells (n=9/42) were significantly modulated by visual pursuit in comparison to 56.9% of cMRF cells (n=33/58) responsive to visual pursuit (with mean $\pm$ SD of 0.7 $\pm$ 0.4 and 0.8 $\pm$ 0.6 for PPN and cMRF, respectively). Furthermore, while only 12.5% of PPN cells (n=5/40) were modulated by all three stimulus types (rotation, translation, pursuit), more than a third of cMRF cells were (n=19/55, 34.5%) (Table 1). Therefore, compared to the cMRF which has large proportions of cells responsive to vestibular stimuli and/or to visual pursuit, the PPN appears to be primarily characterized by cells responding only to vestibular stimuli.

This difference between the two structures is also evident when comparing PPN and cMRF cell types following classification as PV, EH, VE, EO, or VO cells based on responses during HF rotation and pursuit (Table 2; see Methods for a more detailed description of cell classification). The majority of recorded cells in the PPN were VO cells and thus were significantly modulated during HF rotation but lacked any significant response to pursuit eye movement (n=29/42, 72.5%). Most of the remaining minority of PPN cells were modulated during both HF rotation and pursuit eye movements (classified as PV, EH, or VE, n=6/42, 15%) with only 3 (7.2%) cells responding to visual pursuit alone. In contrast, similar proportions of cMRF cells were modulated during rotation alone (classified as VO, n=23/56, 41.1%) or during both HF rotation and pursuit eye movement (classified as PV, EH, or VE, n=25/56, 44.6%) (Table 2).

Different cell sub-types in the PPN and cMRF were distributed evenly in both structures. Cells were recorded in a 5 mm medio-lateral by 7 mm antero-posterior area encompassing both the PPN and cMRF. Cells anterior to the PPN and inferior to the cMRF were also recorded, but not included in further analyses (Fig. 3, gray symbols). As the focus of this work is to demonstrate responses to vestibular stimuli in the PPN and cMRF and then to compare these responses to those in the vestibular nuclei, cerebellar nuclei, and vestibular thalamus, only cells tested with HF rotation and pursuit (and, therefore, cells that could be classified as PV, EH, VE, VO, or EO as classically described in the vestibular nuclei (Scudder and Fuchs, 1992, Meng et al., 2005)) were included in further analyses.

PPN and cMRF neural response amplitudes and phases during rotation and pursuit are similar between the two structures and across cell types

In order to see whether PV, EH, VO, and EO cells in the PPN and cMRF behave like their similarly classified counterpart cells in the vestibular nuclei, gains and phases are compared between SF rotation and either HF rotation (Fig. 4A) or pursuit (Fig. 4B). For each cell, response properties during SF yaw rotation and SF pitch rotation are graphed on the same plots and compared with HF yaw rotation and HF pitch rotation, respectively (Fig. 4A). SF yaw rotation gains and phases were compared to those during horizontal pursuit while pitch rotation was compared to vertical pursuit (Fig. 4B). When comparing gains during SF

rotation to those during HF rotation or pursuit, previous work has shown that PV cells in the vestibular nucleus demonstrate greater neural response gains during SF rotation relative to gains during the other two stimuli (Miles, 1974, Fuchs and Kimm, 1975, Keller and Daniels, 1975, Keller and Kamath, 1975, King et al., 1976, Chubb et al., 1984, Tomlinson and Robinson, 1984, McFarland and Fuchs, 1992, Scudder and Fuchs, 1992, Cullen et al., 1993, Cullen and McCrea, 1993, Angelaki et al., 2001, Roy and Cullen, 2003, Meng et al., 2005). Conversely, EH cells in the vestibular nuclei demonstrate smaller response gains during SF rotation when compared to gains during HF rotation and pursuit. Since VO cells respond only to rotation, VO cells demonstrate similar response gains between SF rotation and HF rotation. EO cells, which respond only to pursuit, demonstrate similar response gains between SF rotation and pursuit (Meng et al., 2005).

However, PV and EH cells in the PPN and cMRF do not appear to be characterized by these properties of PV and EH cells in the vestibular nucleus. Regardless of cell type (PV/EH/VE/VO/EO) or area of recording (PPN/cMRF), response gains were not significantly different between SF rotation and HF rotation (repeated measures ANOVA, $p=0.39$) or between SF rotation and pursuit (repeated measures ANOVA, $p=0.26$). Gains were significantly correlated (type II regression, $p<0.05$) and were similar between SF rotation and HF rotation and between SF rotation and pursuit when data from all cell types and recording areas were grouped (linear regression slopes were not significantly different from unity, $p<0.05$, type II regression). Mean response gains (computed as preferred direction from yaw/pitch rotation and horizontal/vertical pursuit responses) for SF rotation (0.7 ± 0.5 sp/s/°/s), HF rotation (0.7 ± 0.5 sp/s/°/s), and pursuit (0.8 ± 0.4 sp/s/°/s) were also not significantly different from each other (Table 3).

Cells that were significantly modulated during both SF rotation and HF rotation or during both SF rotation and pursuit had similar response phases between these stimuli (Table 3, Fig. 4A, B, bottom). Again, this relationship did not differ between cell type or recording area (repeated measures ANOVA, $p>0.05$) and showed a significant 1:1 correlation between stimuli (type II regression, $p<0.05$). Phases were distributed across a wide range with no significant difference from a uniform distribution ($p>0.05$) (Table 3, Fig. 4A, B, marginal distributions, bottom panels).

PPN cells respond preferentially to nose-down pitch rotation while cMRF cells respond preferentially to ipsilateral yaw rotation

PPN and cMRF preferred directions for HF yaw/pitch rotation and horizontal/vertical pursuit (directions of rotation and pursuit where the cells are maximally modulated) are shown in Fig. 5 as polar plots where polar angle represents preferred direction and radius represents response gain. The aforementioned striking differences in cell type distribution between the PPN and cMRF can be visualized in these plots. The majority of PPN cells are VO (Fig. 5A, left panel, green) with very few eye movement responsive cells (Fig. 5A and Fig. 5C, left panel, red and blue symbols). In contrast, the cMRF has an equal number of VO cells (Fig. 5A, right panel, green) and eye-movement responsive cells (Fig. 5A and 5C, right panels, red and blue symbols). More cells were recorded from the left brainstem (closed symbols, Fig. 5A, 5C) than from the right brainstem (open symbols, Fig. 5A, 5C) in both structures. Thirty-two (76%) PPN cells and thirty-six (62%) cMRF cells tested with HF rotation and pursuit were recorded in the left brainstem. Despite the predominance of cells from the left PPN and left cMRF, ipsi cells (e.g., a left brainstem cell whose preferred direction is $<90^\circ$ or $>270^\circ$, favoring ipsilateral left yaw rotation) and contra cells (e.g., a left brainstem cell whose preferred direction is $>90^\circ$ and $<270^\circ$, favoring contralateral right yaw rotation) were present in both the left and right PPN and cMRF (Fig. 5A, 5C).

In order to determine whether PPN and cMRF cells demonstrated a laterality preference during rotation or pursuit, distributions of ipsilateral and contralateral preferred directions are shown in Fig. 5B and 5D. In these distributions, preferred directions are expressed such that 0° represents ipsilateral preferences and 180° represents contralateral preferences (90° corresponds to neurons preferring vertical directions). Cells modulated during both HF rotation and pursuit (PV, EH, and VE cells) were grouped as eye-movement (EM) cells for ease of interpretation (open bars). EM cells in the cMRF showed a preference for ipsilateral yaw rotation. The distribution of preferred directions of cMRF EM cells was significantly different from uniformity with a mode ($n=11$) between 0–22.5° ($p<0.05$, see Methods for description of resampling analysis). All other distributions were not significantly different from uniformity indicating no preference for ipsilateral or contralateral rotation or pursuit eye movements.

Preferred directions of PPN (purple) and cMRF (orange) cells across all three axes of rotation (yaw, pitch, and roll) are shown in Fig. 6. Cells are differentiated by recording area (PPN or cMRF) and by cell type (VO: filled symbols; EM: open symbols; the latter group again encompasses PV, EH, and VE cells). PPN cells, both VO and EM cells taken together, and VO cells alone, show a preference for nose-down pitch rotation (approaching 270° on the azimuth). Specifically, the distribution of PPN preferred directions along the azimuth is significantly different from uniformity with a mode ($n=15$) between 200°–280° ($p<0.05$). In contrast, cMRF cells did not demonstrate any pitch or roll rotation direction preference, but showed a clear preference for left yaw rotation as the significantly non-uniform distribution of these cells showed a mode ($n=7$) between –51° and –90° ($p<0.05$). Given that the majority of cMRF cells recorded were from the left brainstem, the left yaw directional preference further supports our finding that the cMRF cells show a preference for ipsilateral yaw rotation (see also Fig. 5B, orange).

PPN cells exhibit higher amplitude modulation to translation than do cMRF cells

Preferred directions and gains of PPN and cMRF cells responding to translation are shown as polar plots in Fig. 7A. Overall, PPN cells had significantly higher response gains to translation than did cMRF cells ($p<0.05$). The geometric mean of PPN response gains across all cell types was 137 ± 3 sp/s/G while the mean cMRF response gain was 68 ± 2 sp/s/G. There was no dependence on cell type (ANOVA, $p=0.43$).

Ipsi and contra cells were recorded in both the left and right brainstem in the PPN and cMRF and exhibited a wide range of preferred directions to lateral and fore-aft translation. Distributions of preferred directions of ipsilaterally and contralaterally-tuned VO and EM cells are shown in Fig. 7B. In these distributions, directions close to 0° represent ipsilateral preferences, whereas directions close to 180° represent contralateral preferences (90° corresponds to neurons preferring fore-aft motion). There were no significant differences between these distributions and uniformity ($p>0.05$), suggesting no preference for ipsilateral versus contralateral translation in the PPN or cMRF.

Discussion

We have shown responses to vestibular stimuli and visual pursuit in the macaque PPN and cMRF. The prevalence, amplitude, and directional preferences of these responses differ between structures. The majority of PPN cells respond exclusively to vestibular stimuli and not to visual pursuit while cells responding to both vestibular stimuli and visual pursuit are more common in the cMRF. The amplitudes of responses during rotation and pursuit were similar between structures, but PPN cells have higher amplitude responses to translation than do cMRF cells. Finally, PPN cells show a preference for nose down pitch rotation while cMRF cells show a preference for ipsilateral yaw rotation. These results suggest likely

sources of vestibular input to the PPN and cMRF and support a role for both nuclei in vestibular signal processing, especially in the context of falls and turns.

Comparison of vestibular responses in the PPN and cMRF with those in vestibular nuclei

Cell type distributions, direction preferences, and response amplitudes in the PPN and cMRF are largely different from those reported previously in the vestibular nuclei. In general, most neurons in the rostral vestibular nuclei are sensitive to visual pursuit (McCrea et al., 1987, Scudder and Fuchs, 1992, Cullen and McCrea, 1993), unlike cells in the PPN, where more than 70% of all cells are VO cells, and the cMRF, where almost half of all cells are VO cells (Table 1). Also unlike the PPN and cMRF, the vestibular nucleus shows a preference for lateral translation but no clear directional preference for rotation (Angelaki and Dickman, 2000, Dickman and Angelaki, 2002). The PPN and cMRF populations both exhibited preferred directions for rotation but showed no translation directional preferences (Figs. 5–7). Finally, response gains in the vestibular nuclei for rotation tend to be larger than response gains in the PPN and cMRF (Table 2) (Fuchs and Kimm, 1975, Keller and Daniels, 1975, Keller and Kamath, 1975, Chubb et al., 1984, Tomlinson and Robinson, 1984, McFarland and Fuchs, 1992, Scudder and Fuchs, 1992, Cullen and McCrea, 1993, Angelaki et al., 2001, Roy and Cullen, 2003, Meng et al., 2005). Translation response gains in the vestibular nuclei are comparable to those in the PPN, but larger than translation response gains in the cMRF (Angelaki et al., 2001, Meng et al., 2005).

Perhaps the most striking difference is that, unlike in the PPN or cMRF, SF rotation response gains in EM vestibular nuclei cells are either larger (PV cells) or smaller (EH cells) than HF rotation response gains (Chubb et al., 1984, Tomlinson and Robinson, 1984, Roy and Cullen, 2003, Meng et al., 2005). This relationship was not observed in the PPN or cMRF where response gains during VOR (SF rotation) were not significantly different than those during VOR cancellation (HF rotation) or visual pursuit alone (Fig. 4). These response characteristics may be due to fundamental differences in response amplitude scaling during the VOR. Such properties have also been reported in supplementary and frontal eye fields (Fukushima et al., 2009, Fukushima et al., 2010, Fukushima et al., 2011), areas that project to the PPN/cMRF. Alternatively, as is true for the vestibular nuclei, viewing distance to the target may play a large role in the dampening of linear supposition (Meng et al., 2005, Khojasteh and Galiana, 2009). Linear summation of rotation and visual pursuit gains in the vestibular nucleus occurs only when viewing far targets (80 cm) but not when viewing near targets (20 cm) (Meng et al., 2005). Given that our target distance was 33 cm, perhaps a farther target would result in greater separation between PV, EH, and VO cell response gains in the cMRF or PPN.

Roles of the PPN and cMRF in the vestibular circuit

There are multiple sources of vestibular input to the PPN and cMRF. The premotor cortex, motor cortex, supplementary eye fields, and frontal eye fields, all areas with known vestibular responses (Fukushima et al., 2000, Fukushima et al., 2004a, Fukushima et al., 2004b, Fukushima et al., 2006, Shinder and Taube, 2010, Fukushima et al., 2011), project to the PPN (Stanton et al., 1988a, Matsumura et al., 2000). The supplementary and frontal eye fields also project to the cMRF (Huerta and Kaas, 1990, Shook et al., 1990). Projections to the PPN from the vestibular nuclei exist in rodents (Horowitz et al., 2005) but have not yet been demonstrated in primates. The PPN also receives input from the cMRF (Rodriguez et al., 2001). However, the disparity in response properties we have demonstrated between the PPN and cMRF and between the PPN and vestibular nuclei suggest that these structures may contribute to but are not the primary sources of PPN vestibular modulation.

The fastigial nucleus (FN), which has well-characterized vestibular response properties (Gardner and Fuchs, 1975, Buttner et al., 1991, Siebold et al., 1997, Siebold et al., 1999, Zhou et al., 2001, Shaikh et al., 2004, Shaikh et al., 2005), may be a more likely source of vestibular input for the PPN and cMRF. The deep cerebellar nuclei, including the FN, project to both the PPN and cMRF in primates and rodents. All deep cerebellar nuclei project to the PPN and cMRF in rats, with the PPN receiving its most dense input from the FN (Teune et al., 2000). In primates, collaterals of deep cerebellar nuclei projections to the thalamus diffusely arborize through the PPN (Hazrati and Parent, 1992). However, investigation of specifically the caudal FN in primates has yielded projections to the contralateral cMRF, but not the PPN (Noda et al., 1990), suggesting that FN projections to the PPN and cMRF may be segregated between the rostral and caudal FN.

This possible differential distribution of FN projections is supported by response property similarities between the rostral FN and PPN and between the caudal FN and cMRF. Cells in the rostral FN, as do cells in the PPN, respond to vestibular stimuli but are not modulated by visual pursuit (Siebold et al., 1997, Siebold et al., 1999, Zhou et al., 2001, Shaikh et al., 2004, Shaikh et al., 2005). Given the nose-down pitch preference of PPN cells, it is also interesting that almost all vestibular responsive rostral FN cells (77–100%) respond to pitch or roll rotation (Siebold et al., 1999, Shaikh et al., 2005) while less than half respond to yaw rotation (Shaikh et al., 2005). In contrast to the rostral FN and PPN, but similar to the cMRF, cells in the caudal FN are modulated during smooth pursuit, rotation, and translation stimuli (Gardner and Fuchs, 1975, Buttner et al., 1991, Siebold et al., 1997, Siebold et al., 1999, Zhou et al., 2001, Shaikh et al., 2004, Shaikh et al., 2005). Rotation-sensitive caudal fastigial neurons demonstrate the greatest modulation with contralateral yaw rotation, but have no clear directional preference for visual pursuit (Gardner and Fuchs, 1975, Buttner et al., 1991). Given that the caudal FN projects to the contralateral cMRF (Noda et al., 1990), the FN preference for contralateral yaw rotation could manifest as an ipsilateral yaw rotation preference in the cMRF, as we have indeed found here. Given these observations, rostral and caudal FN projections may topographically distinguish between the PPN and cMRF in primates and may be a primary source of vestibular input to these nuclei.

Both the PPN and cMRF project to multiple thalamic nuclei (Bowsher, 1975, Veazey and Severin, 1980a, Smith et al., 1988, Steriade et al., 1988, Lavoie and Parent, 1994b, Newman and Ginsberg, 1994, Erro et al., 1999, Rodriguez et al., 2001), including the ventral nuclei comprising the vestibular thalamus (Buttner and Henn, 1976, Buttner et al., 1977, Magnin and Fuchs, 1977, Lang et al., 1979, Asanuma et al., 1983, Meng et al., 2007, Meng and Angelaki, 2010). Approximately 10% of ventral thalamic cells respond to vestibular stimuli but not to visual pursuit or saccadic eye movements. In fact, very few ventral thalamic cells (1%) are eye-movement sensitive and the remaining cells do not respond to eye-movement or vestibular stimuli (Meng et al., 2007). These relative proportions of eye-movement responsive and vestibular responsive cells in the vestibular thalamus recall PPN cell-type distribution where vestibular responsive cells also vastly outnumber eye-movement responsive cells. These observations suggest that VO cells in the PPN, perhaps more so than VO cells in the cMRF, potentially provide vestibular input to the thalamus.

Via these connections, the PPN and cMRF could modulate thalamo-cortical transmission and processing of vestibular signals. Stimulation of the cMRF has been shown to hyperpolarize ventral thalamic neurons projecting to the motor cortex (Yasuda and Shimono, 1978) or posterior parietal cortex (Sasaki et al., 1976), and result in desynchronization of cortical EEG in rats. Cholinergic input to the thalamus, largely from the PPN (Fitzpatrick et al., 1989), results in prolonged depolarization of thalamo-cortical neurons (Fitzpatrick et al., 1989, Raczkowski and Fitzpatrick, 1989, Steriade et al., 1990, Curro Dossi et al., 1991, McCormick, 1992, Steriade et al., 1993). Noting that the PPN and

cMRF, ventral thalamus, and premotor/motor cortices project serially to each other, the PPN and cMRF could function as part of a thalamo-cortico-brainstem loop governing vestibular processing. The cMRF, via cervical spinal cord connections (Veazey and Severin, 1980b, Warren et al., 2008), and PPN, via pontine and medullary reticulospinal connections (Garcia-Rill and Skinner, 1987, Skinner et al., 1990b, Takakusaki et al., 1996, Whelan, 1996, Jordan, 1998, Garcia-Rill et al., 2001), could then presumably initiate compensatory changes in neck (Pathmanathan et al., 2006a, Pathmanathan et al., 2006b), postural, and limb tone (Takakusaki et al., 1994, Takakusaki et al., 2003, Takakusaki et al., 2004a, Takakusaki et al., 2004b) to respond to vestibular stimuli. .

Functional correlates of PPN and cMRF visual and vestibular response properties – implications for falls, gaze control, and turning

The PPN responses to translation and rotation that we have described support the PPN's clinically proposed role in postural stability (Ferraye et al., 2010, Moro et al., 2010, Hamani et al., 2011, Khan et al., 2011, Thevathasan et al., 2011). PPN degeneration is associated with falls in Parkinsonism (Hirsch et al., 1987, Zweig et al., 1987, Zweig et al., 1989, Rinne et al., 2008) and deep brain stimulation of the PPN in Parkinson's disease patients results in decreased frequency of falls (Moro et al., 2010). Since the majority of falls in Parkinson's disease patients are falls forward in space (Bloem et al., 2004, Grimbergen et al., 2004, Kerr et al., 2010), the nose-down pitch preference of PPN cells may be important clinically. Noting PPN connections with the motor cortex, basal ganglia, thalamus, and reticulospinal neurons mediating locomotion and postural tone, perhaps high PPN sensitivity to nose-down pitch (which would result in increased PPN firing rate during an ongoing forward fall), is key for signaling that a fall is taking place and for initiating compensatory postural mechanisms for halting the fall.

The visual pursuit responses we found in the cMRF are in line with its hypothesized role in gaze control (Graf and Ugolini, 2006, Ugolini et al., 2006). Since the cMRF projects directly to slow extra-ocular muscle motor neurons subserving fixation and slow eye movements (Ugolini et al., 2006) and also projects to cervical spinal cord motor nuclei (Veazey and Severin, 1980b, Warren et al., 2008), the cMRF is anatomically poised to modulate visual smooth pursuit and neck movements concurrently. In fact, cMRF neurons modulated by head rotation following gaze shifts have been previously described (Pathmanathan et al., 2006a, Pathmanathan et al., 2006b). Similar to the pursuit-responsive cells we found, head rotation cMRF neurons also have a wide range of directional preferences. Given that half (44.6%) of cMRF neurons we recorded respond to both visual pursuit and whole body rotation while visually tracking a head-fixed target, the cMRF is capable of integrating visual and vestibular input as would be necessary in gaze control.

We have also demonstrated a clear cMRF preference for ipsilateral yaw rotation. This result is in line with lesioning studies showing that putative disruption of inhibitory GABAergic outflow from the cMRF (Appell and Behan, 1990, Rodriguez et al., 2001, Gonzalez-Hernandez et al., 2002) results in repetitive ipsilateral turning in rats even in the presence of nigral or striatal lesions that result in dopamine-potentiated contralateral turning (Imperato and Di Chiara, 1981, Imperato et al., 1981, Morelli et al., 1981, Di Chiara et al., 1982, Vaccarino et al., 1985). Furthermore, the small amplitude cMRF responses to translation relative to the PPN and vestibular nuclei (Angelaki and Dickman, 2000, Angelaki et al., 2001, Meng et al., 2005) suggest that the cMRF responds mostly and preferentially to rotatory stimuli. Taken together, our findings further support an integral role for the cMRF in turning perception and the processing of yaw rotation.

The projection from the cMRF to the PPN (Rodriguez et al., 2001) allows for integration of their two rotatory signals – the PPN tuned to nose-down forward rotation and the cMRF

tuned to ipsilateral rotation. This projection could also be important in understanding falls in Parkinson's disease patients. The most common event preceding a forward fall in Parkinson's disease patients is a lateral turn (Bloem et al., 2004, Grimbergen et al., 2004, Kerr et al., 2010). The cMRF might thus be involved in postural control during turning via its connections with the PPN. The PPN, in turn, can modulate postural tone (Takakusaki et al., 1994, Takakusaki et al., 2003, Takakusaki et al., 2004a, Takakusaki et al., 2004b) and locomotion (Garcia-Rill, 1986, Garcia-Rill et al., 1987, Garcia-Rill and Skinner, 1988, Garcia-Rill et al., 2004) via connections with pontine and medullary reticulospinal neurons (Garcia-Rill and Skinner, 1987, Skinner et al., 1990b, Takakusaki et al., 1996, Whelan, 1996, Jordan, 1998, Garcia-Rill et al., 2001) and subsequent activation of cervical, thoracic, and lumbar spinal motoneurons (Grillner and Shik, 1973, Steeves and Jordan, 1980, Noga et al., 1991, Whelan, 1996, Jordan, 1998, Noga et al., 2003, Dai et al., 2005).

In summary, the PPN and cMRF have prevalent responses to vestibular stimuli, clear rotational directional preferences, and numerous connections with the vestibular circuit such that both structures could function as part of thalamo-cortico-brainstem loops involved in recognizing and initiating descending reticulospinal responses to vestibular perturbations like falls and turns. Vestibular responses in both structures could be further characterized using a larger number of translation and rotation directions in 3D space. We recorded from cMRF and PPN neurons during vestibular and visual pursuit stimuli, but not during saccade stimuli. Recording from the same neurons during vestibular, pursuit, and saccade stimuli could help further delineate the overlap between visually-responsive and vestibular-responsive neurons. Finally, given the input to both structures from visuomotor cortical areas where there is convergence of vestibular and self-motion perception signals, PPN and cMRF integration of visual and vestibular information could be further interrogated by comparing 3D vestibular responses with 3D optic flow responses. Future experiments will further explore such signal convergence in the PPN and cMRF.

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Abbreviations

cMRF	central mesencephalic reticular formation
contra	cells tuned to contralateral rotation or translation
dark	stimulus condition allowing for reflexive eye movements in complete darkness
EH	eye-head
EM	eye-movement
EO	eye-only
FN	fastigial nucleus
HF	head-fixed
ipsi	cells tuned to ipsilateral rotation or translation
P	pursuit
PPN	pedunclopontine nucleus
PV	position-vestibular
R	rotation

SF	space-fixed
T	translation
VE	vestibular-eye
VN	vestibular nucleus
VOR	vestibulo-ocular reflex

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Highlights

1. The PPN and cMRF respond to vestibular (rotation/translation) stimuli.
2. Visual pursuit responses are more frequent in the cMRF than in the PPN.
3. Rotation preferences differ for the PPN (nose down pitch) and cMRF (ipsilateral yaw).
4. PPN translation response amplitudes are higher than those in the cMRF.
5. The PPN and cMRF could initiate responses to vestibular stimuli like falls and turns.

Figure 1.

Responses from a PPN vestibular-only (VO) cell during rotation, translation, and visual pursuit. Significant modulation occurs during rotation and translation, but not during visual pursuit, thus classifying this cell as VO. Responses for rotation are shown during darkness (Dark), during vestibulo-ocular reflex (VOR) cancellation while tracking a head-fixed target (HF), and while engaging VOR when tracking a space-fixed target (SF). Responses to translation were tested in darkness only. From top to bottom: instantaneous firing rate (IFR), stimulus (head velocity, Hvel, for rotation; head acceleration, Hacc, for translation; target motion, T, for pursuit), vertical eye position (Evert), and horizontal eye position (Ehor). Positive directions of eye position, yaw rotation and lateral translation are leftwards. Positive direction of pitch rotation is nose-down. Positive direction of roll rotation is left-ear down. Positive direction of fore-aft translation is fore.

Figure 2.

Responses from a cMRF vestibular-eye movement (VE) cell during rotation, translation, and visual pursuit. Peak modulation during yaw rotation is in-phase ($\pm 90^\circ$) with peak modulation during horizontal pursuit while peak modulation during pitch rotation is out of phase with modulation during vertical pursuit, thus classifying this cell as VE. Responses for rotation are shown during darkness (Dark), during vestibulo-ocular reflex (VOR) cancellation while tracking a head-fixed target (HF), and while engaging VOR when tracking a space-fixed target (SF). Responses to translation were tested in darkness only. From top to bottom: instantaneous firing rate (IFR), stimulus (head velocity, Hvel, for rotation; head acceleration, Hacc, for translation; target motion, T, for pursuit), vertical eye position (Evert), and horizontal eye position (Ehor). Positive directions of eye position, yaw rotation and lateral translation are leftwards. Positive direction of pitch rotation is nose-down. Positive direction of roll rotation is left-ear down. Positive direction of fore-aft translation is fore.

Figure 3.

Map of recorded PPN (purple) and cMRF (orange) cell locations in two macaques (Monk1: Δ; Monk2: *). The trochlear nucleus (CNIV Nu) and rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) were used as landmarks delineating the antero-posterior (AP) extent of the cMRF and PPN. The inferior colliculus (IC) was used to delineate between the cMRF and PPN by depth (dorso-ventral, DV). Neurons recorded deep to the cMRF but greater than 3 mm anterior to the trochlear nucleus were deemed outside of the PPN and excluded from further analysis (gray).

Figure 4.

Gains (top) and phases (bottom) during rotation while tracking a space-fixed (SF) target compared to gains and phases during **A**: rotation while tracking a head-fixed (HF) target; or **B**: visual pursuit. For all cells, response properties for both SF yaw and SF pitch rotation are plotted against those for HF yaw and HF pitch rotation, respectively (**A**), or against horizontal and vertical pursuit, respectively (**B**). Gains (top) are plotted regardless of whether the cells were significantly modulated during rotation or pursuit, as cells that were not significantly modulated consistently have small response gains. Phases (bottom) are plotted only for those cells significantly modulated during both stimuli, as cells that were not significantly modulated can have erratic phases. Different colors and symbols are used for different cell types and recording areas: PPN (purple, Δ), cMRF (orange, $\circ$), neurons modulated during both rotation and visual pursuit (EM, open symbols), neurons modulated during rotation but not during visual pursuit (VO, closed symbols). Response gains and

phases between SF rotation and HF rotation and between SF rotation and pursuit were not significantly different from each other regardless of cell type or area of recording (repeated measures ANOVA, $p > 0.05$). All neurons were subsequently grouped for further analyses. Dotted lines denote unity slope lines. Solid lines denote linear regressions for all cell types and recording areas. Marginal distributions are shown along plot axes and were not significantly different from ideal uniform distributions ($p > 0.05$, see Methods for description of resampling analysis). Gains and phases between SF and HF rotation and between SF rotation and pursuit were significantly correlated (type II regression, $p < 0.05$) and slopes (Table 3) were not significantly different from unity based on 95% confidence intervals.

Figure 5.

Response properties of PPN and cMRF neurons during rotation (A and B) and pursuit (C and D). **A and C:** Polar plots showing the preferred directions of maximum response gains in the PPN (left) and cMRF (right) during rotation (A) and pursuit (C). Different colors and symbols are used for different cell types (dark blue: eye-head, EH; cyan: position-vestibular, PV; light blue: vestibular-Eye, VE; green: vestibular-only, VO; red: eye-only, EO) and recording lateralities (filled symbols: left brainstem, L; open symbols: right brainstem, R). VO neurons (green) were not modulated during pursuit and EO neurons (red) were not modulated during rotation. The distance of each symbol from the center indicates the gain (spikes/sec/°/sec) while the angular position corresponds to the cell's preferred direction (per inset at top: left yaw rotation at 0°, right yaw rotation at 180°, nose-up pitch at 90°, nose-

down pitch at 270°). **B and D:** Distributions of preferred directions, expressed relative to ipsilateral (ipsi, 0°) vs. contralateral (contra, 180°) direction preferences. For ease of interpretation, cells modulated during both HF rotation and pursuit (PV, EH, and VE cells) were grouped as eye-movement (EM) cells (bottom) and were separated from VO cells (top). Purple and orange bars illustrate PPN and cMRF, respectively. Asterisks indicate modes of distributions significantly different from uniformity ($p > 0.05$).

Figure 6. Rotation preferred directions in 3D. The data are illustrated using spherical coordinates (i.e., azimuth and elevation) plotted on Cartesian axes that represent the Lambert cylindrical equal area projection of the spherical stimulus space. Preferred directions corresponding to the azimuth and elevation angles are indicated along the axes (elevation: left yaw rotation at 0° , right yaw rotation at 180° ; azimuth: left-ear down roll at 0° , nose-up pitch at 90° , right ear down roll at 180° , nose-down pitch at 270°). Different colors and symbols are used to distinguish recording areas: PPN (purple, Δ), cMRF (orange, $\circ$). Open symbols designate neurons that were modulated during both rotation and visual pursuit (EM); Filled symbols mark neurons that were modulated during rotation but not during visual pursuit (VO). Marginal distributions are shown along the top and right sides of the plot with cells separated by type (open bars: EM; filled bars: VO) and recording area. Asterisks indicate modes of distributions significantly different from uniformity ($p > 0.05$).

Figure 7. Response properties of PPN and cMRF neurons during translation. **A:** Polar plots showing the distribution of preferred vector orientations (i.e. directions of maximum response gain) in the PPN (left) and cMRF (right). Different colors and symbols are used for different cell types (dark blue: eye-head, EH; cyan: position-vestibular, PV; light blue: vestibular-Eye, VE; green: vestibular-only, VO) and recording lateralities (filled symbols: left brainstem, L; open symbols: right brainstem, R). The distance of each symbol from the center indicates the gain (spikes/sec/G) while the angular position corresponds to the cell's preferred direction (per inset at top: left linear translation at 0°, right at 180°, up at 90°, down at 270°). **B:** Distributions of preferred directions, separated into ipsilateral (ipsi, 0°) vs. contralateral (contra, 180°) direction preferences. For ease of interpretation, cells modulated during both HF rotation and pursuit (PV, EH, and VE cells) were grouped as eye-movement (EM) cells (bottom) and were separated from VO cells (top). Purple and orange bars illustrate PPN and cMRF, respectively. Distributions were not significantly different from ideal uniform distributions ($p>0.05$).

Table 1

Percentages of PPN and cMRF neurons that were modulated during rotation, translation, and visual pursuit.

Stimulus		N _{modulated} /N _{tested} , %	
		PPN	cMRF
R	SF	27/42, 64.3%	42/57, 73.7%
	HF	31/42, 73.8%	43/58, 74.1%
	Dark	28/42, 66.7%	34/56, 60.7%
T		30/40, 75.0%	38/55, 69.1%
P		9/42, 22.5%	33/58, 56.9%
R and T		26/40, 61.9%	35/55, 63.6%
R and P		8/42, 20.0%	30/58, 51.7%
T and P		7/40, 16.7%	21/55, 38.2%
R, T and P		5/40, 12.5%	19/55, 34.5%
R and T, but not P		20/40, 50.0%	16/55, 29.1%

Numbers reflect neurons that were modulated significantly (N_{modulated}) (see Methods) during fore-aft or lateral translation (T), horizontal or vertical visual pursuit (P), and/or during yaw, pitch, or roll rotation (R) while tracking a space-fixed target (SF), head-fixed target (HF), or in complete darkness (Dark). Percentages are relative to the total number of neurons tested (N_{tested}) with a given stimulus. All neurons were recorded during at least HF rotation and visual pursuit.

Table 2

Cell types and percentages of neurons that were modulated during HF rotation and/or visual pursuit.

Cell Type		N/N _{tested} %	
		PPN	cMRF
EM	PV	2/40, 64.3%	11/56, 19.6%
	EH	3/40, 73.8%	12/56, 21.4%
	VE	1/40, 66.7%	2/56, 3.6%
	EO	3/40, 7.5%	7/56, 12.5%
	Total EM	9/40, 22.5%	32/56, 57.1%
VO		29/40, 72.5%	23/56, 41.1%

Totals refer to neurons tested during at least HF rotation and visual pursuit (N_{tested}=40 for PPN; N_{tested}=56 for cMRF). Cells that responded to translation and not rotation or visual pursuit (2 PPN cells and 1 cMRF cell) were excluded from further analysis. Neurons are classified by cell type: Eye movement (EM) responsive cells are comprised of position-vestibular (PV), eye-head (EH), vestibular-eye (VE), and eye-only cells (EO). The rest were classified as vestibular-only cells (VO).

Table 3

Comparison of gains and phases between SF rotation, HF rotation, and visual pursuit

	Gain		Phase	
	Mean	Slope, [95% CI]	Mean	Slope, [95% CI]
SF Rotation	0.7±0.5	--	5±44	--
HF Rotation	0.7±0.5	1.2, [0.9, 1.4]	11±44	1.0, [0.9, 1.2]
Pursuit	0.8±0.4	1.1, [0.5, 3.7]	-2±48	0.8, [0.3, 1.2]

Type II linear regression analyses were used to compare gains and phases between space-fixed (SF) rotation and head-fixed (HF) rotation or between SF rotation and visual pursuit across all cell types and recording areas. Gain and phase means $\pm$ standard deviations and linear regression slopes with 95% confidence intervals (CI) are shown.