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Cortical Integration of Vestibular and Visual Cues for Navigation, Visual Processing, and Perception

Sepiedeh Keshavarzi, Mateo Velez-Fort, and Troy W. Margrie

The Sainsbury Wellcome Centre for Neural Circuits and Behavior, University College London, London, United Kingdom; email: t.margrie@ucl.ac.uk

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Abstract

Despite increasing evidence of its involvement in several key functions of the cerebral cortex, the vestibular sense rarely enters our consciousness. Indeed, the extent to which these internal signals are incorporated within cortical sensory representation and how they might be relied upon for sensory-driven decision-making, during, for example, spatial navigation, is yet to be understood. Recent novel experimental approaches in rodents have probed both the physiological and behavioral significance of vestibular signals and indicate that their widespread integration with vision improves both the cortical representation and perceptual accuracy of self-motion and orientation. Here, we summarize these recent findings with a focus on cortical circuits involved in visual perception and spatial navigation and highlight the major remaining knowledge gaps. We suggest that vestibulo-visual integration reflects a process of constant updating regarding the status of self-motion, and access to such information by the cortex is used for sensory perception and predictions that may be implemented for rapid, navigation-related decision-making.

Contents

INTRODUCTION

Head movements increase the breadth of the sensory world vertebrates survey when engaged in natural behavior (Ericsson et al. 2013). While these movements are important for perception (e.g., generating motion parallax for depth perception) and spatial orientation (e.g., orienting toward the source of a sound or an odor and planning one's directional heading), they also pose a challenge for the brain to determine the precise location and motion status of external objects as the observer moves through space. For instance, because motion on the retina can arise either from an external object moving in the scene or from head and eye movements, the brain must disambiguate this retinocentric input by combining it with head and eye motion cues. Beyond compensating for sensor movements and maintaining a coherent perception of the external world, the integration of visual and head motion cues also increases the accuracy of self-motion and orientation computations, effectively supporting successful navigation.

The brain can derive head motion information from multiple sources, including vestibular sensors that detect angular and linear acceleration of the head in multiple planes, efference copy of the motor command when movement is self-initiated, and neck muscle proprioception. Electrical stimulation of the vestibular nerve in deeply anesthetized rodents evokes widespread activation of sensory and motor cortical areas (Rancz et al. 2015), suggesting that vestibular signals are broadcast to brain regions engaged in the generation of movement and sensation during locomotion. Over the past few years, studies on primates have significantly advanced our knowledge of how visual and vestibular cues can combine for optimal heading perception (Butler et al. 2010; Fetsch et al. 2009, 2011; Gu et al. 2008; Jurgens & Becker 2006; Noel & Angelaki 2022; Prsa et al. 2012). However, the circuit mechanisms that support this multimodal integration and its functional significance in cortical networks involved in perception and spatial navigation remain poorly understood. Despite differences in the structure and statistics of natural vestibular input between rodents and primates (Carriot et al. 2017), the rodent model presents significant advantages in terms of experimental throughput and the existing array of transgenic and viral tools that can be adapted to study the neural circuits for vestibular processing in general, and vestibulo-visual integration in particular. In addition, while our knowledge of neural computations for navigation is largely based on experiments in rodents, and despite the importance of head motion cues in these computations, experimental data on vestibular signals in the rodent cortex and their integration with visual cues are only just emerging. Here, we summarize and discuss these recent findings, focusing on cortical circuits that are involved in visual perception and spatial navigation. We highlight

major unresolved questions regarding the role of vestibular and visual integration during behavior and the underlying circuit mechanisms, and we propose experimental approaches to address them.

VESTIBULAR AND VISUAL INTEGRATION FOR NAVIGATION

To successfully navigate through the environment, animals rely on their ability to know their heading orientation. At least two types of cells identified in the rodent's brain—as well as in other animals, including insects (Green et al. 2017, Seelig & Jayaraman 2015, Turner-Evans et al. 2017), fish (Vinepinsky et al. 2020), birds (Ben-Yishay et al. 2021), bats (Finkelstein et al. 2015), and primates (Baumann & Mattingley 2010, Robertson et al. 1999, Shine et al. 2016)—are thought to subserve the sense of orientation:

1. Head direction (HD) cells (Chen et al. 1994; Cho & Sharp 2001; Taube 1995; Taube et al. 1990a,b), which are tuned, in allocentric coordinates, to the orientation of the head in the azimuthal plane and are thought to form an internal neural compass; and
2. Angular head velocity (AHV) cells (Bassett & Taube 2001, Keshavarzi et al. 2022, Sharp & Turner-Williams 2005, Sharp et al. 2001, Spalla et al. 2022), which signal the speed and direction of head turns and can therefore generate and update the head direction signal via an angular path integration mechanism (Blair & Sharp 1995, Laurens & Angelaki 2018, McNaughton et al. 1991, Redish et al. 1996, Skaggs et al. 1995, Zhang 1996).

Both of these head orientation signals are primarily vestibular in origin (Keshavarzi et al. 2022, Muir et al. 2009, Shinder & Taube 2011, Stackman & Taube 1997, Valerio & Taube 2016), but they can also be modulated by efference copy of active head movements and neck proprioception (Keshavarzi et al. 2022, Stackman et al. 2003). In addition, the combination of visual input with these signals is important for reliable orientation computations (Arleo et al. 2013, Goodridge & Taube 1995, Keshavarzi et al. 2022, Taube et al. 1990b), as detailed in the following sections.

Head Direction Cells

The HD signal is thought to be generated by temporal integration of the AHV signal at the interface between the dorsal tegmental nucleus and the lateral mammillary nucleus (Bassett & Taube 2001, Bassett et al. 2007, Blair et al. 1998, Sharp et al. 2001, Taube 2007) (**Figure 1**). It is then relayed via the thalamus to cortical regions of the navigation system where it ultimately integrates with map-like representations in entorhinal and hippocampal networks (Calton et al. 2003, Gerlei et al. 2020, Harland et al. 2017, Peyrache et al. 2017, Winter et al. 2015a). Vision stabilizes the HD signal by anchoring it to the external environment (Goodridge & Taube 1995, Taube et al. 1990b). In particular, prominent and stable visual cues known as visual landmarks strongly control the preferred firing direction of HD cells. In the absence of vision, the HD signal drifts over time due to the accumulation of path integration error (Bjerknes et al. 2015, Goodridge et al. 1998), which may explain why our sense of orientation is lost in the dark, especially over long distances. The integration of visual information into the HD system occurs at the earliest stage of this hierarchical network, with HD cells in the lateral mammillary nucleus already showing landmark control (Yoder et al. 2015) (**Figure 1**).

How are visual landmarks detected, stored, and integrated into the HD system? Lesion experiments have highlighted the significance of two cortical regions for transferring landmark information into the HD cell network: the postsubiculum (Goodridge & Taube 1997, Yoder et al. 2015) and the retrosplenial cortex (Clark et al. 2010) (**Figure 1**). Lesioning either region leads to
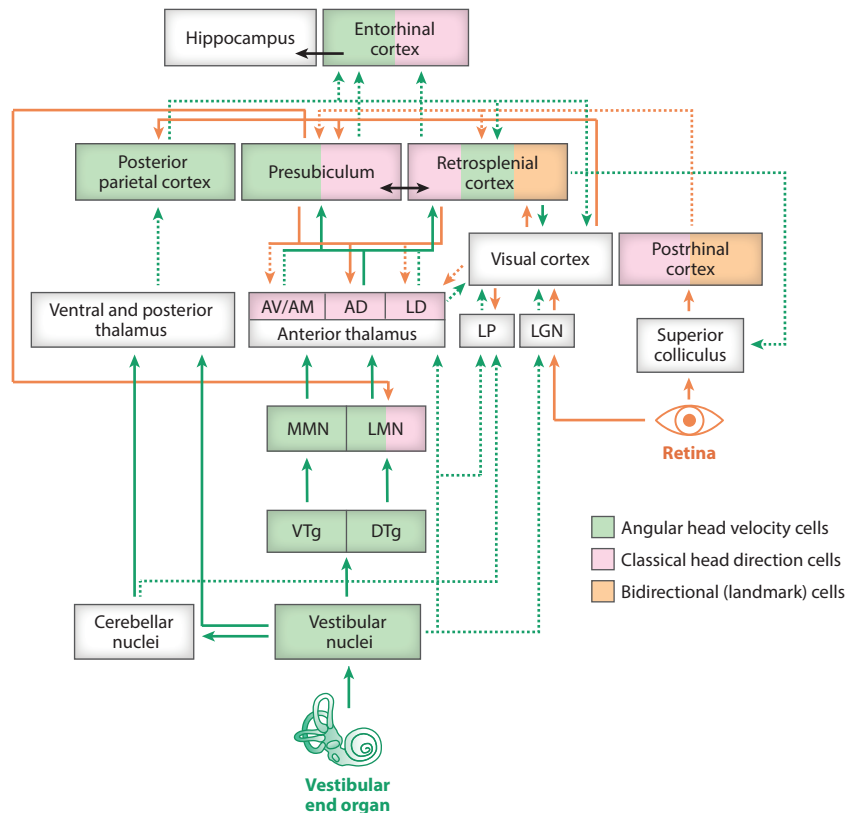
Figure 1

Neural circuits for the integration of visual and head motion cues in the rodent brain. The simplified
diagram shows neural pathways that convey vestibular (*green arrows*) and visual (*orange arrows*) information to
cortical areas involved in spatial navigation and visual perception. Solid and dashed lines represent
established pathways and putative routes that require further experimental evidence, respectively. Black
arrows represent pathways that carry other signals relevant to spatial navigation. For simplicity and due to
limited data on translational vestibular signals, only angular head velocity and head orientation pathways are
shown. Abbreviations: AD, anterodorsal thalamic nucleus; AM, anteromedial thalamic nucleus; AV,
anteroventral thalamic nucleus; DTg, dorsal tegmental nucleus of Gudden; LD, lateral dorsal thalamic
nucleus; LGN, lateral geniculate nucleus; LMN, lateral mammillary nuclei; LP, lateral posterior thalamic
nucleus; MMN, medial mammillary nuclei; VTg, ventral tegmental nucleus of Gudden.

impaired landmark control in upstream parts of the HD system. Yet, whether they actively detect
and store landmark information by assessing the input from visual cortical areas, or whether they
inherit and further integrate it in the HD system, remains unknown. In addition, it is unclear how
visual information flows between these areas and whether they provide redundant information
or have complementary integrative roles that support HD signaling. Reciprocal connections
between retrosplenial cortex and postsubiculum (Sugar et al. 2011, Wyss & Van Groen 1992)
and their anatomical proximity further complicates the interpretation of lesion experiments. For
instance, it is likely that the observed impact of postsubicular lesions is, at least in part, due to
lesions extending into the overlaying retrosplenial and visual cortices (Yoder et al. 2015) or due
to the disruption of HD and landmark computations in the retrosplenial cortex following the loss
of postsubicular input. Refined circuit-selective inactivation with the use of novel genetic and

viral tools (Huang & Zeng 2013) will help disambiguate the specific role that these regions play in detection, storage, and integration of visual landmarks into the HD system.

Recent neurophysiological experiments have identified the neural representation of visual landmarks in the dysgranular division of the retrosplenial cortex (Fischer et al. 2020, Jacob et al. 2017, Sit & Goard 2022). In particular, a subset of directional cells in this area are dominated by visual landmarks, showing bidirectional firing in a visually symmetrical two-compartment environment (Jacob et al. 2017) (**Figure 1**). Theoretical work has proposed that these cells assess the stability of visual landmarks and incorporate them into the HD system through Hebbian plasticity between visual and vestibular-dependent HD input (Page & Jeffery 2018). Although experimental evidence in support of this model is yet to be found, it aligns with human neuroimaging data that suggest a role for the retrosplenial cortex in the processing of landmark permanence (Auger & Maguire 2013, Auger et al. 2012). Whether neural representation of landmarks also exists in the postsubiculum and how it relates to those in the retrosplenial cortex remains to be determined.

Landmark-dominated directional cells have also been reported in the postrhinal cortex (LaChance et al. 2022) (**Figure 1**), yet lesion experiments suggest that this area does not play a major role in landmark control of thalamic HD cells (Peck & Taube 2017). Nevertheless, considering the substantial reciprocal connections of the postrhinal area with the retrosplenial cortex and postsubiculum (Agster & Burwell 2013), this region may also contribute to visual landmark processing in cortical and hippocampal navigation networks. In addition to revealing the circuit logic of visual landmark integration into the HD network, future experiments should aim to understand how different cortical areas evaluate the stability and spatial location of visual cues to determine whether they can be used as reliable landmarks and the cellular and synaptic mechanisms for integration of landmark information into the vestibular-dependent HD signal.

What is the behavioral significance of the HD signal and its integration with visual cues? Navigation tasks aimed at answering this question have shown mixed results. While in some tasks no correlation between HD cell activity and navigation performance was found (Dudchenko & Taube 1997, Golob et al. 2001, Muir & Taube 2004), a few studies that employed a homing task—in which the animal has to find its way back to a home base to consume the food it has collected—have shown significant correlation between the stability of the HD signal and heading accuracy during return (Butler et al. 2017, Valerio & Taube 2012, van der Meer et al. 2010) (**Figure 2a**). Moreover, since the preferred orientation of HD cells can drift in the absence of stabilizing visual landmarks (Goodridge & Taube 1997, Yoder et al. 2011) (**Figure 2a**), the animal's heading performance may be impacted in the dark. Experimental designs that aim to remove all potential sources of orienting landmark information, such as tactile, sound, and olfactory cues, are required to test the behavioral significance of visual cues during such tasks.

Angular Head Velocity Cells

Visual inputs also influence the AHV system. A recent study identified AHV-tuned cells in the mouse retrosplenial cortex during open field exploration and subsequently recorded their activity in a head-fixed apparatus that permits isolation of both vestibular and visual contributions (Keshavarzi et al. 2022). These experiments showed that while AHV cells rely on vestibular input, the combination of visual and vestibular cues increases the gain and signal-to-noise ratio of their tuning function, thus improving the accuracy of encoding the direction and speed of head turns. The contribution of vision to AHV computation may arise from the combined effect of increased luminance [i.e., more spikes (Bouvier et al. 2020)], optic flow (more velocity information), and the increased gain of compensatory eye movements (Stahl 2004). Future work should explore these possibilities by manipulating the properties of the surrounding visual stimuli during self-motion. Regardless of how vision improves AHV coding, these findings suggest that the integration of

a Spatial navigation
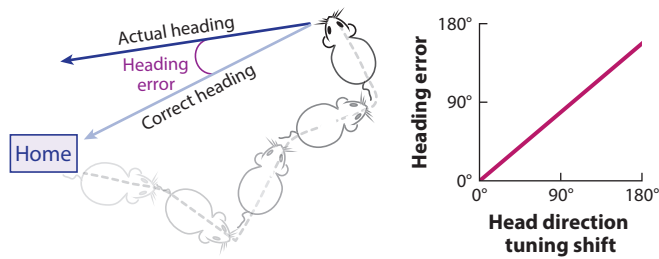
c Visual perception
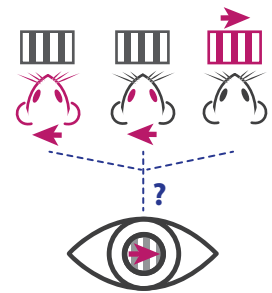
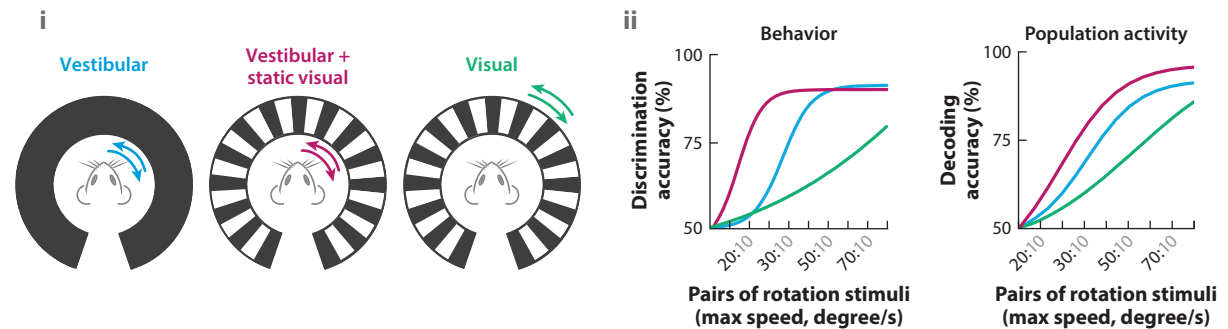

b Self-motion estimation

Figure 2

Behavioral significance of the integration of vestibular and visual cues. (*a*) The integration of visual cues into the vestibular-dependent head direction signal is important for accurate spatial orientation. The stability of the head direction signal—measured as the amount of shift in the tuning of head direction cells—is correlated with the rat's performance in a homing task (*left* and *middle*). In the absence of visual cues, the head direction signal becomes less stable (*right*, increased shift in the tuning of head direction cells), which may lead to more heading errors. Plots are simplified and based on data from Valerio & Taube (2012) (*left*) and Goodridge et al. (1998) (*right*). (*b*) The combination of vestibular and visual cues improves estimation of self-motion. In a rotation-discrimination task in which mice were trained to report their angular speed under different experimental conditions (*i*), their performance improved significantly when both vestibular and visual stimuli were available (*ii*, *left*, *magenta*) compared to when rotated in the dark (*blue*). Similarly, in the retrosplenial cortex, the accuracy of decoding angular self-velocity from population activity increased when both vestibular and visual cues were available (*ii*, *right*). The improved perceptual and decoding accuracy under the multisensory condition could not be explained by the use of vision alone, since both were substantially lower when only visual motion stimuli were present (*green*). Schematics and plots are simplified and based on data from Keshavarzi et al. (2022). (*c*) The integration of head and visual motion signals is essential for disambiguating the source of motion on the retina, which may arise from head and/or eye movements, or motion in the external world.

head motion and visual cues can impact the sense of orientation in two ways: (*a*) It stabilizes the HD signal by anchoring it to reliable visual landmarks in the environment, and (*b*) it optimizes the head velocity estimates, which are used to update the HD signal via path integration.

What could be the behavioral significance of the cortical AHV signal? A recent study on escape behavior in mice has identified a class of cells that encode head orientation relative to a shelter in both the retrosplenial cortex and the superior colliculus (Campagner et al. 2023). Interestingly, the input from the retrosplenial cortex is necessary not only for this shelter-direction tuning in the superior colliculus but also for accurate and rapid execution of head turns toward the optimal shelter trajectory (Campagner et al. 2023). Reminiscent of egocentric goal-direction cells found in the hippocampus (Sarel et al. 2017), the shelter-direction cells likely rely on continuous updating from AHV cells for rapid navigation-related decisions and behaviors. Whether the retrosplenial projections to the superior colliculus convey the AHV input for further computation of these

orientation signals or simply pass on the shelter-direction signal constructed in the cortex remains to be determined, for instance, by imaging the activity of collicular-projecting retrosplenial cells during escape. Further experiments that carefully control and manipulate visual cues and test the animal's orientation ability in more complex and longer paths, which leads to the accumulation of path integration errors, are necessary to fully understand the relevance of visual information in such behavior.

Beyond their role in generating and updating orientation signals, cortical AHV-tuned cells may be important for perception of self-motion. Perhaps the most exciting line of vestibular research to emerge in the last decade is the demonstration that—similar to humans—rodents can be trained to use their vestibular system to report self-motion and their passive rotation speed in go/no-go rotation discrimination tasks (Velez-Fort et al. 2018, Keshavarzi et al. 2022) (**Figure 2b**). Importantly, mice improve their perceptual accuracy in this task when visual cues are present, and this improvement requires the integration of visual and vestibular inputs (Keshavarzi et al. 2022) (**Figure 2b**). Where in the brain this integration might take place is yet to be found. Since the activity of AHV cells in the retrosplenial area mirrors these perceptual data, it is plausible that they contribute to self-motion perception. AHV-tuned cells have also been reported in other parts of the navigation system (Hennestad et al. 2021, Spalla et al. 2022) as well as in primary sensory and motor areas (Hennestad et al. 2021, Long et al. 2022). Whether the same or different AHV populations are involved in orientation computations and perception of self-motion and whether their role differs between brain areas depending on their input-output connectivity remain to be determined in future work.

Another outstanding question concerns the neural pathways by which the AHV signal reaches the brain's navigation system (**Figure 1**). One route may involve the ascending HD system via projections from the anterodorsal thalamic nucleus to the retrosplenial cortex. However, although this thalamic area contains a large number of HD cells, they are not significantly modulated by AHV (Bassett et al. 2007). Despite this, recent computational modeling data suggest that the AHV signal in the retrosplenial cortex can arise from HD-tuned thalamic afferents as a result of their depressing synaptic dynamics (Brennan et al. 2021). The AHV signal can then reach the other parts of the navigation system either via the retrosplenial cortex (Sugar et al. 2011, Velez-Fort et al. 2018, Wyss & Van Groen 1992) or via other thalamocortical routes, such as direct projections from the anterior thalamus to hippocampal formation and entorhinal cortex (Jankowski et al. 2013). Other vestibulo-thalamic pathways that connect the vestibular and cerebellar nuclei to posterior and lateral thalamic regions (Bohne et al. 2019, Nagata 1986, Shiroyama et al. 1999) may also contribute to the cortical AHV signal. Future recordings and targeted manipulation of activity in these thalamocortical projections can elucidate the neural circuits that convey head motion information to cortical and hippocampal centers of the navigation system and further reveal whether the integration of head motion and visual cues occurs primarily in higher-order cortical networks or is inherited from subcortical regions.

Translational Heading Signals

While rotational head motion inputs contribute to the formation and updating of the neural compass, much less is known about how translational head movements may support navigation. Cells that encode the animal's linear locomotion speed have been identified in key parts of the navigation system, including the medial entorhinal cortex (Kropff et al. 2015, Sargolini et al. 2006), parietal and retrosplenial cortices (Alexander et al. 2022, Cho & Sharp 2001, Keshavarzi et al. 2022, Whitlock et al. 2012), and hippocampus (McFarland et al. 1975, McNaughton et al. 1983, Wiener et al. 1989). This speed signal is thought to be important for spatial localization through a path integration mechanism and has been implemented in the vast majority of computational

models of spatial coding (Bush & Burgess 2014, Giocomo et al. 2011, McNaughton et al. 2006). The origin of the cortical speed signal is not well understood. Recent data suggest that in the medial entorhinal cortex and hippocampus it is primarily motor in origin (Winter et al. 2015b) and may be driven by subcortical circuits between the brainstem and basal forebrain (Carvalho et al. 2020, Fuhrmann et al. 2015, Justus et al. 2017; but also see Dannenberg et al. 2019, Hinman et al. 2016). Yet, during real-world navigation in freely moving animals, both translational head motion input from the vestibular (otolith) system (Jacob et al. 2014) and optic flow (Chen et al. 2016, Dannenberg et al. 2020, Peréz-Escobar et al. 2016) may provide additional information about the animal's locomotion speed. The respective role of these various motor and sensory cues in the generation of the speed signal, how their integration may shape and modulate it, and the neural circuits that propagate them to different cortical regions remain open questions for future research.

VESTIBULAR AND VISUAL INTEGRATION FOR CORTICAL VISUAL PROCESSING

Most of our understanding of vestibulo-visual integration in the cortex comes from research on humans and nonhuman primates. These studies have focused on areas dedicated to visual motion perception, particularly the dorsal medial superior temporal area and the ventral intraparietal area (Bremmer et al. 1999, Duffy 1998, Fasold et al. 2002, Thier & Erickson 1992; for reviews, see DeAngelis & Angelaki 2012, Lopez & Blanke 2011). Indeed, only a subset of primary visual cortex (V1) neurons are highly selective for the direction of visual motion, and these cells have small spatiotemporal receptive fields that encode the visual motion of local features (Hubel & Wiesel 1968). In addition, V1 has a high percentage of neurons suppressed by binocular optic flow (Rasmussen et al. 2021). For these reasons, V1 has not been regarded as well suited for processing self-motion information (Noel & Angelaki 2022).

Nonetheless, indirect evidence supporting the presence of vestibular signals in V1 of humans (Bense et al. 2001, Tiecks et al. 1996, Wenzel et al. 1996) and nonhuman animal models has existed for decades. For instance, extracellular recordings of neuronal activity obtained in cats during labyrinthine polarization and/or calorization (Gorgiladze & Smirnov 1967; Grüsser & Grüsser-Cornehls 1960, 1972; Grüsser et al. 1959; Jung et al. 1963), or more physiologically relevant whole-body rotations (Spiegel et al. 1968, Vanni-Mercier & Magnin 1982), have shown a significant proportion of V1 neurons responding to vestibular activation. Comprehensive activation maps of brain regions that respond to vestibular nerve stimulation in rats (Best et al. 2014, Rancz et al. 2015) have now confirmed the presence of cortical vestibular signals not only in V1 but also in other primary sensory cortical areas. Recordings in head-fixed mice from V1 layer 6 in darkness show that many neurons are differentially tuned to the velocity of horizontal rotation (Velez-Fort et al. 2018). Such studies indicate that vestibular modulation of V1 can vary according to cortical depth (Bouvier et al. 2020, Velez-Fort et al. 2018). In superficial layers (layer 2/3 and layer 4), whole-body rotation leads to an overall suppression of neuronal activity, whereas neurons in deep layers (layer 5 and layer 6) are equally distributed between those that are excited and those that are suppressed (Bouvier et al. 2020, but see Velez-Fort et al. 2018). Interestingly, the impact of head motion on V1 activity is light dependent, since most of those units that are suppressed in the dark become excited under ambient light conditions. This light-dependent vestibular response appears to be mediated, at least in part, by a subclass of V1 interneurons (somatostatin-positive cells in deep layers) that integrate vestibular and luminance signals (Bouvier et al. 2020). Together, these findings demonstrate that head motion processing and vestibulo-visual integration in V1 occur in a layer- and cell type–specific manner.

While evidence for their combined representation at the level of the cortex is emerging, the synaptic mechanisms of vestibular and visual integration remain much less studied. In vivo whole-cell recordings in V1 show that horizontal rotation evokes both excitatory and inhibitory subthreshold responses that can be direction selective (Velez-Fort et al. 2018). In layer 6, the amplitude of these subthreshold responses is higher when a static visual cue is present compared to rotation in darkness and matches the arithmetic sum of vestibular-only (rotation of the animal in the dark) and visual-only (rotation of the visual cue) responses. While these data suggest that vestibular and visual inputs converge onto individual V1 cells (Velez-Fort et al. 2018), the biophysical mechanisms of their integration at the synaptic or dendritic level and how they control firing output remain unknown. These questions have been explored to a greater extent outside of the cerebral cortex. For example, in electrotonically compact cerebellar granule cells with small, simple dendritic fields, the amplitude of the mossy fiber to granule cell synaptic response is extremely reliable over a broad range of rotation velocities (Arenz et al. 2008). These cerebellar granule cells also receive visual inputs, which can be readily distinguished from the vestibular inputs due to their distinct synaptic properties (Chabrol et al. 2015). Interestingly, when vestibular and visual afferents are simultaneously activated, their integration produces different firing patterns depending on the type of vestibular afferent involved. The representation of combined vestibular and visual sensory input, therefore, not only causes changes in the firing rate but can also result in discrete changes in the firing pattern of individual neurons. It remains to be determined whether similar biophysical principles govern how visual cortical neurons integrate these two types of sensory inputs.

One drawback of head-fixed experiments that involve passive rotation or translation is the absence of active head movements. The efference copy of motor commands that initiate head movements in freely moving animals is known to integrate at the earliest stage of central vestibular processing in the vestibular nuclei (Cullen & Taube 2017). Vestibular-only (VO) cells in these nuclei, which are sensitive to vestibular stimulation but insensitive to eye movements, are thought to be involved in maintaining posture, self-motion perception, and spatial navigation (Cullen 2019). In mice, these vestibular-only cells respond to both passive whole-body rotation and neck proprioception. However, their activity appears to attenuate during active head movements (Medrea & Cullen 2013), even though, unlike in primates, they still robustly encode head-on-body position during both passive and active motion. Therefore, to fully elucidate the impact of head motion on vision and the role of vestibular signals, it is necessary to investigate these processes in freely moving animals.

Recent development of head-mounted devices, which allows tracking of eye and head movements while recording neuronal activity, has enabled the study of visual processing in freely moving animals (Dugue et al. 2017; Klioutchnikov et al. 2020, 2023; Meyer et al. 2018; Michaiel et al. 2020; Parker et al. 2022a; Sattler & Wehr 2020; Voigts et al. 2013; Wallace et al. 2013; Zong et al. 2017; for a review, see Chaplin & Margrie 2020). With the use of such technical advances, it has been recently discovered that isolated head movements recorded in the dark in freely moving rodents can modulate the activity of over 50% of V1 neurons (Bouvier et al. 2020, Meyer et al. 2018) and that these head motion–related responses become increasingly excitatory under light conditions (Bouvier et al. 2020, Guitchounts et al. 2020). Surprisingly, while general movement such as running increases visual responses in V1 (Niell & Stryker 2010), head-orienting movements appear to suppress visual-evoked activity (Guitchounts et al. 2020), akin to the attenuation of self-generated sound in the auditory cortex (Rummell et al. 2016, Schneider et al. 2014). Whether such findings reflect differences in integration of linear and angular head motion with vision requires further investigation, but regardless, they confirm that head motion signals play a major role at the very first stage of cortical visual processing in rodents.

Vestibular Routes into the Primary Visual Cortex

The neuronal pathways that allow V1 to draw on vestibular information are largely unknown, but several candidates, some of which bypass the canonical anterior and ventral/posterior vestibulo-thalamic pathways, have been put forward. Anatomical (Bohne et al. 2019, Magnin & Kennedy 1979, Nagata 1986, Shiroyama et al. 1999) and functional (Papaioannou 1973, Magnin & Putkonen 1978, Magnin et al. 1974, Matsuo et al. 1994) studies in cats and rats have shown potential pathways linking vestibular nuclei to visual thalamic areas such as the lateral geniculate and the lateral dorsal nuclei (**Figure 1**). In addition, vestibular responses have been reported in the lateral posterior thalamic nucleus (or pulvinar) in cats and monkeys (Marlinski & McCrea 2008, Matsuo et al. 1994, Meng et al. 2007) and, more recently, also in mice (Bouvier et al. 2022). Therefore, multiple thalamic nuclei could serve as the gateway of vestibular information to V1 (**Figure 1**).

V1 has also been shown to receive AHV information directly from the retrosplenial cortex (**Figure 1**). Single-cell anatomical studies using retrograde rabies tracing (Rancz et al. 2011) have shown that layer 6 cortico-thalamic (CT) neurons in V1 receive significantly more inputs from the retrosplenial cortex compared to their neighboring layer 6 cortico-cortical neurons (Velez-Fort et al. 2014) or layer 2/3 principal cells (Brown et al. 2021). It has been recently discovered, using a combination of viral tracing tools and calcium imaging, that the retrosplenial cortical neurons, which directly synapse onto layer 6 CT cells, respond to whole-body rotation in darkness. These data strongly suggest that at least a fraction of vestibular input to V1 is conveyed via the retrosplenial cortex (**Figure 1**). It is worth noting that deep-layer neurons of higher visual areas also receive a significant fraction of their input from the retrosplenial cortex (Galloni et al. 2022), indicating that the influence of this area on V1 activity might take additional cortical routes. Finally, lesioning large parts of the secondary motor cortex leads to a reduction of head motion–related responses in V1 of freely moving rats (Guitchounts et al. 2020). The secondary motor cortex is known to receive vestibular input in rodents (Rancz et al. 2015), but the nature of signals inherited by V1 from this area (motor and/or vestibular) remains unknown. Irrespective of whether motor inputs contribute to such head motion signals, partial lesions of the peripheral vestibular organ almost completely abolish rotation-evoked responses in V1 (Bouvier et al. 2020, Velez-Fort et al. 2018), highlighting their involvement in cortical visual processing.

Functional Relevance of Vestibular Signals for Cortical Visual Processing

One of the first proposed roles of cortical vestibulo-visual integration is to provide visual cortex neurons with a gravity-based reference frame, which would theoretically preserve visual tuning properties independent of the position of the head. One of the first descriptions of head angle–invariant cells was made in the cat V1 (Horn & Hill 1969), whereby the receptive fields of a fraction of V1 neurons compensated for body rotation. These studies and others (Denney & Adorjanti 1972, Horn et al. 1972, Metzler & Spinelli 1979, Tomko et al. 1981) proposed that vestibular, but also proprioceptive, information is integrated in V1 to provide an estimate of the direction of gravity in relation to the visual world. Although only 27% of cells in the cat V1 showed head angle–invariant properties (Tomko et al. 1981), it is the first indication that vestibular and proprioceptive inputs could enable the computation of object orientation independent of head position. In rodents, movement-invariant orientation-selective neurons in deep layers of V1 have been described in freely moving rats (Røe et al. 2018), indicating that vestibular and other types of self-motion inputs can maintain visual tuning properties during natural behavior. In addition, in freely moving mice, a large fraction of visually responsive V1 neurons are tuned to eye position and head orientation (Parker et al. 2022a). In most of these neurons, visual and positional signals combine through a multiplicative (rather than additive) interaction, consistent with a gain field computation

(Salinas & Sejnowski 2001), which has been shown to serve coordinate transformations. This could endow V1 with the computational machinery for embedding visual representations within an egocentric reference frame (Parker et al. 2022a).

Another functional importance of vestibular signals for vision relates to their role in differentiating visual motion generated in the outside world from that caused by the animal's own movements (**Figure 2c**). Both the corollary discharge of head- and eye-movement commands (Crapse & Sommer 2008, von Holst & Mittelstaedt 1950) and the vestibular and proprioceptive signals can contribute to this computation. In primates, multiple visual cortical areas contain both cells that have matched vestibular and visual heading preference (congruent cells) and those with opposing directional tuning for vestibular and visual cues (opposite cells) (Chen et al. 2011; Fetsch et al. 2007, 2011; Gu et al. 2008). While the activity of congruent cells is consistent with vestibulo-visual integration for optimal heading perception and correlates well with perceptual performance, the opposite cells are ill-suited for cue integration (Fetsch et al. 2011, Gu et al. 2008). Instead, these cells respond to a moving object that is not aligned with self-motion and are thought to help dissociate self- and object motion. Indeed, simulations (Kim et al. 2016) and neural decoding data (Sasaki et al. 2017) suggest that the combined activity of congruent and opposite cells can resolve the retinal image into components related to head and object motion. Consistent with these data, behavioral experiments suggest that vestibular cues reduce errors in perception of object direction during self-motion (Dokka et al. 2015b) and can eliminate heading biases caused by a moving object (Dokka et al. 2015a). Whether similar computations parse retinal image motion in the rodent's visual cortex and the extent to which different cortical areas contribute to such computations are yet to be determined.

Vestibular signals in V1 may also contribute to the prediction of visual flow, as previously proposed for motor (stationary running) and coupled optic flow signals (Keller et al. 2012, Leinweber et al. 2017) in a predictive coding framework of cortical function (Keller & Mrsic-Flogel 2018, Rao & Ballard 1999, Spratling 2010). In this framework, vestibular signals are among many types of contextual information—others including the animal's spatial location and orientation (Guitchounts et al. 2022, Fiser et al. 2016, Saleem et al. 2018, Zong et al. 2022) and self-generated movements (Keller et al. 2012, Leinweber et al. 2017)—that is conveyed to V1 via top-down projections to provide predictions of the bottom-up sensory inputs. The difference between the top-down prediction and bottom-up sensory input is then encoded as a prediction error and passed on to other areas to update the internal representation. Based on this model, when an object is moving in the scene, the animal's head movement will be accompanied by a bottom-up visual input that is inconsistent with the predicted optic flow, leading to a prediction error that signals external motion. To date, such speculations about the role of cortical vestibular signals have not been directly tested; thus, whether vestibular inputs in the visual cortex support the predictive coding model remains an outstanding question (Klingner et al. 2016).

Uncoupling Eye- and Head-Movement Cues

Finally, one of the challenges in studying central vestibular integration is that head and eye movements can be interrelated. It is well known that eye movements modulate the activity of V1 in cats (Toyama et al. 1984) and mice (Meyer et al. 2018, Miura & Scanziani 2022, Parker et al. 2022b), and head movements in freely moving rodents are often accompanied by eye movements (Meyer et al. 2018, Wallace et al. 2013). Several experimental approaches have been undertaken to reduce head rotation–related eye movements and, in doing so, isolate the contribution of head movements to brain activity. First, eye movements associated with the vestibulo-ocular reflex can be significantly suppressed by pairing the rotation of the head with the rotation of a visual cue (King et al. 1976). This approach, while suitable in head-fixed preparations, is not practical in freely

moving animals. Second, eye movements can be abolished or significantly reduced by periocular injections of a local anesthetic (Velez-Fort et al. 2018) or by eye muscle resection (Bouvier et al. 2020), both of which remove eye movement–related proprioceptive cues. While these surgical approaches have confirmed that, at least during passive rotation in mice, head motion–evoked activity of V1 neurons is primarily vestibular in origin, the effect of the occlusion of eye movements in freely moving animals is unknown. Recording the activity of V1 neurons in freely moving animals that cannot move their eyes could provide important novel insights into the independent role of head movements in central visual processing.

CONCLUDING REMARKS

Over the past decade or so, considerable evidence has emerged demonstrating that the vestibular modality is pervasive with regard to both its anatomical distribution throughout the cortex and its role in integrative computations. Recent data on vestibulo-visual integration in various cortical networks have now opened the door to study its functional role during behavior. In particular, the use of rodent models that allow high-throughput neuronal recording and precise circuit dissection has provided novel insights into the neural underpinnings of this multisensory integration for visual processing and spatial navigation. We have outlined these recent findings and identified the knowledge gaps that require further research. In particular, determining the organization of neural circuits that convey vestibular information to the cortex and support its integration with vision, understanding the role of vestibular signals and vestibulo-visual integration in cortical computations, and, above all, elucidating their behavioral significance should be the primary focus of future studies in this field. We have outlined some of the key open questions below (see the section titled Future Issues). Addressing these issues in the coming years not only will help us better understand the principles of cortical operations but will also advance our knowledge of neuronal computations underlying perception and naturalistic behaviors.

FUTURE ISSUES

1. What are the routes by which vestibular information reaches the cortex? What are the routes by which optic flow and visual landmark information reaches the head direction network?

2. Does the integration of vestibular and visual cues occur de novo in the cortex, or is the integrated signal largely inherited from subcortical regions?

3. What are the synaptic mechanisms of vestibulo-visual integration in the cortex?

4. What is the behavioral significance of cortical vestibulo-visual integration for visual perception and spatial navigation?

5. How do head motion signals impact visual computations in the cortex? Is there a computational distinction between passive and active movements, and is this consistent with the predictive coding model of cortical function?

6. How does vision impact head motion coding in the cortex? Is the underlying computation similar for horizontal rotation and linear translation?

7. What is the contribution of otolith vestibular inputs to locomotion speed coding? Do they integrate with motor and optic flow inputs to modulate and shape the cortical speed signal?

8. What is the contribution of angular head velocity cells to cortical function? Do they contribute locally to the generation of the head direction signal? Do they have unique functions across different cortical networks?

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Errata

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