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COMMENTARY



## Predictive coding in early vestibular pathways: Implications for vestibular cognition

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Single unit neurophysiological and anatomical studies have provided us with a fundamental understanding of the circuit-based mechanisms by which vestibular information is processed to ensure accurate behaviour and stable perception. The vestibular sensory organs detect head motion, and this information is transmitted via the 8th nerve to the vestibular nuclei. In turn, vestibular nuclei neurons send descending projections to generate vital sensory-motor reflexes (i.e., vestibulo-ocular and vestibulo-spinal reflexes) and modulate autonomic responses (e.g., blood pressure). Information from vestibular nuclei neurons is also transmitted—via two main ascending thalamocortical pathways—to a vast number of cortical brain areas (reviewed in Cullen, 2019). First, the posterior vestibulothalamic pathway comprises projections from the posterior lateral nucleus (VPL) to cortical areas responsible for perception of self-motion. Second, the anterior vestibulothalamic pathway projects through nucleus prepositus (NPH) and supragenual nucleus (SGN) to the head direction (HD) network. Here, neurons that encode directional heading interact with hippocampal neurons that signal spatial location to provide the neural/computational basis of spatial navigation. Together, these two ascending thalamocortical pathways play an essential role in sensorimotor and cognitive functions by ensuring perceptual stability and accurate motor control in everyday life.

In their review, Ferrè and Haggard (2020) summarize current progress in understanding vestibular cortical networks and their role in sensorimotor and cognitive functions. The authors emphasize that prior work on vestibular processing has largely

focused on understanding how subcortical circuits generate vestibulo-motor reflexes (i.e., vestibulo-ocular and vestibulo-spinal reflexes) and modulate essential vestibulo-autonomic responses. In contrast, to date, far less is known regarding the relationship between vestibular input and the activation of vestibular cortical networks in the context of neurocognition. Given that vestibular driven responses have been reported in a vast number of cortical brain areas (reviewed in Cullen, 2019), Ferrè and Haggard further propose that this highly distributed network is of interest for neuropsychological study as a potential point of therapeutic intervention.

In this context, the application of galvanic vestibular stimulation (GVS) to selectively target the vestibular system has become an increasingly popular tool for the assessment and treatment of a wide range of clinical disorders in humans. GVS involves the application of current to external electrodes placed on an individual's mastoid processes. This stimulation activates vestibular primary afferents—in turn evoking ocular and postural responses via subcortical vestibulo-motor pathways. In addition, GVS produces a sensation of virtual self-motion. Interestingly, GVS has been reported to improve outcomes for a wide range of sensorimotor and cognitive disorders including Parkinson's disease, stroke, cerebellar ataxia, vestibulopathy, concussion, as well as patients with aberrant reward sensitivity (See Discussion, Kwan et al., 2019). There is also evidence that loss of vestibular function contributes to the cognitive decline observed in patients with Alzheimer Disease (reviewed in Cullen, 2019). Notably, the hippocampus, which plays a critical

role in spatial navigation and is activated by caloric vestibular stimulation, is one of the first regions to degenerate during the course of Alzheimer disease. Interestingly, it has been proposed recently that the disorientation and cognitive decline observed in some Alzheimer's disease patients can be improved by vestibular physical therapy (Klatt et al., 2019). Future studies will be required to understand the mechanisms underlying the benefits of these vestibular-based therapeutic interventions.

Ferrè and Haggard further emphasize that experiments have not yet explicitly tested how the same vestibular stimulation influences autonomic processing versus higher-level (sensorimotor and cognitive) functions. There is evidence for differences in vestibular reflex responses and self-motion perception (Pettorossi et al., 2013; Seemungal et al., 2011). Additionally, the authors (e.g., Ferrè et al., 2011; Ferre, Bottini et al., 2013; Ferrè, Longo et al., 2013) as well as other investigators (e.g., Huberle & Brugger, 2018) have employed CVS and GVS to understand how activating the vestibular system influences autonomic, sensorimotor and cognitive functions including time judgement. However, to date, there is no systematic standard for the stimulation and/or sampling to simultaneously compare across these three domains. To formalize how this might occur, the authors contrast two alternative theoretical models: one termed the "enabling" model in which vestibular signals indirectly affect the higher-level domains via their general tonic input to autonomic control, and another termed the "independent projections" model in which vestibular signals project directly to each area with a distinct function.

A limitation of both theoretical models, however, is that they are purely feedforward. As a result, the vestibular system is represented in the traditional sense where sensory information is processed sequentially from periphery to vestibular nuclei to cortex. These model structures contrast with recent findings that motor signals are integrated with sensory information at the earliest stages of vestibular processing (reviewed in Cullen, 2019). Specifically, vestibular afferents carry the same information from receptor cells within the semicircular canals and otoliths to the brain regardless of behaviour. In contrast, neurons at the next stage of processing in the vestibular nuclei encode head motion in a behaviourally dependent manner. Notably, neurons that project to

the posterior thalamocortical pathway, as well as vestibulo-spinal pathways preferentially respond to passive head motion, showing marked suppression to self-generated motion. Moreover, neurons that contribute to gaze stabilization via the vestibulo-ocular reflex, are unresponsive to head movements when gaze is redirected.

These single-unit / circuit-based findings are significant since they directly demonstrate how motor-related inputs influence vestibular information before it is transmitted to higher-level cortical networks involved in cognitive function (Cullen, 2019; Cullen & Taube, 2017). For example, self-generated vestibular input is cancelled at the level of the vestibular nuclei by a cerebellar-based mechanism (Brooks et al., 2015; Mackrous et al., 2019) that compares the expected consequences of self-generated movement (an "internal model") with the actual sensory feedback experienced during movement (reviewed in Brooks & Cullen, 2019). This result has important implications for understanding how the brain achieves the flexibility required to continuously calibrate relationships between sensory and motor signals required to ensure perceptual stability. In the context of higher-level vestibular processing, the comparison of expected and resultant sensory feedback, underlies a computation necessary for our subjective awareness of self-motion to know that we control both our actions and the resulting sensory consequences. Thus, given that cortical regions receive a signal that is already integrated with motor signals, the question arises: what are the implications of those early integrative processes for higher-level functions that are modulated by the vestibular system?

We now know that the signal transmitted through the posterior vestibulothalamic pathway selectively encodes unexpected, externally applied head motion (Dale & Cullen, 2019). This is because, as reviewed above, the sensory signals arising from active movements are cancelled at the level of vestibular nuclei neurons that project to the posterior lateral nucleus. As a result, it is most likely that the posterior vestibulothalamic pathway selectively conveys unexpected head motion to its cortical targets, most notably the parietoinsular vestibular cortex (PIVC) and ventral intraparietal cortex (VIP). Given that both areas play a role in self-motion perception, these findings suggest that vestibular coding across vestibular cortical networks is modulated in a behaviourally

dependent manner. Accordingly, formalizations of the architecture of higher-level vestibular processing comprised of distinct sensorimotor and cognitive domains oversimplify how vestibular processing actually occurs in ascending pathways.

Additionally, circuit-level analyses at the level of vestibulothalamic pathways have established that vestibular pathways actually do extract salient perceptual stimuli during self-motion, since unexpected head motion is preferentially encoded. Thus, the results of single unit studies provide evidence against a hypothetical “enabling” model in which the vestibular system provides a general “tonic input” to autonomic pathways that is transmitted to sensorimotor and cognitive functions. Instead, a subject’s current functional goal alters the earliest stages of vestibular processing (e.g., Did I just purposefully move? or did something just move me?). Consider for an example the percept of experiencing an earth quake—the signal of unexpected self-motion is very salient and discrete. Accordingly, it is essential to consider the behavioural context/functional goal when probing higher level vestibular processing.

Finally, as emphasized by Ferrè and Haggard, GVS and caloric stimulation have become increasingly popular methods for investigating the effect of the vestibular system on sensorimotor and cognitive functions in human subjects. Combined with non-invasive methods such as EEG and fMRI, both approaches have been widely used, especially in healthy human subjects. However, these methods have limitations that must be considered in the interpretation of studies aimed at understanding causal relationships between vestibular stimulation and high-level functions. First, these artificial stimuli do not activate the vestibular afferents in the same way as natural head motion. For example, because all canal and otolith afferents are equally responsive to GVS, the activation pattern has no physiological motion equivalent (Kwan et al., 2019). Further, afferent response tuning significantly differs for GVS versus natural motion stimulation (Kwan et al., 2019). Second, the application of GVS at the mastoid level activates cortical areas not only associated with the vestibular system, but also with the auditory and somatosensory systems (e.g., Bucher et al., 1998). Likewise, while caloric stimulation more effectively targets the vestibular system (specifically, semicircular canal), its activation is characterized by slow dynamics and it is difficult to standardize

stimulation across subjects. Lastly and importantly, the eye movements and postural responses evoked by GVS and caloric stimulation will in turn activate cortical and subcortical regions involved in the control of these movements and/or their suppression, further complicating the interpretation of imaging results.

In summary, Ferrè and Haggard make the important points that (i) how vestibular stimulation simultaneously influences autonomic processing versus higher-level sensorimotor and cognitive function is not known and (ii) targeting the vestibular system has potential as a therapeutic intervention in neuropsychological disorders. Here we further emphasize that the vestibular system does not operate in a feed-forward manner. Instead it integrates motor information with vestibular sensory input at the earliest stages of processing. Accordingly, when probing higher level vestibular processing, it is vital to consider the behavioural context/functional goal. Further, limitations inherent to the current standard approaches in the field for activating the vestibular system (i.e., GVS and caloric stimulation) motivate the importance of future studies in patients with peripheral vestibular loss.

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