NEURAL REGENERATION RESEARCH
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Review

Multisensory mechanisms of gait and balance in Parkinson's disease: an integrative review

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https://doi.org/10.4103/NRR.NRR-D-23-01484

Date of submission: September 2, 2023

Date of decision: December 13, 2023

Date of acceptance: January 18, 2024

Date of web publication: March 1, 2024

From the Contents

Abstract

Understanding the neural underpinning of human gait and balance is one of the most pertinent challenges for 21st-century translational neuroscience due to the profound impact that falls and mobility disturbances have on our aging population. Posture and gait control does not happen automatically, as previously believed, but rather requires continuous involvement of central nervous mechanisms. To effectively exert control over the body, the brain must integrate multiple streams of sensory information, including visual, vestibular, and somatosensory signals. The mechanisms which underpin the integration of these multisensory signals are the principal topic of the present work. Existing multisensory integration theories focus on how failure of cognitive processes thought to be involved in multisensory integration leads to falls in older adults. Insufficient emphasis, however, has been placed on specific contributions of individual sensory modalities to multisensory integration processes and cross-modal interactions that occur between the sensory modalities in relation to gait and balance. In the present work, we review the contributions of somatosensory, visual, and vestibular modalities, along with their multisensory intersections to gait and balance in older adults and patients with Parkinson's disease. We also review evidence of vestibular contributions to multisensory temporal binding windows, previously shown to be highly pertinent to fall risk in older adults. Lastly, we relate multisensory vestibular mechanisms to potential neural substrates, both at the level of neurobiology (concerning positron emission tomography imaging) and at the level of electrophysiology (concerning electroencephalography). We hope that this integrative review, drawing influence across multiple subdisciplines of neuroscience, paves the way for novel research directions and therapeutic neuromodulatory approaches, to improve the lives of older adults and patients with neurodegenerative diseases.

Key Words: aging; balance; encephalography; functional magnetic resonance imaging; gait; multisensory integration; Parkinson's disease; positron emission tomography; somatosensory; vestibular; visual

Introduction

Human beings have a most peculiar posture when compared with other animals. While far from being the only bipedal species, adult humans are the only animals that locomote exclusively on two legs, with no aid from the tail or prehensile feet (Skoyles, 2006). Consequently, humans have the most inherently unstable posture, described as an "anti-gravity pole", with constant outflow from the supra-spinal central nervous system locomotor centers being a prerequisite for effective control of balance (Skoyles, 2006). The human central nervous system declines with age (Harada et al., 2013). Thus, considering the unique reliance of balance on neural processing, it is unsurprising that older individuals are highly susceptible to falls (Osoba et al., 2019). Falls are the leading cause of injury, hospitalization, and morbidity in older adults (Peel, 2011; Haagsma et al., 2020). Populations with neurodegenerative disorders, such as Parkinson's disease (PD), are at even greater risk, due to the combined influence of both age- and disease-specific neurobiological changes. Therefore, a comprehensive understanding of the human balance system is needed to devise interventions that would minimize the occurrence of falls in subjects afflicted by neurodegenerative conditions like PD.

Emerging ideas about the causes of falls in the older adults suggest that multisensory integration might be of high importance, with a recent systematic review effectively summarizing the three dominant theoretical angles present in the field (Zhang et al., 2020). "Inverse effectiveness" theories suggest that older adults depend more on multisensory integration for the maintenance of balance because of

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How to cite this article: *Roytman S, Paalanen R, Carli G, Marusic U, Kanel P, van Laar T, Bohnen NI (2025) Multisensory mechanisms of gait and balance in Parkinson's disease: an integrative review. Neural Regen Res 20(1):82-92.*

age-related deterioration in individual sensory modalities. "Attentional control deficit" theory attempts to explain the costliness of dual-task on gait and balance stability by suggesting that attentional resources that would otherwise be allocated to multisensory integration are diverted to the dual-task, leading to impairments in balance. Lastly, "larger time window of integration" theories suggest that multisensory integration depends on the binding of information within discrete temporal windows. With peripheral sensory deficits, such as those encountered in aging, these timeframes extend. This extension results in an amalgamation of incongruent multisensory information, ultimately disrupting the processing associated with maintaining balance. These theories need not be mutually exclusive, but none of them seem to emphasize the specific roles of individual sensory modalities.

The goal of the present review is to examine the evidence for the contribution of specific sensory modalities to gait and balance and examine how perturbations in these systems lead to gait and balance deficits in PD. We will constrain our discussion to the somatosensory, visual, and vestibular systems, since those are commonly conceived of as playing a primary role in balance processes (Peterka, 2018). Special attention will be given to the vestibular system, due to emerging evidence of its involvement in multisensory processes. We will discuss the intersections between the major sensory systems related to gait in balance in the context of established multisensory integration theories described above and give examples of how failure in integration leads to gait and balance deficits in patients with PD. Lastly, we present a body of evidence, implicating cholinergic system changes in the pathogenesis of multisensory integration deficits associated with gait and balance.

Search Strategy

Publication years of reviewed articles ranged from 1993 to 2023, with most reviewed articles published between 2019 and 2023. Initial article search was performed primarily on Google Scholar between May 2023 and August 2023, with some of the following search terms used: "Parkinson's Disease and Gait Impairment," "Vestibular Dysfunction in Parkinson's," "Visual-Vestibular Interaction in PD," "Sensory Integration and Falls in PD," "Cholinergic System Changes in PD," "Proprioception and Postural Control in PD," "Freezing of Gait Mechanisms in PD," "Multisensory Perception in PD," "Age-related Changes in Postural Control," "Neurological Correlates of Falls in Older Adults." Discovered articles were thereafter compiled in a public ResearchRabbit repository (link: https://www.researchrabbitapp.com/collection/public/PLOGRVKMZG). ResearchRabbit functionality was used to discover additional articles which either cited or were cited by articles in the original set, later or earlier works of authors from articles in the original set, or were suggested by ResearchRabbit as "similar works."

Somatosensory Processing

The somatosensory system integrates information from many sensory organs distributed throughout the body (**Figure 1**). Receptor cells in tendons, joints, and, most importantly, muscle spindles provide information about the position and change in position of body segments relative to one another — proprioception. Proprioception is commonly thought of as the most important sensory system for the maintenance of balance (Henry and Baudry, 2019). Somatosensory processing also subsumes vibrotactile sensations those induced by light touch, vibration, or pressure on the skin. A prime example of vibrotactile contributions to gait and balance is foot sole pressure, which relays information about the center of mass relative to the base of support (Li et al., 2019).

Greater age is associated with declines in proprioceptive sensory thresholds in the knee, ankle, and hip joints (Qu et al., 2022). One major contributor to declines in peripheral proprioception is neuropathy, which refers to both age or disease-related damage to peripheral nerves carrying proprioceptive signals to the brain (Li et al., 2019). Peripheral neuropathy can affect either type I or type II sensory afferents, with type I sensory afferents primarily communicating proprioceptive signals, and type II sensory afferents primarily communicating vibrotactile signals (Li et al., 2019). Peripheral neuropathy involving either of these afferents can lead to profound impairment in gait and balance, with type I afferent neuropathy being the most devastating (Li et al., 2019).

PD patients have a greater prevalence of both types of neuropathy (Zis et al., 2017). The severity of PD-related disability was shown to correlate with ankle proprioceptive sensitivity, suggesting that proprioceptive processing declines along with disease progression (Teasdale et al., 2017). A more comprehensive assessment of somatosensory processing demonstrated that PD patients are impaired in their ability to discriminate between different support surface slopes (a function primarily of ankle proprioception), and in their ability to judge step height and surface roughness (a function primarily of foot sole vibrotactile processing) (Gorst et al., 2019). Impairments in these sensory functions were also shown to correlate positively with balance impairments in PD patients (Gorst et al., 2019). These functions play an important role in discerning one's bodily orientation relative to the support surface, especially on rough and uneven terrain. Accordingly, during gait on uneven terrain, a task that engages these somatosensory processes, PD patients adopt a more cautious gait pattern with shorter steps than that observed in healthy controls (Xu et al., 2018). PD-related neuropathy would plausibly account for the presence of these impairments, as it would hinder the transmission of somatosensory signals from peripheral receptor organs to the brain. Indeed, peripheral neuropathy in PD patients has been found to be associated with decreased stride length, decreased walking speed, less mediolateral balance control, and greater risk of falls (Beaulieu et al., 2018; Corrà et al., 2023). It is clear that the great importance of somatosensory processing for gait and balance also makes its disruption a critical vulnerability.

Multiple approaches have been attempted to enhance gait and balance function by targeting the somatosensory system. Textured insoles, which potentiate vibrotactile foot sole signals, were shown to enhance dynamic balance in

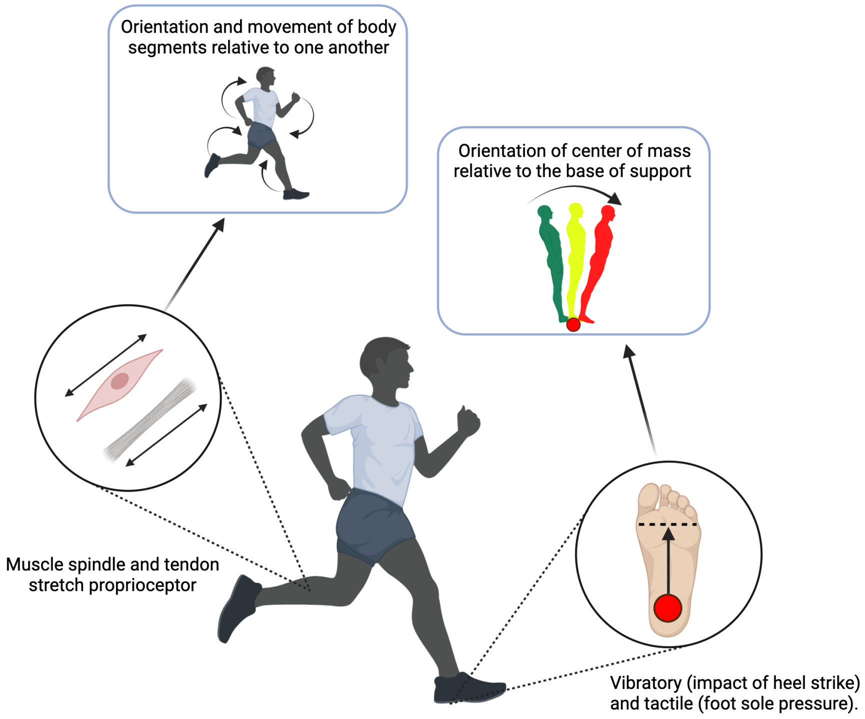

Figure 1 | Somatosensory contributions to gait and balance processing.
Muscle spindle and tendon stretch proprioceptors provide information about the body segments, which is critical for successful motor planning and execution. Vibrotactile receptors of the foot sole provide information about the point of contact between the base of support and the support surface, making it crucial for balance control, during standing and gait. Created with BioRender.com.

healthy young adults (Park et al., 2023). Closed-loop vibratory stimulation delivered to the wrist of PD patients as their ipsilateral foot struck the ground was shown to improve their dynamic gait stability (Fino and Mancini, 2020), suggesting that timing of cue delivery plays an important role. Alternative methods targeting somatosensory processing deliver vibratory stimulation to the waist through a belt-like device (Kingma et al., 2019). The vibratory stimulation is delivered in proportion to the magnitude and directionality of body tilt, as determined by a built-in inertial measurement unit (Kingma et al., 2019). This form of sensory augmentation effectively provides an artificial sensory signal carrying information about bodily verticality through the somatosensory system. In patients with severe bilateral vestibular sensory deficit, the use of a balance belt was shown to improve gait and balance function (Kingma et al., 2019), suggesting that artificial somatosensory signals carrying information about bodily verticality can partially compensate for loss of vestibular gravitational verticality sense.

Interestingly, somatosensory stimulation in itself, regardless of informational content, might enhance gait and balance processing. Delivery of high-frequency vibratory stimulation to the hand was shown to improve gait rhythmicity and symmetry in a small sample of idiopathic PD patients, both acutely and up to one week after stimulation (Syrkin-Nikolau et al., 2018). Authors suggest that observed improvements in gait and balance might be explained by the desynchronization of somatosensory neuronal subpopulations induced by the disruptive, rhythmic stimulus (Syrkin-Nikolau et al., 2018). Taken together, these findings provide reasonable support for further investigating therapies that amplify natural somatosensory signaling, use somatosensation to deliver artificial sensory signals and improve gait and balance through rhythmic sensory-neural entrainment. PD patients might differentially benefit from these interventions, given the profound deficit in gait and balance-related somatosensory processing observed among them.

Visual Processing

The visual system is the primary exteroceptive sense in humans, which means it allows us to orient not only relative to our immediate support surface, but relative to the environment at large (**Figure 2**). Eyes, the primary sensory organs of the visual system, communicate both high-contrast and low-contrast information about the world around us via foveal and peripheral vision, respectively. Identification of the next viable foothold is one of the key functions of vision during gait (Matthis et al., 2018). Walkers generally plan their gait trajectories multiple steps in advance, with a relatively stable look-ahead window of 1.5–2 seconds across individuals (Matthis et al., 2018). Under more complex terrain, walkers direct greater attention towards closer footholds and reduce their gait speed to maintain this temporal look-ahead window (Matthis et al., 2018), suggesting that certainty about upcoming footholds is necessary for effective gait. Orienting visual attention closer to the feet also yields a stabilizing effect on both standing and walking (Koren et al., 2021). Vision also provides a rich source of information about self-motion via optic flow. Stabilizing reflexes minimize visual motion at the point of fixation, and a pattern of visual outflow generated around this fixation point by the observer's movement encodes information about their velocity and heading relative to the fixation point (Matthis et al., 2020).

Freezing of gait is a phenomenon observed in Parkinsonian conditions but not observed in older adults, defined as a "brief episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (Nutt et al., 2011). Among PD patients, walking through doorways is a common

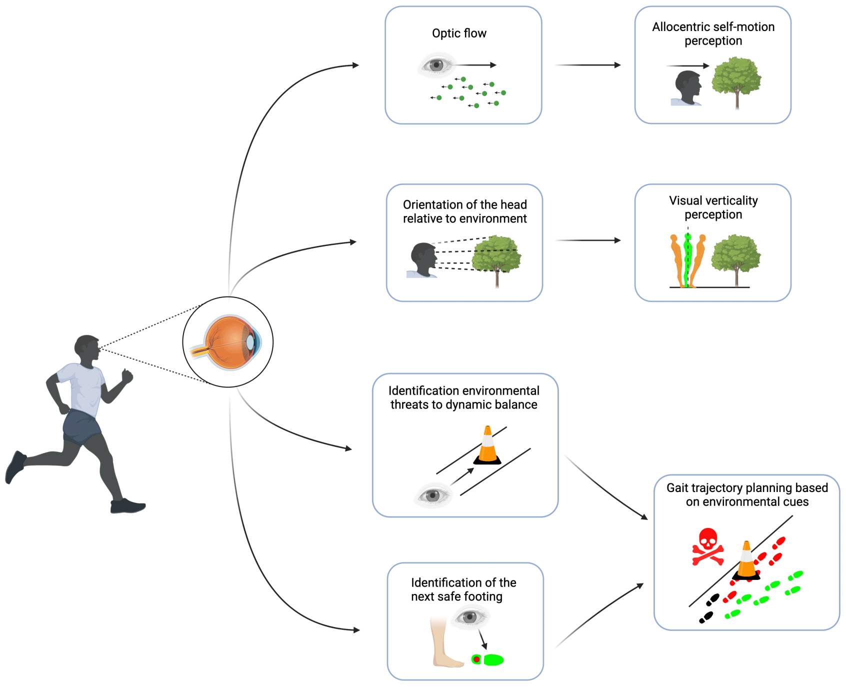

Figure 2 | Visual contributions to gait and balance processing.
Vision takes center stage as the exclusive informant of self-orientation and motion within an allocentric reference frame—an environment-centered perspective. This pivotal sensory modality is indispensable for identifying environmental threats and orchestrating goal-oriented locomotion. Leveraging the dynamic interplay of images relative to the fixation point, known as optic flow, vision unveils a continuous source of self-velocity information. Created with BioRender.com.

trigger for gait changes, including freezing of gait. PD freezers appear to walk through doorways with decreased step length and increased step variability (Almeida and Lebold, 2009). Walking through narrower (Cowie et al., 2010) or visually more salient (Ehgoetz Martens et al., 2013) doorways led to slower gait and a greater incidence of freezing in PD patients. Such a profound vulnerability to a very mundane and commonly encountered stimulus is puzzling. Indeed, it is also distressing for PD patients, because it makes the simple act of transitioning between rooms challenging and stressful (Parry et al., 2019). Most intriguing, this constellation of doorway-related gait impairments emerges early in the progression of PD, being present several years before the diagnosis (Ehgoetz Martens et al., 2022).

Healthy control subjects experience little trouble moving through doorways and exhibit a stereotyped pattern of visual fixations— earlier fixations directed towards the doorways, with later fixations looking through the doorway and towards their next footing on the other side (Higuchi et al., 2009). PD patients who do not freeze while walking through doorways exhibited more fixations towards their feet than healthy controls while walking through a doorway (Hardeman et al., 2020), consistent with greater processing demands of gait, as observed among controls on challenging to traverse surfaces (Matthis et al., 2018). During freezing trials, individuals experiencing freezing episodes tended to focus more on the doorway and less on the area beyond it (Hardeman et al., 2020). This attentional fixation on the doorway seems to divert their attention away from conscious processing where they will step next—a crucial process for these individuals to maintain their walking pattern. This interpretation gains support from findings that restricting the lower visual field for these individuals noticeably hampers their ability to navigate through doorways and results in increased fixation on the doorway (Beck et al., 2015). Notably, patients report coping with the difficulty of moving through doorways by mentally “blocking out” the doorway as they move through it, and consciously focusing their attention through the doorway (Parry et al., 2019).

These findings are suggestive of a primary balance impairment in PD patients, which emerges early in the disease progression, and is initially compensated for by increased visual processing demand. Failure of visual processing due to attentional misallocation towards the doorway stimulus prevents the acquisition of sufficient evidence about footholds 1.5–2 seconds into the future, which leads to a freezing event. In support of this notion, patients report feeling a sense of false imbalance during obstacle and doorway-induced freezing, which they feel prevents them from moving forward without considerable conscious effort (Parry et al., 2019). This sense of imbalance might arise from the experience of continued forward momentum, despite failure to decide on a future foothold, which consequently leads to a protective freezing response that terminates all forward momentum until more information is gathered about the proximal environment.

Visual-Somatosensory Integration

In terms of multisensory integration of older adults, impairments of visual-somatosensory integration have been shown to be a robust predictor of gait and balance deficits (Mahoney and Verghese, 2018; Mahoney et al., 2019). This phenomenon has been studied with a specific paradigm that quantifies visual–somatosensory integration. Subjects are exposed to either only visual, only vibrotactile, or simultaneous visual and vibrotactile cues to the upper limb. The participants are instructed to press on a pedal with their lower limbs as soon as they become aware of the specific sensory cue (Mahoney et al., 2019). The measure is calculated as a deviation of reaction times on multisensory trials from a so-called “race” model. The “race” model predicts the same reaction times on the multisensory trials as on the unisensory trials. Specifically, it postulates that during the simultaneous engagement of multiple sensory modalities (multisensory trial), the brain's response time is expected to align with the rapidity of the individual sensory modality that exhibits the fastest independent reaction time (the modality that wins the race first) (Mahoney and Verghese, 2019). A quicker reaction time in multisensory integration contradicts this model, indicating that having multiple matching sensory cues aids in detecting the stimulus. This aligns with what has been observed (Mahoney et al., 2019). Among older adults, it was shown that diminished visual–somatosensory integration was associated with a greater incidence of falls and poorer postural control (Mahoney et al., 2019). Weaker visual-somatosensory integration was also associated with slower gait speed and greater stride length variability (Mahoney and Verghese, 2018).

Visual-somatosensory integration, as described above, seems to bear some relation to the broader psychological phenomenon of intersensory facilitation, wherein joint presentation of stimuli across multiple modalities either improves recognition or lowers detection thresholds or reaction times (Colonius and Diederich, 2012). For example, tactile and visual intensity thresholds for motion detection are lowered when cues from both modalities are presented jointly, even more strongly when the direction of motion signaled by them is congruent (Gori et al., 2011). Multisensory facilitation between visual and somatosensory processing can plausibly happen during gait between foot sole sensation and visual optic flow, since forward shifts of the center of pressure would produce forward-oriented sensory inputs in both sensory modalities, thus providing a more reliable signal of forward self-motion.

The apparent importance of this multisensory integration phenomenon towards maintaining stable balance and preventing falls in the elderly can be explained concerning the inverse effectiveness theory of multisensory integration (Zhang et al., 2020). Visual-somatosensory facilitation would contribute to better balance by boosting somatosensory signal detection, thereby compensating for uni-modal somatosensory or vestibular deficits. Failure of this compensatory mechanism would then predictably lead to impaired gait and balance along with an increased risk of falls, as observed in those with poor visual-somatosensory integration.

Vestibular System Architecture

The vestibular system is the most inherently multisensory and often neglected sensory modality. The vestibular organ is localized in the inner ear and is composed of multiple specialized parts. The semicircular canals provide information about head rotation and play a role in the vestibulo-ocular reflex, which keeps the visual field stable during head turns (Khan and Chang, 2013). The otolith organ is an accelerometer that is sensitive to tilt, translation, transient movements of the head, and the continuous gravitational force experienced on earth (Khan and Chang, 2013). Age-related declines in vestibular function are well-documented and are largely attributable to the high metabolic demand of type 1 afferent neurons, which encode transient fluctuations in head inertia (Zalewski, 2015).

The vestibular system can be considered the most "multisensory" because it integrates with other sensory modalities at every level of the neural processing hierarchy. The ventral posterior lateral thalamus specializes in the processing of transient head accelerations encoded in vestibular afferents (Cullen and Chacron, 2023). However, many other nuclei of the thalamus that are commonly conceived of as unimodal and non-vestibular, such as lateral geniculate nuclei (thought to specialize in visual processing) and medial geniculate nucleus (thought to specialize in auditory processing), also receive vestibular afferents from brainstem nuclei (Wijesinghe et al., 2015).

Lastly, at the level of the cerebral cortex, the vestibular system is the only one that lacks a strictly unimodal representation. For example, almost all "vestibular" cortical innervation integrates inputs from other sensory modalities (Ventre-Dominey, 2014). In addition, two neocortical streams of self-motion processing have been recognized (Ventre-Dominey, 2014). The ventral (occipito-temporal) stream integrates visual and vestibular sensory information to estimate self-velocity (Ventre-Dominey, 2014). The dorsal (occipito-parietal) stream performs visual–vestibular integration for self-acceleration perception (Ventre-Dominey, 2014). Self-motion information processed along these two cortical streams is then mapped onto a somatosensory reference frame in regions around the temporo-parietal junction (Ventre-Dominey, 2014). In parallel to the neocortical self-motion processing streams, a more evolutionarily ancient, vestibular-dominant gravity-perception network involving cingulate cortices, insular cortices, and hippocampi also contributes to balance-related processes, such as verticality perception (Delle Monache et al., 2021).

Regions belonging to both streams are activated by galvanic and caloric vestibular stimulation (Lopez et al., 2012). This preferentially activates the right hemisphere due to its predominance in vestibular processing (Lopez et al., 2012). The lateralization of vestibular function can be understood from a structural perspective. A diffusion tractography study suggested that brainstem vestibular nuclei exhibit a bias for greater projection fiber crossing from the left to the right hemisphere, which leads to an asymmetry in vestibular innervation, with the right hemispheric vestibular thalamus receiving more vestibular projections (Dieterich et al., 2017). Likewise, parieto-insular vestibular cortices appear to demonstrate greater structural connectivity with the precuneus and subcortical structures on the right hemisphere (Wirth et al., 2018). The functional significance of this lateralization in function is less clear. Activation in the right parieto-occipital cortices during visuospatial orientation processing is inversely proportional to the distance between the observer and the stimulus - the greatest activity is observed when making judgments about stimuli closer to the body (Longo et al., 2015). Cathodal galvanic vestibular stimulation on the right (leading to greater right-hemispheric cortical activity), but not the left side, appears to influence the weighting of visual and somatosensory cues with regard to body ownership (Ferrè et al., 2015). In conclusion, lateralization of vestibular function to the right hemisphere might be related to greater involvement of vestibular cues in the processing of multisensory perception of one's own body and the environment near the body.

Vestibular Processing

The subjective visual vertical test is used to assess otolith function (**Figure 3**). A 2020 study found that poor performance on the subjective visual vertical test was associated with greater postural sway in healthy adults during standing balance (Kwon and Yeo, 2020). Alterations in verticality perception were observed in PD patients on the subjective visual vertical, similar in nature to those seen in older healthy adults, since the very early stage of pathology (Schindlbeck et al., 2018). Additional evidence for early vulnerability of the otolithic vestibular system in PD is the impaired magnitude of ocular vestibular myogenic potentials (Park and Kang, 2021). Extensive impairment of vestibular myogenic potentials is already observed in preclinical phases of PD, up to 10 years before the diagnosis, with ocular vestibular myogenic potentials being the most affected (De Natale et al., 2018). In early PD patients, impairments in ocular vestibular myogenic potentials are positively correlated with subjective dizziness (Park and Kang, 2021), which in turn correlates with poorer cognition and greater severity of postural instability and gait difficulty symptoms (Kwon et al., 2023). Taken together, these findings suggest that vestibular sensory impairment might emerge early in PD progression, affect coordination between visual and vestibular processing through its effect on ocular vestibular myogenic potentials, and be correlated with more severe disease progression.

Vestibular deficits in PD might underpin the impairments in higher-order self-motion perception and related postural control functions, which are also affected. Studies of translational self-motion perception demonstrate that PD patients are impaired in their ability to discriminate directions of translational self-motion using vestibular cues, in a disease severity-dependent manner (Beylergil et al., 2020, 2021). On the vestibular-system driven condition 4 of the modified Romberg test, wherein one has to maintain standing balance with eyes closed (absence of visual cues) on a compliant foam surface (reduced reliability of somatosensory cues), PD freezers are significantly more likely to fall than PD non-freezers (Bohnen et al., 2022a), suggesting a more pronounced vestibular balance control deficit among PD freezers relative to PD non-freezers. PD patients with postural instability, as defined by the inability to maintain balance during retropulsion test, were observed to have greater bodily sway with eyes closed (absence of visual cues) on a sway-referenced support surface (minimizing somatosensory contributions), as compared to PD patients without postural instability (Bohnen et al., 2022b), suggesting that vestibular balance control deficit might be a strong contributing factor to postural instability in PD. Taken together, these findings suggest that both basic vestibular self-motion perception and balance control deficits contribute to gait and balance impairment in PD.

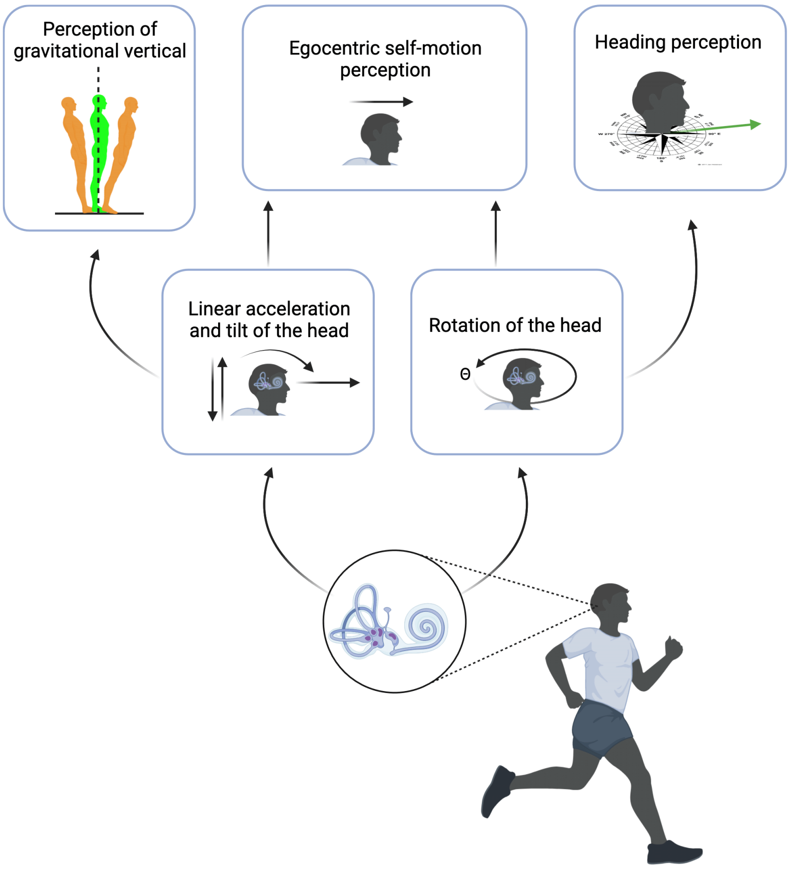

Figure 3 | **Vestibular contributions to gait and balance processing.**
The vestibular system provides the most direct source of information about inertia of the head. It allows for fast inference of instantaneous acceleration and changes in heading via otolith organ and semi-circular canal respectively. Its contributions are critical for efficient and flexible locomotion under gravitational forces experienced on earth. Created with BioRender.com.

Galvanic vestibular stimulation (GVS) is being actively pursued as a non-invasive treatment for postural instability and gait difficulty symptoms in PD. A recent meta-analysis of studies examining the efficacy of galvanic vestibular stimulation for improving postural control in PD patients concluded that there is a statistically significant pooled effect, but with considerable heterogeneity across studies due to methodological differences (Mahmud et al., 2022). Another recent review on the efficacy of GVS in treating axial motor symptoms in PD came to an analogous conclusion, that existing studies show some promise for GVS as a non-invasive treatment, but that the available evidence is insufficient to make definitive claims (Kataoka et al., 2022). The mechanism thought to underpin the effectiveness of GVS in improving gait and balance is poorly understood, with the predominant theory suggesting that the artificial noise introduced into the vestibular system resonates with sub-threshold natural vestibular stimuli, thereby enhancing vestibular perceptual sensitivity - a phenomenon referred to as stochastic resonance (Mahmud et al., 2022).

An alternative explanation might be that GVS improves balance by inducing a re-weighing of visual and somatosensory cues with regard to bodily ownership. Body ownership in PD patients appears to be heavily biased towards visual cues, with greater experience of ownership over an artificial limb placed in front of them, even in the absence of somatosensory stimulation relative to controls (Ding et al., 2017). During synchronous somatosensory stimulation of the real and artificial limb, there is no difference in the experience of body ownership over the artificial limb between PD patients and controls. However, PD patients experience greater ownership over the artificial limb than controls during asynchronous stroking, suggesting that visual cues are given precedence over somatosensory cues in case of inter-sensory conflict among PD patients (Ding et al., 2017). If beneficial effects of GVS improve gait and balance by normalizing the weighing of visual and somatosensory cues with regards to body ownership, then a major source of heterogeneity might be the placement of cathodal and anodal electrodes during stimulation, since right cathodal stimulation was found to be more effective than left cathodal stimulation with regards to influencing body ownership perception (Ferrè et al., 2015). Indeed, neither of the recent works systematically examining the effects of GVS on PD symptoms reported the placement of electrodes across studies (Kataoka et al., 2022; Mahmud et al., 2022). Taking better account of lateralized vestibular multisensory functions might potentially lead to more effective non-invasive treatments of dopamine-refractory postural instability and gait difficulty symptoms among PD patients.

Vestibular Multisensory Integration

Visual and vestibular systems provide strongly overlapping information about velocity and acceleration, which makes for a highly robust system for self-motion perception. Earlier blood flow positron emission tomography studies of visual-vestibular interaction used visual motion stimuli and electrical stimulation of the vestibular organ either jointly or in isolation to reveal that strong inputs to either modality tend to inhibit the other – a dynamic of reciprocal inhibition (Brandt et al., 1998, 2002; Deutschländer et al., 2002). A more recent functional magnetic resonance imaging study largely recapitulated these earlier findings (Della-Justina et al., 2015). A functional explanation of this dynamic points towards a need to maintain congruence between sensory streams, which is compromised during strong stimulation of either modality in isolation, or joint stimulation of both modalities in an incongruent manner (Brandt et al., 2002). However, vestibular stimulation is not exclusively inhibitory towards visual perception. When vestibular cues are signaling motion in a congruent direction to optic flow cues, the sensitivity for visual self-motion detection is enhanced (Edwards et al., 2010), which is more similar to the process of integration discussed for visual and somatosensory cues. *In-vivo* single-unit recordings of neuronal activity in non-human primates during heading perception tasks shed further light on the mechanisms of central visual-vestibular integration (Zheng et al., 2021). Neural processing of vestibular self-acceleration signals occurs earlier than the neural processing of visual self-velocity signals by 200–400 ms (Zheng et al., 2021). Earlier processing of vestibular signals might allow them to set the stage for the integration of signals from other sensory modalities.

Emergent evidence appears to suggest that the vestibular system might play a unique role in multisensory integration through its influence on temporal multisensory binding. “Temporal binding window” is a theoretical construct that refers to a window of time over which sensory cues from multiple modalities are integrated into a unified multisensory percept. The widening of these temporal binding windows is one of the three established theories for the impact of multisensory processing deficits on postural control in older adults (Zhang et al., 2020), but vestibular contributions to this process have scarcely been considered, despite the known vulnerability of the vestibular system to aging-related deteriorations (Zalewski, 2015). A recent study demonstrated that vestibular sensory thresholds correlate positively with the widths of the temporal binding windows in younger adults (Shayman et al., 2018). Subjects with damage to the peripheral vestibular system due to ototoxic antibiotic exposure had the highest vestibular sensory thresholds and the largest temporal binding windows (Shayman et al., 2018). Lastly, a recent study demonstrated that wider temporal binding windows in older as compared to younger adults are also correlated with higher vestibular sensory thresholds (Malone et al., 2023).

The critical time is a stabilogram diffusion analysis posturography measure that captures a construct closely related to the temporal binding window. Critical time refers to the average interval of time over which top-down postural corrections are implemented (Collins and De Luca, 1993), which would be expected to increase as a function of longer multisensory integration times. Older adults have longer critical time intervals (Collins et al., 1995), and these larger critical time intervals are predictive of a greater fall risk (Tuunainen et al., 2014). PD freezers in medication OFF state were also recently shown to exhibit a profound difficulty with balance on unstable support surfaces in association with longer critical time intervals (Roytman et al., 2023).

Thus, convergent ideas appear to point towards the longer time requirement of multisensory integration processes in older adults in relation to gait and balance difficulties. We speculate that longer temporal binding windows might be a consequence of conflict resolution processes, such as between visual and vestibular systems, which come to play a greater role in aging and disease due to unimodal sensory impairments.

Alpha Waves and Vestibular Multisensory Functions

The earliest evidence of oscillatory brain rhythms was published in 1929 by Hans Berger, which included the first mention of alpha oscillations in the literature (Quigley, 2022). Alpha oscillations are rhythmic fluctuations in electrical brain activity that occur at a frequency of 8–11 hertz (originally reported range, but frequency band definitions vary across studies) (Quigley, 2022). They can be detected by surface encephalography (EEG) or intracranial electrode recordings, and are most pronounced when a subject is at rest with their eyes closed. The profound, visually discernible expression of alpha oscillations on EEG recordings from the occipital cortex in subjects with closed eyes has been named the Berger effect (Quigley, 2022). Intracranial electrode recordings in epilepsy patients demonstrated that the colloquial characterization of neural oscillations as "brain waves" might not be too far from the truth (Halgren et al., 2019). Through analysis of phase lags between electrodes in a multielectrode array, it was demonstrated that alpha band neural oscillations are underpinned by spatio-temporal waves of traveling electrical activity with a specific topography (Halgren et al., 2019). Alpha waves tended to travel from multisensory to unimodal cortical regions, and from cortical regions to thalamic nuclei (Halgren et al., 2019), hinting at their potential role in top-down modulation of neural activity. Event-related synchronization, or an increase in alpha wave power, reflects an inhibitory process that reduces overall neural excitability, whereas event-related desynchronization, or a decrease in alpha wave power, reflects the lifting of inhibition (Klimesch, 2012).

A growing body of evidence points towards a link between the vestibular system and alpha waves (**Figure 4**). Induction of visual illusory self-motion (vection) during standing (but not while laying down) was associated with event-related synchronization of occipito-parietal alpha waves (Harquel et al., 2020), consistent with the visual inhibition of vestibular-dominant self-acceleration processing in the dorsal self-motion pathway (Ventre-Dominey, 2014). Effective balance among healthy controls under somatosensory perturbation (via musculo-skeletal vibration) and in the absence of visual cues (closed eyes) was dependent on the flexibility of an alpha wave network centered on the right temporo-parietal junction and extending to visual-vestibular multisensory regions (Barollo et al., 2022). This finding suggests that effective vestibular-driven balance control depends on inhibitory top-down interactions between multisensory regions related to self-motion perception. A "living" meta-analysis of 27 studies demonstrates a robust link between features of alpha oscillations and temporal binding windows (Samaha and Romei, 2023), which raises a possibility that vestibular influence on temporal binding windows is mediated by alpha wave dynamics, but this hypothetical relationship has yet to be empirically confirmed. Given the well-recognized role of alpha oscillations in mediating inhibitory functions that underpin selective attention (Klimesch, 2012), the influence of vestibular processing on multisensory integration via alpha oscillations might instead be more closely related to multisensory attentional allocation, the deficit of which is hypothesized by the third predominant theory of multisensory gait and balance deficits (Zhang et al., 2020). Based on the findings presented above, it seems plausible that alpha waves might serve as a substrate of vestibular-multisensory interactions in the brain.

Cholinergic Underpinnings of Alpha Waves and Multisensory Integration

Though a definitive neural substrate for multisensory alpha waves has yet to be revealed, the available evidence points towards the closest association between the cholinergic system and a feature of alpha waves called "alpha reactivity." Alpha reactivity refers to a decrease in alpha power over the visual cortex and other posterior regions that occur when transitioning from closed to open eyes. A multimodal

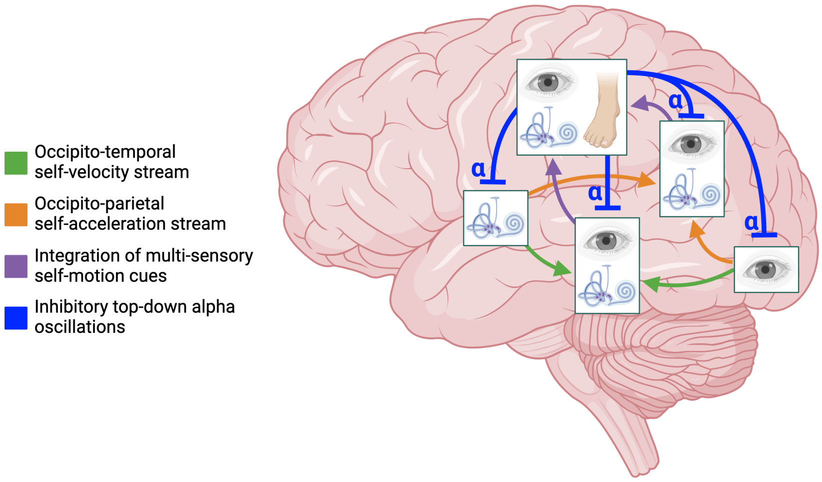

Figure 4 | Central mechanisms of multisensory self-motion perception. Information from early sensory regions is aggregated in first-order multisensory cortices, where it contributes to the estimation of self-velocity, self-acceleration, and potentially other relevant self-motion parameters. These self-motion estimates are integrated into second-order multisensory regions, where they are mapped to the internal representation of the self within an environment. Second-order multisensory representations of self-motion bias processing in first-order multisensory and early sensory regions based on what is currently perceived and what is most conducive to task performance in any given context. Created with BioRender.com.

magnetic resonance imaging and EEG study among younger and older control patients demonstrated that the magnitude of alpha reactivity is positively correlated with the magnitude of increase in functional connectivity between the cholinergic basal forebrain (principal source of cortical acetylcholine) and occipital cortices when going from closed-eyes to open-eyes state (Wan et al., 2019). Older adults were found to have lower alpha reactivity than younger adults in proportion to the severity of white matter lesions along fiber tracts that carry cholinergic projections from the basal forebrain to posterior cortical regions (Wan et al., 2019). Vestibular system function also factors into this relationship, since individuals with impaired vestibular function and visual dependence for verticality perception also exhibit impaired alpha reactivity (Ibitoye et al., 2023). Lesions to the right posterior cortical hemisphere led to a more profound disruption of alpha reactivity than lesions to the left posterior cortical hemisphere (Gallina et al., 2022), which suggests that the relationship between vestibular function and alpha reactivity might be mediated by vestibular thalamo-cortical projections.

Alpha reactivity was also shown to be diminished in Alzheimer's disease and to a greater extent in Lewy body dementia patients in a manner proportional to decreases in cholinergic basal forebrain volumes (Schumacher et al., 2020). A similar effect was observed in a sample of PD patients (Rea et al., 2021). The volume of the cholinergic basal forebrain was recently shown to robustly associate with the integrity of its widespread cholinergic projections to the cerebral cortex (Ray et al., 2023). Indeed, PD patients demonstrate widespread cortical cholinergic degeneration in association with cognitive, gait, and balance deficits (Bohnen et al., 2022c). Lastly, recent findings demonstrate that suppression of the right hemispheric cortical cholinergic system in PD patients by high anti-cholinergic burden profoundly affects their ability to effectively integrate visual and vestibular cues for balance on an unstable support surface in medication OFF state (Roytman et al., 2023). Taken together, these findings suggest that cholinergic signaling might play an important role in releasing the inhibition of neural function exerted by alpha oscillations, a function that might be modulated by vestibular sensory processing. Disruption of this function in patients with cholinergic system deficits might account for the wide range of multisensory integration-related impairments of gait and balance observed among them.

Conclusion

Our review of the literature focused less on depth and more on the breadth of examined topics, intending to provide a fertile common ground for multi-disciplinary collaborations in pursuit of novel research endeavors and therapeutic approaches. Despite the many decades of outstanding scientific work, multisensory mechanisms of gait and balance remain a riddle unsolved. We hope that the present work inspires new lines of investigation that will bring us closer to the answer, one step at a time.

Author contributions: *Conceptualization: SR, NIB; methodology, writing (original draft): SR; writing (review & editing): SR, RP, GC, NIB; supervision: UM, PK, TL, NIB. All authors approved the final version of the manuscript.*

Conflicts of interest: *The authors declare no conflicts of interest.*

Data availability statement: *Not applicable.*

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C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y