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Review

Unraveling the threads of stability: A review of the neurophysiology of postural control in Parkinson's disease

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ABSTRACT

Postural instability is a detrimental and often treatment-refractory symptom of Parkinson's disease. While many existing studies quantify the biomechanical deficits among various postural domains (static, anticipatory, and reactive) in this population, less is known regarding the neural network dysfunctions underlying these phenomena. This review will summarize current studies on the cortical and subcortical neural activities during postural responses in healthy subjects and those with Parkinson's disease. We will also review the effects of current therapies, including neuromodulation and feedback-based wearable devices, on postural instability symptoms. With recent advances in implantable devices that allow chronic, ambulatory neural data collection from patients with Parkinson's disease, combined with sensors that can quantify biomechanical measurements of postural responses, future work using these devices will enable better understanding of the neural mechanisms of postural control. Bridging this knowledge gap will be the critical first step towards developing novel neuromodulatory interventions to enhance the treatment of postural instability in Parkinson's disease.

Introduction

Postural instability (PI) is a common and disabling motor symptom of Parkinson's disease (PD), associated with more severe disease progression and mortality [1–4]. This "cardinal symptom" has been shown to occur in 20% of people at PD onset, increasing to 90% after 15 years of disease [3,5]. While many definitions exist, it is generally thought that PI results from alterations in one's static posture and/or postural reflexes, creating abnormal difficulty when an individual's balance is challenged through static and dynamic environmental or task constraints [6–10]. These deficits are thought to be caused by the underlying pathophysiology of PD, which includes dopaminergic and cholinergic neuronal dysfunction, leading to deficits in cognitive function and sensory integration, grey matter atrophy and white matter abnormalities, and decreased connectivity at motor cortical and brainstem motor areas [9,11–13]. These deficits often are detrimental to one's quality of life, among other negative sequelae, largely due to increased fall risk and fear of falling [7,9].

People with PI often have difficulty with task transitions involving rapid changes in sensory and/or motor demands [10]. PI can also lead to and co-occur with freezing of gait (FoG) [10,14], which is a sudden, brief, and involuntary arrest or reduction of walking [15]. Examples of "triggering" events leading to PI (and/or FoG) can include mobilizing within confined spaces, turning, starting to walk ("gait initiation") and increasing cognitive load while performing tasks (such as talking, walking under time-constraints, or holding objects) [15,16]. Clinical tests utilizing these tasks are commonly used by neurologists to evaluate for the presence and severity of PI in people with PD. Assessments of postural control in PD include the Mini Balance Evaluation Systems Test (Mini-BEST) and Part III of the Movement Disorder Society's (MDS) Unified Parkinson's Disease Rating Scale (UPDRS III) [6,9,17]. Scores on the MDS-UPDRS are often used to classify PD symptoms into motor subtypes, including one called "Postural Instability (and) Gait Difficulty-predominant" disease (PIGD) [1,5,18]. While the purpose of clustering motor subtypes was to streamline treatment approaches, identifying reliable classifications and effective treatments tailored towards PIGD symptoms remain elusive [19].

PI remains difficult to treat, likely due to both its paroxysmal nature and the complex and interrelated nature of multiple motor and sensory circuits underlying the various domains of postural control [10,20]. Unfortunately, levodopa often has a negligible or even worsening effect on PI symptoms [9,21–25]. While various brain regions have been

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implicated in the pathophysiology of PD and likely contribute to symptoms of PI, the specific mechanisms underlying abnormal postural control remain poorly understood.

Combining insights from studies utilizing novel methods in human neurophysiology and biomechanical data collection, we hope to shed light on the pathophysiology of PI in PD and identify knowledge gaps necessary to both improve our understanding of and treat this disabling symptom. This review will discuss current neural and biomechanical perspectives of postural control in people with PD exhibiting PI, as well as the effects of neuromodulation and common feedback-based interventions on these symptoms. We will conclude by proposing future therapeutic targets for treating PI using individualized, circuit-based approaches. Greater understanding of the neural circuitry underlying postural control will lead to improved understanding of how to effectively treat these symptoms in people with PD.

Biomechanical Basis of Postural Instability in Parkinson's Disease

Static postural responses

Previous biomechanical studies in people with PD have provided robust data quantifying various postural control deficits during motor tasks and transitions, as well as *static* (quiet) standing postural responses. Using force plates and posturography to analyze spontaneous postural sway during quiet standing, people with PD have been found to display variations in sway aspects including deviations in antero-posterior and medio-lateral sway areas compared to healthy subjects [24–28]. Such postural sway metrics have been associated with disease progression and UDPRS-MDS scores in PD patients [24–26]. Additional alterations in *static* postural alignment often seen in PD, such as truncal rigidity, stooped posture, and increased coactivation in torso and leg musculature, can subsequently contribute to dysfunctional postural responses [25,26,29–32]. It is theorized the adaptation of a stooped posture places one's center of pressure more anteriorly to increase stability and simplifies the selection of *reactive* postural responses [26].

Anticipatory postural responses

Another commonly studied aspect of PI in this population relates to the *anticipatory* balance domain, specifically among anticipatory postural adjustments (APAs). APAs are a set of stereotypical, highly regulated muscle activations which shift one's center of pressure towards the stepping (swing) leg while stabilizing the body's center of mass over the stance leg in preparation for stepping or change of direction [32–34]. Force plate and inertial measurement unit assessments of APAs during gait initiation often suggest that people with PD have variable, hypometric APAs with dysfunctional timing [32,34–36]. Similarly, turns in people with PD are generally slower, less stable, and more variable, all of which are thought to compensate for postural control difficulties [37–39]. Because anticipatory alterations to one's center of mass and orientation are also required for successful turning [40], these findings suggest that PI during turning in this population may be due to APA dysfunction.

Reactive postural responses

Another feature of PI in PD is dysfunctional *reactive* balance responses. Many previous studies have characterized reactive balance deficits in this population through the delivery of multi-directional perturbations requiring a balance strategy or protective stepping response to avoid a fall. These studies have shown that people with PD often generate slower, inappropriately scaled responses and take more steps when executing a *reactive* postural response, resulting in increased fall rates compared to healthy controls [21,23,32,41,42]; It is thought these responses are driven by abnormal antagonist leg muscle activity [43], APA presence [42], and difficulty switching between balance strategies (ankle vs. hip vs. stepping) depending on the surface and disturbance [8].

Neural Circuits Involved With Postural Control

Inferring from mostly animal studies, gross human postural control is thought to be governed by dopaminergic and non-dopaminergic circuits spanning cortical and subcortical areas with various sensory inputs. These inputs include the visual, vestibular, and somatosensory processing systems [6,44–48]. These inputs are chiefly integrated at the cortex and cerebellum, with postural responses (particularly APAs) initiated via the premotor cortex (PMC) and supplementary motor areas (SMA) [44,45]. Following refinement at the basal ganglia and cerebellum, the outgoing response is sent to the primary motor cortex (M1) and to locomotive centers at the brainstem, including the pedunculopontine nucleus (PPN), and downstream pathways such as the corticospinal tract [44,45]. The basal ganglia, particularly relevant to PD, is also thought to serve important roles in postural control besides motor refinement and execution, including somatosensory integration, automatic postural responses, and muscle tone maintenance [49].

While this general schema is thought to be shared among other fundamental human motor tasks such as gait, additional circuits are implicated in posture control. One critical element is the maintenance of appropriate muscle tension and length ("muscle tone") throughout the body, largely driven by spinal reflexes using inputs from receptors in the soft tissues and joints [47,50]. These spinal reflexes also receive input from supraspinal regions including the motor cortical areas, cerebellum, reticular formation, and vestibular nuclei, which contribute to the descending reticulospinal and vestibulospinal tracts in the spinal cord [45,50]. Prevailing theories suggest that the postural control domains discussed in this review result from dynamic combinations of reflexes, multisensory integration and reweighting, and changes in one's internal schema of body posture, which are driven by different underlying neuronal populations [20,44,45,47]. It is also hypothesized that various postural responses are mediated by different neural circuits, which are automatically selected by factors such as the magnitude and predictability of a perturbation, latency allowed, and/or one's own capabilities [20,46].

These underlying neuronal circuits are also thought to be diverse and interrelated, which further complicates the study and treatment of postural control impairments. In PD, the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) alters their efferent striatal neuronal activities and their subsequent downstream targets in the basal ganglia thalamocortical circuit, which results in the characteristic motor symptoms [44,45,49]. Additionally, the basal ganglia have additional downstream GABAergic connections with the thalamus and brainstem, including the PPN [44,45]. The PPN, in turn, sends cholinergic projections onto the SNpc, with various cholinergic and non-cholinergic synapses at the cortex, thalamus, basal ganglia, cerebellum, and spinal cord locomotive network [44,45,49]. Thus, it is likely that dysfunction among these overlapping circuits contributes to the various postural control deficits seen in PD [44,45].

Role of Cortex in Postural Control

Cortical involvement of postural control has been predominantly studied using non-invasive electroencephalogram (EEG) recordings and motor tasks eliciting postural responses. Cortical power across multiple frequency bands: delta (1–3 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–50 Hz), have all displayed modulation during bipedal postural responses. We will focus on more recent works that continue to validate and expand on previous theories regarding the cortex's role in postural control.

Static and anticipatory postural responses

EEG has been used to characterize cortical activity associated with *static* standing as well as self-initiated postural sway movements to probe one's limits of stability. During a *static* standing balance task, older adults were found to have greater low frequency power (e.g. delta) in the frontal

cortical regions, whereas younger adults had higher power in frontal and occipital areas for beta and gamma frequencies; these differences were thought to be caused by additional attention-related reserves utilized by the elderly subjects to maintain their balance [51]. Similar results were also found during a progressively more challenging *static* balancing task, with frontal and central theta power increasing alongside task difficulty in healthy adolescents [52].

EEG recordings from a postural sway task in young, healthy subjects were also found to display large, movement-related cortical potentials (MRCPs) over the SMA area and sensorimotor cortex during initiation of *anticipatory* postural responses, with gamma bursts at fronto-central areas coinciding with onset of postural instability [53]. Additional data from *anticipatory* postural responses also found decreases in alpha and beta power at central cortical locations immediately prior to the movement in healthy adults, with significant interactions between power modulation and postural sway direction which were especially pronounced for the medio-lateral direction [54]. Therefore, the cortex appears to display regional frequency-specific changes in APA.

Reactive postural responses

EEG studies have also identified the presence of a perturbation-evoked potential, labeled "N1," over the fronto-centro-parietal regions during *reactive* postural responses in healthy subjects [55–60]. This evoked potential results in increased power and synchronization among delta, theta, alpha, and beta frequencies [55,59,60], is affected by perturbation parameters [56,60], and may represent the selection or integration of postural reactions [56,59].

More specifically, different brain regions seem to display task-related frequency changes during *reactive* postural control challenges. At the fronto-central cortical regions, increased delta and theta power have been associated with the maintenance of standing balance during progressively more difficult tasks and reactive stepping responses following perturbation, suggesting their roles in situations requiring higher attention and cognitive demands when conditions become unstable [57,61–66].

In these same regions, increased alpha power was found to be associated with perturbation onset [57,62] and altered by one's attentional focus under conflicting visual input [67], while trends in alpha modulation appear sub-band dependent and largely decrease during progressively more difficult *reactive* balance tests [64,66,68]. These findings support hypotheses that alpha power reflects perhaps complementary, higher-level sensory processing and/or inhibitory mechanisms to control the degrees of freedom available for *reactive* balance responses [64,66].

The central areas (motor and somatosensory cortices) also showed evidence of significant beta modulation with *reactive* balance tasks, as greater beta suppression was displayed during stepping responses in the contralateral hemisphere to the support leg [57]. Additionally, central beta band event-related desynchronizations, followed immediately by event-related beta synchronizations, have been associated with preparation and execution, respectively, of the balance responses for postural recovery [58]. Interestingly, another study found increased beta power at this location may be associated with more challenging perturbations and lower balance ability, suggesting a greater utilization of one's motor skills or sensorimotor engagement [69].

EEG data examining these responses at parietal and occipital locations have suggested modulation across theta and alpha frequency bands to be largely similar to that at the central cortical areas [57,63,68]. However, these regions especially exhibited gamma power modulation, which was associated with transition to unstable postures and dual-task balancing; these differences are thought to mediate visual-related processing and sustained attention during cognitive and motor tasks [63,65,68].

Postural control and dysfunction in PD

While these studies have mostly examined EEG activity in healthy subjects, some works have also characterized cortical neural activity in people with PD during standing balance tasks designed to challenge various aspects of postural control. Cortical data recorded during *static* balancing on foam, theorized to decrease one's ability to use proprioceptive and vestibular input for maintaining balance [70], showed much lower theta power among mid-frontal and mid-cerebellar locations in people with PD exhibiting PI (PD-PI+), compared to PD patients without PI (PD-PI-) and healthy controls [71]. Additionally, people with PD were found to have increased postural sway and widespread cortical power differences among alpha and beta bands during a *static*, semi-tandem balance task (decreasing the base of support to increase task difficulty) while "ON" levodopa medication compared to "OFF" periods [72].

In another study comparing EEG changes during *anticipatory* postural responses between healthy young adults and people with PD, movement-related potentials (MRPs) at the central cortical area differed between the two groups for early slope and peak amplitude metrics; furthermore, early slope of the MRP was found to be inversely related to stride length in the PD-PI- sub-group [73]. Thus, it was suggested stride length during gait initiation may be coded early in MRPs, with this phase disrupted in PD-PI+ individuals [73].

Another study characterizing EEG activity during gait over planned and unplanned obstacles (requiring both *anticipatory* and *reactive* postural responses, respectively), found that people with PD "ON" medication exhibited altered theta and beta cortical modulation compared to age-matched control subjects during multiple phases of the task [74]. During the pre-stepping phase, theta power was observed to be attenuated in people with PD for steps over unplanned obstacles (*"reactive"* responses); this contrasted with beta power, which remained higher-than-expected in people with PD under both types of obstacles [74]. Within the post-stepping phase, the authors also observed a lower-than-expected theta and beta "rebound" in people with PD during both obstacle types [74]. These findings suggest that people with PD may experience dysfunctional cortical modulation, which likely mediates impairments in cognitive-motor control and resulting *anticipatory* and *reactive* postural response deficits [74].

Also examining *reactive* postural responses, a study found that people with PD were shown to display similar architecture of the elicited N1 potential while "OFF" medication during unexpected perturbations compared to healthy older adults, however its correlations with various balance metrics and individuals' abilities differed [75]. In PD, earlier and narrower N1 peak widths correlated with more severe PIGD scores and lower balance abilities and confidence [75]. While these findings suggest a potential link between cortical activity and falls in PD, more investigation is warranted to characterize the presumably overlapping domains of cognitive function and balance ability, as well as the effects of dopamine medication and patients' perceptions of falling and balance ability during such tasks [75].

In summary, PD patients with PI show altered modulation among the theta, alpha, and beta frequency ranges compared to healthy subjects during *static*, *anticipatory*, and *reactive* postural tasks. This highlights the importance of widespread cortical network activity in regulating postural control.

Neuroimaging Examination of Postural Control

To study neural regions not accessible by EEG, functional neuroimaging has revealed global brain areas' involvement in postural control. A recent systematic review and meta-analysis of various neuroimaging modalities including whole-brain positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in human postural control emphasized the cerebellum's role in *static* balance and postural sway tasks (often using motor imagery), along with activation in subcortical regions including the thalamus, brainstem, midbrain, and basal ganglia [76]. During *reactive* postural control tasks (using simulations), the thalamus, cerebellum, SMA, temporal, and occipital lobes were consistently activated [76]. These results support the working model of postural control consisting of cortical and subcortical circuits involving the sensorimotor cortex, cerebellum, and basal ganglia [46].

A recent resting state functional connectivity study using fMRI in people with PD and older adults also validated the existence of unique circuits underlying the various domains of postural control. Deficits in single-task *anticipatory* postural control were associated with increased activation of prefrontal and parietal cortical regions in people with PD when compared to older adults, resembling more of a dual-tasking state; this work also found functional connectivity between frontoparietal and ventral-attention circuits to predict APAs in people with PD [77]. Similarly, connectivity between subcortical-cerebellar and visual and auditory networks predicted *reactive* postural responses in people with PD, while additional circuits correlated with clinical PIGD scores [77]. These results were summarized by the authors, suggesting that central motor planning areas are implicated in APAs, with cerebellar and sensory processing areas involved in *reactive* responses, and attention-related networks prominent in *static* postural maintenance [77].

In people with PD classified into the PIGD subtype (PD-PIGD), fMRI during active ankle movements combined with backwards counting displayed increased cognition-related cerebellar and reduced motor-related cerebellar and putamen activation compared to healthy controls, suggesting a possible compensatory mechanism for PD pathophysiology [78]. PD-PIGD individuals also exhibited increased frontal and SMA activity during this task, with reduced activity in the caudate and sensorimotor integration areas compared to healthy controls [79].

These populations have also demonstrated differences in glucose metabolism using PET imaging, with PD-PIGD individuals exhibiting hypometabolism at fronto-parietal and striatal areas which correlated with PIGD symptom severity [80]. PET imaging differences at the left caudate nucleus and nucleus accumbens were also shown to correlate with various UPDRS PIGD items, using normalized radiolabeled tracer values identifying dysfunctional nigrostriatal dopamine projections in people with PD [81]. Another PET imaging study in people with PD also found uptake ratios of vesicular monoamine transporter (facilitating dopamine utilization) to be significantly lower in PD-PI+ individuals at the caudate nucleus and putamen when compared to those without PIGD symptoms [82]. Other PET imaging studies have characterized various pre- and post-deep brain stimulation (DBS) physiological changes in people with PD. Particularly relevant, one study found post-subthalamic nucleus DBS (STN-DBS) increases in metabolism at the dorsal midbrain and pons, including PPN, and right motor cerebellum in people who developed PIGD symptoms following DBS surgery [83]. Taken altogether, these PET imaging findings continue to validate the critical roles of the basal ganglia, PPN, cerebellum, thalamus, and cortex in postural control.

While neuroimaging is helpful in identifying multiple brain regions likely grossly implicated in postural control mechanisms, the tasks are often simplistic and don't offer multifaceted balance challenges, suggesting uncertain transferability to upright, bipedal situations across varying postural control domains [84]. Additionally, common functional imaging approaches may have limited spatial-temporal resolution, suggesting additional methodology may need to be used for deciphering these complex circuits [85].

Invasive Neurophysiological Studies Examining Postural Control

Invasive neurophysiological studies in PD have largely relied on local field potentials (LFPs) recorded from implanted DBS electrodes in patient who underwent surgery for treatment of their Parkinson's symptoms. While these studies have greatly expanded our understanding of human basal ganglia neurophysiology in different medication and movement states in PD, very little is known about oscillatory changes that occur in the basal ganglia during postural control. However, since PI is a prominent feature in PD patients with FoG, we will focus on reviewing existing studies that have characterized basal ganglia LFP activity associated with FoG in this population.

STN oscillations in freezing of gait

The STN is a primary region in which neurophysiological data during FoG episodes have been examined. Relating to lower frequencies, theta and low beta modulation may serve as spectral correlates with FoG, as increased STN LFP theta and low beta power were observed during periods of "vulnerable" gait" [86]. Theta was also implicated in comparisons between "effective" gait and FoG periods, with STN LFPs and cortical EEG recordings exhibiting low frequency (4–13 Hz) synchronization during "effective" walking and FoG associated with cortical-subthalamic decoupling in the hemisphere with less striatal dopaminergic innervation [87]. These findings have led to the idea that theta cortical-subthalamic decoupling may be associated with a transition to FoG in this population [88].

For alpha and beta frequencies, STN LFPs recorded during forward gait, stepping in place, and a turns and barriers course displayed changes in power and entropy between people with PD who experienced FoG (PD-FoG+) and those who did not (PD-FoG-), as well as task-specific modulation in these sub-populations [89]. The increased entropy in PD-FoG+ was thought to perhaps serve as a compensatory mechanism for improving FoG in this population [89]. Severe akinesia in FoG was also shown by another study to be correlated with increased STN low beta power when comparing PD-FoG+ to PD-FoG-individuals during treadmill walking [90]; more specifically, an 18 Hz frequency band has gained attention for its potential link to FoG in this population [86]. Another neurophysiological signature of FoG is sustained beta burst duration, as this feature differentiated between PD-FoG+ and PD-FoG-individuals during forward walking and a stepping in place task [91]. The authors found that attenuation of these pathologic bursts using STN-DBS therapy was linked to gait improvements [91].

Pedunculopontine nucleus (PPN) oscillations in freezing of gait

Abnormal neural activities of brainstem locomotor region (PPN) have also been implicated in FoG. A recent study reported PPN and cortical alpha and beta band power modulation is associated with contralateral gait cycle events during stepping and free walking [92]. Additionally, utilizing a stepping task, another study found levodopa-related PPN oscillatory changes in PD-FoG+ patients; it was observed that alpha power increased, and beta and gamma power decreased while "ON" medication, which was not observed during quiet standing and sitting [93]. The authors suggested that perhaps FoG in PD could be due to an imbalance between low and high frequency oscillations at the PPN which were alleviated via levodopa [93].

Effects of Neuromodulation on Postural Control in People with PD

While little work has examined the subcortical involvement in various domains of postural control, the effects of stimulating these areas can offer additional insights into their roles in maintaining postural stability. DBS of the basal ganglia (STN-DBS or GPi-DBS) or brainstem locomotive region (PPN-DBS) are the most common therapies. While DBS technology has been used for over twenty years to treat most of the "cardinal" motor symptoms of PD, controversy remains whether it improves (or worsens) symptoms of PI, especially long-term, and which region and setting configuration offers the most effective therapeutic benefit [94,95]. Previous research has consistently shown, however, that medication-responsive PI symptoms will likely have the greatest improvement with DBS therapy regardless of target [96,97].

Subthalamic nucleus DBS (STN-DBS) on postural control

There is greater data (especially in the short-term) examining STN-DBS's effects on PIGD symptoms and postural control in people with PD compared to other DBS targets. Specific to *static* postural control, studies

have generally suggested that STN-DBS improves most postural sway metrics [24,25,95,98,99]. For *anticipatory* postural control, a review found STN-DBS has a generally positive effect on APAs through amplitude, propulsion, and alignment improvements [96], with its effects varying with displacement direction, hemisphere stimulated, and frequency of stimulation [95]. However, another study suggested medication and STN-DBS together worsened APAs and their responsiveness to levodopa during gait initiation upon 6-month follow-up [100]. Similar work also found STN-DBS and medication together had limited benefit on APA metrics compared to medication alone, with both treatment groups continuing to displaying abnormal lower-extremity muscle activation and co-contraction compared to healthy subjects [101].

Related to the *reactive* postural domain, STN-DBS and medication together have been found to both impair [102], and partially improve, the speed of postural reflexes and co-contraction ratios compared to healthy subjects [101]. Another study found initial improvement with STN-DBS in compensatory stepping abilities, however this benefit was lost and reversed after six months when compared to subjects' "ON" medication function prior to surgery [103]. The combined effects of STN-DBS (at least 1-year post-implant) and levodopa during *reactive* balance responses were also found to have a beneficial effect on PI and fall risk, however no treatment combination achieved superior benefit in postural control compared to both "OFF" medication and stimulation conditions [22]. Conversely, other studies found STN-DBS with or without medication to improve PIGD subscores [104], postural bradykinesia and abnormal sensory aspects of PI following 6–12 months of therapy [105], as well as the ability to improve one's postural strategies [106], despite them remaining at least partially ineffective compared to healthy controls [105,106].

Longitudinally in PD patients with PI symptoms (PD-PIGD), STN-DBS's effects on PI symptoms has been mixed, likely complicated by individualized disease progression [107,108]. Many studies have reported a loss of therapeutic resolution on axial symptoms, including PI, within one year [109] to ten years after implantation of STN-DBS [107, 108]. Despite this, others have reported continued benefit during that timeframe [104]. Interestingly, STN-DBS in the PD-PIGD population was shown to become less effective in treating "ON" medication PI symptoms over time, while still improving "OFF" medication symptoms [104]. Factors such as disease progression, outcomes selected, medication and DBS testing states, and/or pre-surgery PI symptom levodopa responsiveness are all probable sources of variability which could have contributed to the mixed results seen in STN-DBS's effects on PI symptoms.

It is thought that low-frequency (60–80 Hz) stimulation is most effective for targeting axial PD symptoms such as PI [110], which is much lower than settings often used to treat other "cardinal symptoms" of PD such as tremor and bradykinesia. Thus, commonly used, and continuous high-frequency settings may not be as effective in treating patients also demonstrating PI. Despite the lack of consensus regarding the long-term effects of STN-DBS in treating PI, findings showing that targeting this region affects postural responses in this population provides confirmation of its role in human postural control.

Globus pallidus internus DBS (GPi-DBS)

The GPi is also a common DBS target to resolve motor symptoms in PIGD-PD individuals. While longitudinal outcomes of PI symptom resolution using GPi-DBS are relatively limited, GPi-DBS with medication was shown to be superior to STN-DBS with medication on PIGD outcomes at six months and two years post-surgery [103,111]. Other long-term results using GPi-DBS have suggested that continued therapeutic benefit may be limited to tremor and dyskinesia symptoms only [107,112].

GPi-DBS has also been found to have some benefit on *static* and dynamic postural control while counteracting the negative effects levodopa may have [95,113]. In the *reactive* postural domain, GPi-DBS was found to be superior to STN-DBS in improving compensatory stepping and falls, however GPi-DBS and medication combined were no better than the medication-only state prior to surgery [102]. A recent study also suggested GPi-DBS can improve multiple PD-related postural deformities [114] which may influence postural responses as well.

These findings collectively have led to the suggestion that GPi-DBS may offer greater benefit in people with PI also looking for effective "cardinal symptom" resolution for issues such as tremor, bradykinesia, and rigidity [97]. Due to the lack of longitudinal outcomes and limited research exploring the effects of GPi-DBS on various domains of postural control, much work needs to be done in these areas before strong recommendations can be made to guide providers and patients. Like STN-DBS, the effects of GPi-DBS on postural control continues to implicate this region in the current schema of the neural circuits underlying this phenomenon.

Pedunculopontine nucleus DBS (PPN-DBS)

The PPN, as previously mentioned, is a brainstem locomotive center with cholinergic and non-cholinergic connections to the cortex, thalamus, basal ganglia, cerebellum, and spinal cord [44,45,115]. As a result of animal studies implicating this region in automatic gait, it was once viewed as a promising DBS target for people with PD-PIGD [115]. There has since been much debate regarding the ideal location and reproducibility of lead placement within this target, as well as concerns regarding the long-term effects of PPN-DBS in symptom resolution [115]. Previous studies with limited longitudinal follow-up have provided evidence that PPN-DBS may improve PIGD symptoms, as well as FoG and falling, depending on the length of follow up and outcome measures utilized [115–119]. Mid-caudal PPN stimulation was found to improve FoG symptoms in this population, perhaps through alpha power modulation [120]. APAs were also shown to improve with PPN-DBS [119]. More research is still warranted investigating whether this DBS target is an effective, consistent, and long-lasting option for the treatment of PI symptoms [118,119].

Considerations of DBS treatment on PI

To summarize the effects of conventional DBS on individuals with PI, it is important to consider the variability inherently present in this complex and dynamic phenomenon and patient population. There is much heterogeneity in the PIGD criteria and classification itself, as well as patient-specific factors relating to disease progression and responsiveness of PI symptoms to medication. Given this variability, it may be unlikely that a single set of stimulation parameters or sole therapeutic target will be sufficient in effectively addressing the spectrum of rapidly fluctuating symptoms experienced by people with PD [11,97]. Existing research does not offer providers clear prognostic data and/or selection criteria to inform decision-making regarding DBS therapy and target selection versus other interventions to address PI instead [11].

Additional Neuromodulatory Interventions on Postural Instability

The effects of other neuromodulation interventions on PI have been investigated in people with PD, including noninvasive methods such as transcranial direct current stimulation (tDCS), galvanic vestibular stimulation (GVS), transcranial magnetic stimulation (TMS) and transcutaneous vagal nerve stimulation (tVNS), as well as invasive techniques such as spinal cord stimulation.

A growing body of research has found that non-invasive tDCS applied at the cortex can influence PI and FoG symptoms. A meta-analysis found significant improvements using tDCS and/or TMS in people with PD on FoG and UPDRS III scores, with M1 stimulation doubly effective compared to that of the frontal cortex [121]. Another study found improvements using tDCS over M1 in subjects' recovery time and calf muscle activation during *reactive* responses, which were inversely related

to subjects' baseline levels of postural control [122]. Contrasting with these results, a crossover study found tDCS applied over M1 did not significantly improve *static* postural control during a tandem balance task in people with PD compared to sham; however, this study did not gather baseline data of subjects' postural control abilities [123].

GVS is another type of non-invasive stimulation investigated for treating PI thought to modulate the vestibular afferents, which are functionally connected to the cerebellum, and basal ganglia [124]. A previous study found at least partial improvements on subjects' *reactive* postural control using GVS applied to the trunk or neck [124]; it also had similar mixed success in treating *static* postural deficits compared to sham [124]. An additional study used GVS applied to the mastoid process and C7 vertebrae, with small improvements seen in PD subjects' antero-posterior sway while *static* balancing on foam with their eyes closed; this result was only seen with low intensity stimulation, however [126]. These results and others were combined in a recent meta-analysis, which suggested that GVS likely has an overall positive effect on PI in this population, but the existing data is relatively inconclusive [127]. While both tDCS and GVS remain promising options for treating PI in people with PD, much additional work is needed to optimize stimulation protocols, including the number of treatment sessions, intensity and location of stimulation, and selection of appropriate subjects [125,127].

Like tDCS, repetitive TMS (rTMS) consists of non-invasive stimulation applied to the cortex but uses a magnetic coil instead. A previous study investigating its use for PIGD symptoms applied TMS to the leg regions of the bilateral primary motor cortices in people with PD, and found it improved UPDRS III scores and PIGD subscores [128], however the long-term benefits of this therapy are less certain [129]. It is thought that TMS can modulate cortical excitability while also affecting basal ganglia activity [128]. More research is warranted exploring various postural domains, patient presentations, and longitudinal follow-up before recommendations can be made regarding this modality's effectiveness in treating symptoms of PI.

Other non-invasive interventions trialed include stimulation of various peripheral nerves which carry sensory, motor, and autonomic information involved in postural control and have connections with various regions in the cortico-basal ganglia-cerebellar circuit. One such study used sub-threshold transcutaneous electrical stimulation (TENS) applied to the intrinsic auricular muscle zones in people with PD; modulation here is thought to influence activity of the C2 spinal nerve, and the trigeminal, facial, and vagus nerves [130]. The authors found clinically significant improvements in UPDRS III scores post-treatment compared to sham stimulation and placebo [130]. Subsequent research has focused on this region primarily for transcutaneous vagal nerve stimulation (tVNS), thought to affect activity in the nucleus tractus solitarus and locus coeruleus, which relay afferent sensory information via connections to the thalamus, orbitofrontal cortex, and medulla [131,132]. Multiple recent studies found tVNS improved various gait parameters in people with PD, including those with FoG, however, had mixed success in improving UPDRS III scores [133–137]. While these results suggest its promise in treating gait impairments in PD, tVNS' effects on PIGD symptoms remain relatively unknown.

More invasively, epidural spinal cord stimulation (SCS) has also shown promise in improving UPDRS-MDS scores, primarily for gait, in people with PD [138–141]. Despite this finding, there are limited studies analyzing this intervention on PI symptoms in the long-term, especially given the significant heterogeneity among studies in settings and implant locations [138–140]. A recent study did find, however, that thoracic SCS improved FoG symptoms and UPDRS III scores in people with PD, showing reversibility upon 28-day follow-up [142]. It is important to mention that most previous studies exploring SCS in PD have focused on pain alleviation [138–141], rendering PI much less-explored. The mechanisms underlying SCS's effects remain unclear, however it is theorized to perhaps interrupt pathological beta oscillatory activity which has been linked to motor symptoms in PD [138].

Very recently, a novel, investigational closed loop neuroprosthesis was recently developed and implanted into an individual with severe and refractory PD symptoms, including gait and balance deficits [143]. The device successfully delivered stimulation to the patient's lumbosacral spinal dorsal roots and acted synergistically with STN-DBS to improve FoG and balance [143]. While the sample size receiving this treatment is limited, it suggests that further exploration of non-DBS neuromodulation therapies is warranted in improving PI symptoms in this population.

Future Directions for Effective Treatment of Postural Instability

Studying postural control using chronic ambulatory neural data

The first step to improve therapy to treat PI is to gain a better understanding the neurophysiology of postural control in humans. Utilizing novel methodologies combining biomechanical quantification of postural responses with ambulatory, chronic neural recordings devices (such as with the investigative Medtronic devices Activa® PC + S or Summit RC + S®, or the FDA-approved Percept® PC device) in individuals experiencing PI, we can embark on studies that would greatly expand our knowledge of neural dynamics of effective and dysfunctional postural control. Ongoing work in our lab utilizes such devices synchronized with external sensors to explore the neural correlates of postural control, such as *static* postural maintenance and *anticipatory* postural adjustments during various motor tasks and transitions. Such information would inform circuit-based dynamics that regulate postural control and identify potential biomarkers of postural instability and targets for neuromodulation therapy.

Specifically, one such project examines globus pallidus LFP and motor cortical electrocorticogram (ECoG) data in people with PD during epochs of a gait initiation task challenging various domains of postural control. Potential correlations were examined between each epoch's average power and coherence with amplitude and timing APA metrics reflecting postural control quality. Preliminary (unpublished) data suggests that patient-specific patterns of neural modulation exist at multiple task epochs, brain regions, and frequency bands, which are correlated with various APA balance deficits in PD-PI+ patients [144]. We hope to identify neural signatures of PI as a first step to develop closed-loop neuromodulation to treat PI.

Adaptive DBS and neurofeedback technologies

Another application utilizing these bidirectional devices is the development of adaptive DBS therapy. Consisting of a closed loop system where the implanted neural device can both "sense" and stimulate subcortical areas when appropriate based on a neurophysiological symptom biomarker [145,146], the identification of biomarkers associated with PI across various postural domains is a necessary next step in developing effective therapies for this symptom. Emerging work related to gait improvements has demonstrated the technical feasibility and motor benefits which could be provided using adaptive DBS technologies in this population [145].

A related novel technology which has been recently explored involves delivering neurofeedback via implanted STN-DBS electrodes to people with PD performing a motor task [147]. Following a short training session to teach subjects how to control their excess beta-oscillatory activity using visual neurofeedback, patients were able to improve their motor performance and maintain beta power reductions even after removal of the neurofeedback [147]. While these effects were only examined in the short-term, the authors speculated that these effects could be improved with longer neurofeedback training, which may be possible with continued DBS technological advancements.

Feedback-based and physical therapy interventions

While these neuromodulation technologies offer great promise in treating symptoms of PI, other likely effective and less-invasive interventions should also be considered [11]. Many emerging therapies have focused on the delivery of haptic feedback to a patient via a wearable device or surface. Previous work delivering vibration at the feet (theorized to increase proprioception at the soles) benefitted multiple APA metrics in people with PD [148]. Similar studies testing the effects on PI using textured insoles (providing greater sensory feedback) showed improvements in postural sway [149] and turning in people with PD [150]. Another study utilized a novel vibro-feedback device worn on the upper back during *static* balancing and dynamic gait; while benefit was found during sitting and standing postural alignment in people with PD, these results were not maintained during walking [151]. Due to the potential benefits of using such wearable technologies to improve PI, it is expected that continued work will further improve and characterize their effectiveness.

Physical therapy (PT) is also often used solely or in conjunction with the neuromodulatory interventions discussed in this review for PD-PI + individuals. A recent clinical practice guideline (CPG) released by the American Physical Therapy Association to summarize the quality and strength of existing research to guide PTs in treating PD strongly recommended the use of balance training to improve various domains of postural control in this population, including *static* posture (postural sway), as well as *anticipatory* and *reactive* responses [152]. While intervention modalities included by the recommendation were quite varied, core-training, aquatic therapy, and the use of novel rehabilitation technologies (sensors, exergaming) were all associated with increased benefit with PT in treating PI [152]. Given this review's discussion of neuromodulation in treating PI and its commonality in clinical practice, it is important to note the lack of research examining combined PT and neuromodulatory interventions [152]. Continued research characterizing and classifying the neural and biomechanical deficits present among various domains of postural control in this population will similarly improve the selection of and effectiveness of PT interventions as well.

PI remains a treatment challenge for PD patients. With the novel tools at our disposal to investigate the neurophysiology of postural control, we can begin to unravel the brain network dynamics that will ultimately lead to effective therapies to restore postural stability to our patients.

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Declaration of competing interest

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References

[1] Aleksovski D, Miljkovic D, Bravi D, Antonini A. Disease progression in Parkinson subtypes: the PPMI dataset. Neurol Sci 2018;39:1971–6.
[2] Lo RY, Tanner CM, Albers KB, Leimpeter AD, Fross RD, Bernstein AL, et al. Clinical features in early Parkinson disease and survival. Arch Neurol 2009;66:1353–8.
[3] Hely MA, Morris JG, Reid WG, Trafficante R. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 2005;20:190–9.
[4] Rajput AH, Pahwa R, Pahwa P, Rajput A. Prognostic significance of the onset mode in parkinsonism. Neurology 1993;43:829–30.
[5] Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990;40:1529–34.
[6] Viseux FJF, Delval A, Defebvre L, Simoneau M. Postural instability in Parkinson's disease: review and bottom-up rehabilitative approaches. Neurophysiol Clin 2020;50:479–87.
[7] Mancini M, Rocchi L, Horak FB, Chiari L. Effects of Parkinson's disease and levodopa on functional limits of stability. Clin Biomech (Bristol, Avon) 2008;23:450–8.
[8] Horak FB, Nutt JG, Nashner LM. Postural inflexibility in parkinsonian subjects. J Neurol Sci 1992;111:46–58.
[9] Crouse JJ, Phillips JR, Jahanshahi M, Moustafa AA. Postural instability and falls in Parkinson's disease. Rev Neurosci 2016;27:549–55.
[10] Bekkers EMJ, Dijkstra BW, Heremans E, Verschueren SMP, Bloem BR, Nieuwboer A. Balancing between the two: are freezing of gait and postural instability in Parkinson's disease connected? Neurosci Biobehav Rev 2018;94:113–25.
[11] Muller M, Marusic U, van Emde Boas M, Weiss D, Bohnen NI. Treatment options for postural instability and gait difficulties in Parkinson's disease. Expert Rev Neurother 2019;19:1229–51.
[12] Gu Q, Huang P, Xuan M, Xu X, Li D, Sun J, et al. Greater loss of white matter integrity in postural instability and gait difficulty subtype of Parkinson's disease. Can J Neurol Sci 2014;41:763–8.
[13] Herman T, Rosenberg-Katz K, Jacob Y, Giladi N, Hausdorff JM. Gray matter atrophy and freezing of gait in Parkinson's disease: is the evidence black-on-white? Mov Disord 2014;29:134–9.
[14] Nonnekes J, de Kam D, Oude Nijhuis LB, van Geel K, Bloem BR, Geurts A, et al. StartReact effects support different pathophysiological mechanisms underlying freezing of gait and postural instability in Parkinson's disease. PLoS One 2015;10:e0122064.
[15] Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 2011;10:734–44.
[16] Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. J Neurol 2001;248:950–8.
[17] Krzyszton K, Stolarski J, Kochanowski J. Evaluation of balance disorders in Parkinson's disease using simple diagnostic tests-not so simple to choose. Front Neurol 2018;9:932.
[18] Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord 2013;28:668–70.
[19] Kotagal V. Is PIGD a legitimate motor subtype in Parkinson disease? Ann Clin Transl Neurol 2016;3:473–7.
[20] Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing 2006;35(Suppl 2):ii7–11.
[21] Horak FB, Frank J, Nutt J. Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. J Neurophysiol 1996;75:2380–96.
[22] Leodori G, Santilli M, Modugno N, D'Avino M, De Bartolo MI, Fabbrini A, et al. Postural instability and risk of falls in patients with Parkinson's disease treated with deep brain stimulation: a stabilometric platform study. Brain Sci 2023;13:13.
[23] Bloem BR, Beckley DJ, van Dijk JG, Zwinderman AH, Remler MP, Roos RA. Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. Mov Disord 1996;11:509–21.
[24] Nantel J, McDonald JC, Bronte-Stewart H. Effect of medication and STN-DBS on postural control in subjects with Parkinson's disease. Parkinsonism Relat Disorders 2012;18:285–9.
[25] Rocchi L, Chiari L, Horak FB. Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73:267–74.
[26] Blaszczyk JW, Orawiec R, Duda-Klodowska D, Opala G. Assessment of postural instability in patients with Parkinson's disease. Exp Brain Res 2007;183:107–14.
[27] Mancini M, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Chiari L. Trunk accelerometry reveals postural instability in untreated Parkinson's disease. Parkinsonism Relat Disorders 2011;17:557–62.
[28] Mangalam M, Kelty-Stephen DG, Seleznov I, Popov A, Likens AD, Kiyono K, et al. Older adults and individuals with Parkinson's disease control posture along suborthogonal directions that deviate from the traditional anteroposterior and mediolateral directions. Sci Rep 2024;14:4117.

[29] Carpenter MG, Allum JH, Honegger F, Adkin AL, Bloem BR. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:1245–54.
[30] Horak FB, Dimitrova D, Nutt JG. Direction-specific postural instability in subjects with Parkinson's disease. Exp Neurol 2005;193:504–21.
[31] Jacobs JV, Dimitrova DM, Nutt JG, Horak FB. Can stooped posture explain multidirectional postural instability in patients with Parkinson's disease? Exp Brain Res 2005;166:78–88.
[32] Schoneburg B, Mancini M, Horak F, Nutt JG. Framework for understanding balance dysfunction in Parkinson's disease. Mov Disord 2013;28:1474–82.
[33] Winter DA. Human balance and posture control during standing and walking. Gait Posture 1995;3:193–214.
[34] Mancini M, Zampieri C, Carlson-Kuhta P, Chiari L, Horak FB. Anticipatory postural adjustments prior to step initiation are hypometric in untreated Parkinson's disease: an accelerometer-based approach. Eur J Neurol 2009;16:1028–34.
[35] Lin CC, Creath RA, Rogers MW. Variability of anticipatory postural adjustments during gait initiation in individuals with Parkinson disease. J Neurol Phys Ther 2016;40:40–6.
[36] Lencioni T, Meloni M, Bowman T, Marzegan A, Caronni A, Carpinella I, et al. Events detection of anticipatory postural adjustments through a wearable accelerometer sensor is comparable to that measured by the force platform in subjects with Parkinson's disease. Sensors 2022;22.
[37] El-Gohary M, Pearson S, McNames J, Mancini M, Horak F, Mellone S, et al. Continuous monitoring of turning in patients with movement disability. Sensors 2013;14:356–69.
[38] Mellone S, Mancini M, King LA, Horak FB, Chiari L. The quality of turning in Parkinson's disease: a compensatory strategy to prevent postural instability? J NeuroEng Rehabil 2016;13:39.
[39] Mancini M, El-Gohary M, Pearson S, McNames J, Schlueter H, Nutt JG, et al. Continuous monitoring of turning in Parkinson's disease: rehabilitation potential. NeuroRehabilitation 2015;37:3–10.
[40] Orendurff MS, Segal AD, Berge JS, Flick KC, Spanier D, Klute GK. The kinematics and kinetics of turning: limb asymmetries associated with walking a circular path. Gait Posture 2006;23:106–11.
[41] King LA, Horak FB. Lateral stepping for postural correction in Parkinson's disease. Arch Phys Med Rehabil 2008;89:492–9.
[42] King LA, St George RJ, Carlson-Kuhta P, Nutt JG, Horak FB. Preparation for compensatory forward stepping in Parkinson's disease. Arch Phys Med Rehabil 2010;91:1332–8.
[43] Lang KC, Hackney ME, Ting LH, McKay JL. Antagonist muscle activity during reactive balance responses is elevated in Parkinson's disease and in balance impairment. PLoS One 2019;14:e0211137.
[44] Takakusaki K. Functional neuroanatomy for posture and gait control. J Mov Disord 2017;10:1–17.
[45] Takakusaki K, Takahashi M, Noguchi T, Chiba R. Neurophysiological mechanisms of gait disturbance in advanced Parkinson's disease patients. Neurology and Clinical Neuroscience 2022;11:201–17.
[46] Jacobs JV, Horak FB. Cortical control of postural responses. J Neural Transm 2007;114:1339–48.
[47] Ivanenko Y, Gurfinkel VS. Human postural control. Front Neurosci 2018;12:171.
[48] Bolton DA. The role of the cerebral cortex in postural responses to externally induced perturbations. Neurosci Biobehav Rev 2015;57:142–55.
[49] Visser JE, Bloem BR. Role of the basal ganglia in balance control. Neural Plast 2005;12:161–74. ; discussion 263-72.
[50] Ganguly J, Kulshreshtha D, Almotiri M, Jog M. Muscle tone physiology and abnormalities. Toxins 2021;13.
[51] Rubega M, Formaggio E, Di Marco R, Bertuccelli M, Tortora S, Menegatti E, et al. Cortical correlates in upright dynamic and static balance in the elderly. Sci Rep 2021;11:14132.
[52] Gebel A, Lehmann T, Granacher U. Balance task difficulty affects postural sway and cortical activity in healthy adolescents. Exp Brain Res 2020;238:1323–33.
[53] Slobounov S, Hallett M, Stanhope S, Shibasaki H. Role of cerebral cortex in human postural control: an EEG study. Clin Neurophysiol 2005;116:315–23.
[54] Slobounov S, Hallett M, Cao C, Newell K. Modulation of cortical activity as a result of voluntary postural sway direction: an EEG study. Neurosci Lett 2008;442:309–13.
[55] Varghese JP, Marlin A, Beyer KB, Staines WR, Mochizuki G, McIlroy WE. Frequency characteristics of cortical activity associated with perturbations to upright stability. Neurosci Lett 2014;578:33–8.
[56] Varghese JP, McIlroy RE, Barnett-Cowan M. Perturbation-evoked potentials: significance and application in balance control research. Neurosci Biobehav Rev 2017;83:267–80.
[57] Solis-Escalante T, van der Cruijsen J, de Kam D, van Kordelaar J, Weerdesteyn V, Schouten AC. Cortical dynamics during preparation and execution of reactive balance responses with distinct postural demands. Neuroimage 2019;188:557–71.
[58] Nakamura A, Suzuki Y, Milosevic M, Nomura T. Long-lasting event-related beta synchronizations of electroencephalographic activity in response to support-surface perturbations during upright stance: a pilot study associating beta rebound and active monitoring in the intermittent postural control. Front Syst Neurosci 2021;15:660434.
[59] Varghese JP, Staines WR, McIlroy WE. Activity in functional cortical networks temporally associated with postural instability. Neuroscience 2019;401:43–58.
[60] Solis-Escalante T, Stokkermans M, Cohen MX, Weerdesteyn V. Cortical responses to whole-body balance perturbations index perturbation magnitude and predict reactive stepping behavior. Eur J Neurosci 2021;54:8120–38.
[61] Hulsdunker T, Mierau A, Neeb C, Kleinoder H, Struder HK. Cortical processes associated with continuous balance control as revealed by EEG spectral power. Neurosci Lett 2015;592:1–5.
[62] Stokkermans M, Staring W, Cohen MX, Solis-Escalante T, Weerdesteyn V. Cortical midfrontal theta dynamics following foot strike may index response adaptation during reactive stepping. Sci Rep 2022;12:17748.
[63] Slobounov S, Cao C, Jaiswal N, Newell KM. Neural basis of postural instability identified by VTC and EEG. Exp Brain Res 2009;199:1–16.
[64] Buchel D, Lehmann T, Ullrich S, Cockcroft J, Louw Q, Baumeister J. Stance leg and surface stability modulate cortical activity during human single leg stance. Exp Brain Res 2021;239:1193–202.
[65] Ozdemir RA, Contreras-Vidal JL, Lee BC, Paloski WH. Cortical activity modulations underlying age-related performance differences during posture-cognition dual tasking. Exp Brain Res 2016;234:3321–34.
[66] Hulsdunker T, Mierau A, Struder HK. Higher balance task demands are associated with an increase in individual alpha peak frequency. Front Hum Neurosci 2015;9:695.
[67] Ma L, Marshall PJ, Wright WG. The impact of external and internal focus of attention on visual dependence and EEG alpha oscillations during postural control. J NeuroEng Rehabil 2022;19:81.
[68] Aubonnet R, Shoykhet A, Jacob D, Di Lorenzo G, Petersen H, Gargiulo P. Postural control paradigm (BioVRSea): towards a neurophysiological signature. Physiol Meas 2022;43.
[69] Ghosn NJ, Palmer JA, Borich MR, Ting LH, Payne AM. Cortical beta oscillatory activity evoked during reactive balance recovery scales with perturbation difficulty and individual balance ability. Brain Sci 2020;10.
[70] Anson E, Bigelow RT, Studenski S, Deshpande N, Agrawal Y. Failure on the foam eyes closed test of standing balance associated with reduced semicircular canal function in healthy older adults. Ear Hear 2019;40:340–4.
[71] Bosch TJ, Kammermeier S, Groth C, Leedom M, Hanson EK, Berg-Poppe P, et al. Cortical and cerebellar oscillatory responses to postural instability in Parkinson's disease. Front Neurol 2021;12:752271.
[72] Araujo-Silva F, Santinelli FB, Felipe IIL, Silveira APB, Vieira LHP, Alcock L, et al. Temporal dynamics of cortical activity and postural control in response to the first levodopa dose of the day in people with Parkinson's disease. Brain Res 2022;1775:147727.
[73] Shoushtarian M, Murphy A, Iansek R. Examination of central gait control mechanisms in Parkinson's disease using movement-related potentials. Mov Disord 2011;26:2347–53.
[74] Mustile M, Kourtis D, Edwards MG, Ladouce S, Volpe D, Pilleri M, et al. Characterizing neurocognitive impairments in Parkinson's disease with mobile EEG when walking and stepping over obstacles. Brain Commun 2023;5:fcad326.
[75] Payne AM, McKay JL, Ting LH. The cortical N1 response to balance perturbation is associated with balance and cognitive function in different ways between older adults with and without Parkinson's disease. Cereb Cortex Commun 2022;3:tgac030.
[76] Dijkstra BW, Bekkers EMJ, Gilat M, de Rond V, Hardwick RM, Nieuwboer A. Functional neuroimaging of human postural control: a systematic review with meta-analysis. Neurosci Biobehav Rev 2020;115:351–62.
[77] Ragothaman A, Mancini M, Nutt JG, Fair DA, Miranda-Dominguez O, Horak FB. Resting state functional networks predict different aspects of postural control in Parkinson's disease. Gait Posture 2022;97:122–9.
[78] Gardoni A, Agosta F, Sarasso E, Basaia S, Canu E, Leocadi M, et al. Cerebellar alterations in Parkinson's disease with postural instability and gait disorders. J Neurol 2023;270:1735–44.
[79] Sarasso E, Gardoni A, Piramide N, Volonte MA, Canu E, Tettamanti A, et al. Dual-task clinical and functional MRI correlates in Parkinson's disease with postural instability and gait disorders. Parkinsonism Relat Disorders 2021;91:88–95.
[80] Zhang L, Li TN, Yuan YS, Jiang SM, Tong Q, Wang M, et al. The neural basis of postural instability gait disorder subtype of Parkinson's disease: a PET and fMRI study. CNS Neurosci Ther 2016;22:360–7.
[81] Chung M, Park YS, Kim JS, Kim YJ, Ma HI, Jang SJ, et al. Correlating Parkinson's disease motor symptoms with three-dimensional [(18)F]FP-CIT PET. Jpn J Radiol 2015;33:609–18.
[82] Wang H, Li HY, Guo X, Zhou Y. Association of posture instability with dopamine drop of nigrostriatal system and hypometabolism of cerebral cortex in Parkinson's disease. Curr Neurovascular Res 2021;18:244–53.
[83] Ahrweiller K, Houvenaghel JF, Riou A, Drapier S, Sauleau P, Haegelen C, et al. Postural instability and gait disorders after subthalamic nucleus deep brain stimulation in Parkinson's disease: a PET study. J Neurol 2019;266:2764–71.
[84] Wittenberg E, Thompson J, Nam CS, Franz JR. Neuroimaging of human balance control: a systematic review. Front Hum Neurosci 2017;11:170.
[85] Hendriks AD, D'Agata F, Raimondo L, Schakel T, Geerts L, Luijten PR, et al. Pushing functional MRI spatial and temporal resolution further: high-density receive arrays combined with shot-selective 2D CAIPIRINHA for 3D echo-planar imaging at 7 T. NMR Biomed 2020;33:e4281.
[86] Chen CC, Yeh CH, Chan HL, Chang YJ, Tu PH, Yeh CH, et al. Subthalamic nucleus oscillations correlate with vulnerability to freezing of gait in patients with Parkinson's disease. Neurobiol Dis 2019;132:104605.
[87] Pozzi NG, Canessa A, Palmisano C, Brumberg J, Steigerwald F, Reich MM, et al. Freezing of gait in Parkinson's disease reflects a sudden derangement of locomotor network dynamics. Brain 2019;142:2037–50.
[88] Nwogo RO, Kammermeier S, Singh A. Abnormal neural oscillations during gait and dual-task in Parkinson's disease. Front Syst Neurosci 2022;16:995375.

[89] Syrkin-Nikolau J, Koop MM, Prieto T, Anidi C, Afzal MF, Velisar A, et al. Subthalamic neural entropy is a feature of freezing of gait in freely moving people with Parkinson's disease. Neurobiol Dis 2017;108:288–97.
[90] Singh A, Plate A, Kammermeier S, Mehrkens JH, Ilmberger J, Bötzel K. Freezing of gait-related oscillatory activity in the human subthalamic nucleus. Basal Ganglia 2013;3:25–32.
[91] Anidi C, O'Day JJ, Anderson RW, Afzal MF, Syrkin-Nikolau J, Velisar A, et al. Neuromodulation targets pathological not physiological beta bursts during gait in Parkinson's disease. Neurobiol Dis 2018;120:107–17.
[92] He S, Deli A, Fischer P, Wiest C, Huang Y, Martin S, et al. Gait-phase modulates alpha and beta oscillations in the pedunculopontine nucleus. J Neurosci 2021;41:8390–402.
[93] Fraix V, Bastin J, David O, Goetz L, Ferraye M, Benabid AL, et al. Pedunculopontine nucleus area oscillations during stance, stepping and freezing in Parkinson's disease. PLoS One 2013;8:e83919.
[94] Cossu G, Pau M. Subthalamic nucleus stimulation and gait in Parkinson's Disease: a not always fruitful relationship. Gait Posture 2017;52:205–10.
[95] Collomb-Clerc A, Welter ML. Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: a systematic neurophysiological review. Neurophysiol Clin 2015;45:371–88.
[96] Potter-Nerger M, Volkmann J. Deep brain stimulation for gait and postural symptoms in Parkinson's disease. Mov Disord 2013;28:1609–15.
[97] Ramirez-Zamora A, Ostrem JL. Globus pallidus interna or subthalamic nucleus deep brain stimulation for Parkinson disease: a review. JAMA Neurol 2018;75:367–72.
[98] Rocchi L, Chiari L, Cappello A, Gross A, Horak FB. Comparison between subthalamic nucleus and globus pallidus internus stimulation for postural performance in Parkinson's disease. Gait Posture 2004;19:172–83.
[99] Colnat-Coulbois S, Gauchard GC, Maillard L, Barroche G, Vespignani H, Auque J, et al. Bilateral subthalamic nucleus stimulation improves balance control in Parkinson's disease. J Neurol Neurosurg Psychiatry 2005;76:780–7.
[100] Rocchi L, Carlson-Kuhta P, Chiari L, Burchiel KJ, Hogarth P, Horak FB. Effects of deep brain stimulation in the subthalamic nucleus or globus pallidus internus on step initiation in Parkinson disease: laboratory investigation. J Neurosurg 2012;117:1141–9.
[101] Hess T, Oehlwein C, Milani TL. Anticipatory postural adjustments and compensatory postural responses to multidirectional perturbations-effects of medication and subthalamic nucleus deep brain stimulation in Parkinson's disease. Brain Sci 2023;13.
[102] St George RJ, Carlson-Kuhta P, King LA, Burchiel KJ, Horak FB. Compensatory stepping in Parkinson's disease is still a problem after deep brain stimulation randomized to STN or GPi. J Neurophysiol 2015;114:1417–23.
[103] St George RJ, Carlson-Kuhta P, Burchiel KJ, Hogarth P, Frank N, Horak FB. The effects of subthalamic and pallidal deep brain stimulation on postural responses in patients with Parkinson disease. J Neurosurg 2012;116:1347–56.
[104] Shin HW, Kim MS, Kim SR, Jeon SR, Chung SJ. Long-term effects of bilateral subthalamic deep brain stimulation on postural instability and gait difficulty in patients with Parkinson's disease. J Mov Disord 2020;13:127–32.
[105] Shivitz N, Koop MM, Fahimi J, Heit G, Bronte-Stewart HM. Bilateral subthalamic nucleus deep brain stimulation improves certain aspects of postural control in Parkinson's disease, whereas medication does not. Mov Disord 2006;21:1088–97.
[106] Patel M, Nilsson MH, Rehncrona S, Tjernstrom F, Magnusson M, Johansson R, et al. Strategic alterations of posture are delayed in Parkinson's disease patients during deep brain stimulation. Sci Rep 2021;11:23550.
[107] Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. Nat Rev Neurol 2019;15:234–42.
[108] Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. Arch Neurol 2011;68:1550–6.
[109] Szlufik S, Kloda M, Friedman A, Potrzebowska I, Gregier K, Mandat T, et al. The neuromodulatory impact of subthalamic nucleus deep brain stimulation on gait and postural instability in Parkinson's disease patients: a prospective case controlled study. Front Neurol 2018;9:906.
[110] Sirica D, Hewitt AL, Tarolli CG, Weber MT, Zimmerman C, Santiago A, et al. Neurophysiological biomarkers to optimize deep brain stimulation in movement disorders. Neurodegener Dis Manag 2021;11:315–28.
[111] St George RJ, Nutt JG, Burchiel KJ, Horak FB. A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD. Neurology 2010;75:1292–9.
[112] Tsuboi T, Lemos Melo Lobo Jofili Lopes J, Moore K, Patel B, Legacy J, Ratajska AM, et al. Long-term clinical outcomes of bilateral GPi deep brain stimulation in advanced Parkinson's disease: 5 years and beyond. J Neurosurg 2020:1–10.
[113] Johnson L, Rodrigues J, Teo WP, Walters S, Stell R, Thickbroom G, et al. Interactive effects of GPI stimulation and levodopa on postural control in Parkinson's disease. Gait Posture 2015;41:929–34.
[114] Lizarraga KJ, Fasano A. Effects of deep brain stimulation on postural trunk deformities: a systematic review. Mov Disord Clin Pract 2019;6:627–38.
[115] French IT, Muthusamy KA. A review of the pedunculopontine nucleus in Parkinson's disease. Front Aging Neurosci 2018;10:99.
[116] Yu K, Ren Z, Hu Y, Guo S, Ye X, Li J, et al. Efficacy of caudal pedunculopontine nucleus stimulation on postural instability and gait disorders in Parkinson's disease. Acta Neurochir 2022;164:575–85.
[117] Wang JW, Zhang YQ, Zhang XH, Wang YP, Li JP, Li YJ. Deep brain stimulation of pedunculopontine nucleus for postural instability and gait disorder after Parkinson disease: a meta-analysis of individual patient data. World Neurosurg 2017;102:72–8.
[118] Thevathasan W, Debu B, Aziz T, Bloem BR, Blahak C, Butson C, et al. Pedunculopontine nucleus deep brain stimulation in Parkinson's disease: a clinical review. Mov Disord 2018;33:10–20.
[119] Welter ML, Demain A, Ewenczyk C, Czernecki V, Lau B, El Helou A, et al. PPNa-DBS for gait and balance disorders in Parkinson's disease: a double-blind, randomised study. J Neurol 2015;262:1515–25.
[120] Thevathasan W, Pogosyan A, Hyam JA, Jenkinson N, Foltynie T, Limousin P, et al. Alpha oscillations in the pedunculopontine nucleus correlate with gait performance in parkinsonism. Brain 2012;135:148–60.
[121] Kim YW, Shin IS, Moon HI, Lee SC, Yoon SY. Effects of non-invasive brain stimulation on freezing of gait in parkinsonism: a systematic review with meta-analysis. Parkinsonism Relat Disorders 2019;64:82–9.
[122] Beretta VS, Orcioli-Silva D, Conceicao NR, Nobrega-Sousa P, Pereira MP, Gobbi LTB, et al. tDCS application for postural control in Parkinson's disease: effects are associated with baseline characteristics. Parkinsonism Relat Disorders 2021;93:62–5.
[123] Legutke BR, Gobbi LTB, Orcioli-Silva D, Santos P, Moraca GAG, Vitorio R, et al. Transcranial direct current stimulation suggests not improving postural control during adapted tandem position in people with Parkinson's disease: a pilot study. Behav Brain Res 2023;452:114581.
[124] Kataoka H, Okada Y, Kiriyama T, Kita Y, Nakamura J, Morioka S, et al. Can postural instability respond to galvanic vestibular stimulation in patients with Parkinson's disease? J Mov Disord 2016;9:40–3.
[125] Beretta VS, Vitorio R, Nobrega-Sousa P, Conceicao NR, Orcioli-Silva D, Pereira MP, et al. Effect of different intensities of transcranial direct current stimulation on postural response to external perturbation in patients with Parkinson's disease. Neurorehabilitation Neural Repair 2020;34:1009–19.
[126] Pal S, Rosengren SM, Colebatch JG. Stochastic galvanic vestibular stimulation produces a small reduction in sway in Parkinson's disease. J Vestib Res 2009;19:137–42.
[127] Mahmud M, Hadi Z, Prendergast M, Ciocca M, Saad AR, Pondeca Y, et al. The effect of galvanic vestibular stimulation on postural balance in Parkinson's disease: a systematic review and meta-analysis. J Neurol Sci 2022;442:120414.
[128] Okada KI, Takahira M, Mano T, Uga T, Konaka K, Hosomi K, et al. Concomitant improvement in anti-saccade success rate and postural instability gait difficulty after rTMS treatment for Parkinson's disease. Sci Rep 2021;11:2472.
[129] Zanjani A, Zakzanis KK, Daskalakis ZJ, Chen R. Repetitive transcranial magnetic stimulation of the primary motor cortex in the treatment of motor signs in Parkinson's disease: a quantitative review of the literature. Mov Disord 2015;30:750–8.
[130] Cakmak YO, Apaydin H, Kiziltan G, Gunduz A, Ozsoy B, Olcer S, et al. Rapid alleviation of Parkinson's disease symptoms via electrostimulation of intrinsic auricular muscle zones. Front Hum Neurosci 2017;11:338.
[131] George MS, Sackeim HA, Rush AJ, Marangell LB, Nahas Z, Husain MM, et al. Vagus nerve stimulation: a new tool for brain research and therapy. Biol Psychiatr 2000;47:287–95.
[132] Sigurdsson HP, Raw R, Hunter H, Baker MR, Taylor JP, Rochester L, et al. Noninvasive vagus nerve stimulation in Parkinson's disease: current status and future prospects. Expet Rev Med Dev 2021;18:971–84.
[133] Zhang H, Cao XY, Wang LN, Tong Q, Sun HM, Gan CT, et al. Transcutaneous auricular vagus nerve stimulation improves gait and cortical activity in Parkinson's disease: a pilot randomized study. CNS Neurosci Ther 2023;29:3889–900.
[134] Marano M, Anzini G, Musumeci G, Magliozzi A, Pozzilli V, Capone F, et al. Transcutaneous auricular vagus stimulation improves gait and reaction time in Parkinson's disease. Mov Disord 2022;37:2163–4.
[135] Lench DH, Turner TH, McLeod C, Boger HA, Lovera L, Heidelberg L, et al. Multi-session transcutaneous auricular vagus nerve stimulation for Parkinson's disease: evaluating feasibility, safety, and preliminary efficacy. Front Neurol 2023;14:1210103.
[136] Mondal B, Choudhury S, Banerjee R, Roy A, Chatterjee K, Basu P, et al. Effects of non-invasive vagus nerve stimulation on clinical symptoms and molecular biomarkers in Parkinson's disease. Front Aging Neurosci 2023;15:1331575.
[137] Morris R, Yarnall AJ, Hunter H, Taylor JP, Baker MR, Rochester L. Noninvasive vagus nerve stimulation to target gait impairment in Parkinson's disease. Mov Disord 2019;34:918–9.
[138] de Andrade EM, Ghilardi MG, Cury RG, Barbosa ER, Fuentes R, Teixeira MJ, et al. Spinal cord stimulation for Parkinson's disease: a systematic review. Neurosurg Rev 2016;39:27–35. discussion.
[139] Streumer J, Selvaraj AK, Kurt E, Bloem BR, Esselink RAJ, Bartels R, et al. Does spinal cord stimulation improve gait in Parkinson's disease: a comprehensive review. Parkinsonism Relat Disorders 2023;109:105331.
[140] Sarica C, Zemmar A, Yousefi O, Yang AC, Uzuner A, Sheng Z, et al. Spinal cord stimulation for Parkinson's disease: a systematic review and meta-analysis of pain and motor outcomes. Stereotact Funct Neurosurg 2023;101:244–53.
[141] Vanegas-Arroyave N, Jankovic J. Spinal cord stimulation for gait disturbances in Parkinson's disease. Expert Rev Neurother 2023;23:651–9.
[142] Reis Menezes J, Bernhart Carra R, Aline Nunes G, da Silva Simoes J, Jacobsen Teixeira M, Paiva Duarte K, et al. Transcutaneous magnetic spinal cord stimulation for freezing of gait in Parkinson's disease. J Clin Neurosci 2020;81:306–9.
[143] Milekovic T, Moraud EM, Macellari N, Moerman C, Raschella F, Sun S, et al. A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease. Nat Med 2023;29:2854–65.
[144] Bath JB, L, K, Balakid, J, Fekri Azgomi, H, Wang, DD. The cortical and subcortical controls of gait initiation in people with Parkinson's disease. Presented at society

for neuroscience annual conference nanosymposium, Nov. 13, 2023; Washington, DC.
[145] Louie KH, Gilron R, Yaroshinsky MS, Morrison MA, Choi J, de Hemptinne C, et al. Cortico-subthalamic field potentials support classification of the natural gait cycle in Parkinson's disease and reveal individualized spectral signatures. eNeuro 2022:9.
[146] Gilron R, Little S, Perrone R, Wilt R, de Hemptinne C, Yaroshinsky MS, et al. Long-term wireless streaming of neural recordings for circuit discovery and adaptive stimulation in individuals with Parkinson's disease. Nat Biotechnol 2021;39:1078–85.
[147] Bichsel O, Stieglitz LH, Oertel MF, Baumann CR, Gassert R, Imbach LL. Deep brain electrical neurofeedback allows Parkinson patients to control pathological oscillations and quicken movements. Sci Rep 2021;11:7973.
[148] Creath RA, Prettyman M, Shulman L, Hilliard M, Martinez K, MacKinnon CD, et al. Self-triggered assistive stimulus training improves step initiation in persons with Parkinson's disease. J NeuroEng Rehabil 2013;10:11.
[149] Qiu F, Cole MH, Davids KW, Hennig EM, Silburn PA, Netscher H, et al. Effects of textured insoles on balance in people with Parkinson's disease. PLoS One 2013;8:e83309.
[150] Robb KA, Perry SD. Textured foot orthotics on dynamic stability and turning performance in Parkinson's disease. J Mot Behav 2020;52:396–403.
[151] Stuart S, Godfrey A, Mancini M. Staying UpRight in Parkinson's disease: a pilot study of a novel wearable postural intervention. Gait Posture 2022;91:86–93.
[152] Osborne JA, Botkin R, Colon-Semenza C, DeAngelis TR, Gallardo OG, Kosakowski H, et al. Physical therapist management of Parkinson disease: a clinical practice guideline from the American physical therapy association. Phys Ther 2022:102.