THE NEURAL CONTROL OF LOCOMOTION: CURRENT KNOWLEDGE AND FUTURE RESEARCH

EDITED BY: Monika Pötter-Nerger and Ioannis Ugo Isaias
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THE NEURAL CONTROL OF LOCOMOTION: CURRENT KNOWLEDGE AND FUTURE RESEARCH

Topic Editors:
Monika Pötter-Nerger, University of Hamburg, Germany
Ioannis Ugo Isaias, Julius Maximilian University of Würzburg, Germany

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EDITORIAL
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Editorial: The Neural Control of Locomotion: Current Knowledge and Future Research

Monika Pötter-Nerger[1*†] *and Ioannis U. Isaias*[2,3*†]

[1] Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2] Department of Neurology, University Hospital Würzburg, Würzburg, Germany, [3] Parkinson Institute Milan, ASST G. Pini-CTO, Milan, Italy

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Editorial on the Research Topic

The Neural Control of Locomotion: Current Knowledge and Future Research

Gait disturbances represent one of the most disabling symptoms in parkinsonian patients. In particular, freezing of gait is a peculiar gait derangement characterized by a sudden and episodic inability to produce effective stepping, causing falls, mobility restrictions, poor quality of life, and increased morbidity and mortality with high economic burden. Freezing of gait represents an enigmatic phenomenon and became the focus of intense basic and clinical research due to incomplete pathophysiological understanding and therapeutically limited options. This e-book, *The Neural Control of Locomotion: Current Knowledge and Future Research*, aims to collect scientific contributions regarding advances in the understanding and treatment of the Parkinsonian gait disorder. A total of sixteen papers with six original research manuscripts, eight reviews and two opinion papers have been included into this special issue to bridge pathophysiological knowledge from animal research to human gait studies covering three main topics. The first gathers different methodological approaches for a more accurate and standardized gait assessment such as gait analysis in fully immersive virtual reality environments, portable technologies, mobile electroencephalography, and the role of motor imagery. In the second section, research methods are integrated to illustrate complementary hypotheses on the pathophysiology of gait and gait freezing. This section begins with new hypotheses on freezing of gait as a generalized network phenomenon and a redefinition of the clinical symptomatology of freezing of gait. In addition to general considerations of locomotor network derangements in animal models and humans, specific aspects of locomotor control are discussed, such as the role of subpopulations of striatal neurons, the importance of low-frequency electromyographic activity of synergistic muscles and anticipatory postural adjustments during gait initiation. The third section bridges pathophysiological insights to actual and new therapeutic concepts. Beginning with a review of state-of-the-art medical concepts, novel rehabilitative strategies, such as repeated gait perturbation training, and new translational approaches using deep brain stimulation are discussed. Particularly, the benefits of deep brain stimulation with trouble-shooting options for gait are reviewed and new stimulation paradigms, e.g., combined subthalamic and nigral stimulation and lead symmetry are presented to improve gait control in parkinsonian patients. This e-book provides the opportunity to bridge the gap between basic neuroscience innovative therapeutic and rehabilitative concepts for further understanding and better treatment of parkinsonian gait disorder.

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Julie Duque,
Catholic University of Louvain, Belgium

***Correspondence:**
Monika Pötter-Nerger
m.poetter-nerger@uke.de
Ioannis U. Isaias
isaias_i@ukw.de

†These authors have contributed equally to this work

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MINI REVIEW
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Striatal Control of Movement: A Role for New Neuronal (Sub-) Populations?

*Tim Fieblinger**

Institute for Synaptic Physiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

The striatum is a very heterogenous brain area, composed of different domains and compartments, albeit lacking visible anatomical demarcations. Two populations of striatal spiny projection neurons (SPNs) build the so-called direct and indirect pathway of the basal ganglia, whose coordinated activity is essential to control locomotion. Dysfunction of striatal SPNs is part of many movement disorders, such as Parkinson's disease (PD) and L-DOPA-induced dyskinesia. In this mini review article, I will highlight recent studies utilizing single-cell RNA sequencing to investigate the transcriptional profiles of striatal neurons. These studies discover that SPNs carry a transcriptional signature, indicating both their anatomical location and compartmental identity. Furthermore, the transcriptional profiles reveal the existence of additional distinct neuronal populations and previously unknown SPN sub-populations. In a parallel development, studies in rodent models of PD and L-DOPA-induced dyskinesia (LID) report that direct pathway SPNs do not react uniformly to L-DOPA therapy, and that only a subset of these neurons is underlying the development of abnormal movements. Together, these studies demonstrate a new level of cellular complexity for striatal (dys-) function and locomotor control.

Keywords: striatum, spiny projection neuron, Parkinson's disease, single-cell RNA sequencing, scRNAseq, movement, L-DOPA-induced dyskinesia

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Romulo Fuentes Flores, University of Chile, Chile

***Correspondence:**
Tim Fieblinger
tim.fieblinger@zmnh.uni-hamburg.de

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INTRODUCTION

The striatum is an evolutionarily conserved brain area and input structure to the basal ganglia (Grillner et al., 2013). Functionally, it is a critical hub for the control of locomotion. The classical "box-and-arrow" model of the basal ganglia postulates that the *direct* and *indirect* pathways, originating in the striatum, work in antagonistic ways to exert locomotor control (Albin et al., 1989; DeLong, 1990). Lesion or loss-of-function of the *direct* pathway reduces locomotion in animals, whereas disabling the *indirect* pathway results in hyperlocomotion (Durieux et al., 2009, 2012; Bateup et al., 2010). This is furthermore corroborated by optogenetic studies, showing that overt activation of the *direct* pathway induces locomotion, and activation of the *indirect* pathway leads to a cessation of ongoing movement (Kravitz et al., 2010). The "box-and-arrow" model has been instrumental to a better understanding of the network changes underlying movement disorders and locomotor dysfunction; however, it has become apparent that the model does not reflect the true complexity of the basal ganglia network (Calabresi et al., 2014; Plotkin and Goldberg, 2019). For example, *in vivo* imaging of striatal neurons in freely moving animals has shown that both pathways are simultaneously active during self-initiation of movements (Cui et al., 2013) and it is the coordinated and clustered activity of both pathways that is lost in a mouse model

of Parkinson's disease (PD; Parker et al., 2018). Nevertheless, it is undisputed that the striatum is a key region for locomotor control, and that SPN dysfunction leads to severe motor deficits.

PD patients suffer from loss of normal motor function, caused by the degeneration of dopamine (DA) producing neurons in the substantia nigra. The subsequent lack of DA signal in the striatum causes the hypo- and bradykinetic symptoms (Schneider and Obeso, 2015). Post mortem studies showed that striatal neurons do not *per se* degenerate in PD, yet they become atrophic with loss of dendrites and dendritic spines (McNeill et al., 1988; Stephens et al., 2005; Zaja-Milatovic et al., 2005). This has also been observed in rodent models of PD (Fieblinger and Cenci, 2015). Treatment with L-DOPA is the current gold-standard therapy to restore motor function in PD patients, with typically good responses for bradykinesia and rigidity, yet lesser efficacy for other symptoms, such as posture and gait problems or tremor (for a recent review of PD treatment, see Lee and Yankee, 2021). However, L-DOPA's benefits come at a price. The majority of patients experience involuntary movements, L-DOPA-induced dyskinesia (LID), with prolonged treatment (Ahlskog and Muenter, 2001). Animal research has, over decades, advanced our understanding of the mechanisms underlying the occurrence of LID. Yet, an effective treatment is still missing. One hurdle has always been the complex and vastly heterogenous organization of the striatum.

In this mini review article, I will shortly recapitulate the anatomical, compartmental, and neuronal divisions of the striatum, which create a complex and overlapping field of diversity. Recent studies using single-cell transcriptomics have now shed new light on this issue. The transcriptional profiles of striatal neurons harbor a code for their anatomical and compartmental identity, and also reveal the existence of previously unknown, discrete neuron populations and sub-populations. How these newly identified neurons participate in the overall striatal function and locomotor control is however yet to be determined. In a parallel development, studies investigating striatal neurons in animal models of LID have shown that—in contrast to previous expectations—not all striatal neurons of a given class are equally contributing to the generation of abnormal movements. Together, these developments suggest a previously overlooked genetic diversity of striatal neurons that might be critically linked to locomotor control and neurological disorders affecting the striatum.

DIVISIONS OF THE STRIATUM

The striatum is one of the largest structures in the rodent brain. Although lacking clear internal demarcations, the striatum has a complex organization which divides it along several, overlapping parameters (**Figure 1A**).

STRIATAL ANATOMICAL DOMAINS AND CORTICAL INPUT ZONES

The striatum is commonly divided into a dorsolateral (DL), -medial (DM), and ventral domain (**Figure 1A**). Each domain is not marked by anatomical borders but defined through functional differences (Yin and Knowlton, 2006; Graybiel and Grafton, 2015). While the DL striatum is dominantly involved in sensorimotor function (e.g., locomotor control and habit formation), the DM striatum takes preferentially part in associative tasks (e.g., goal-directed behavior) and the ventral striatum is often considered part of the limbic system and thus involved in e.g., motivational behavior. This function-based anatomical division is also reflected in the type of inputs these different domains receive. A study mapping different cortical inputs to the striatum showed that they are largely overlapping with the three different domains. There is a distinct DM region of the striatum with highly convergent cortical innervation, a DL region receiving dense sensory-motor inputs, and a ventral region, mostly innervated by limbic areas (Hunnicutt et al., 2016). Based on this type of mapping, the posterior striatum constitutes an additional, fourth anatomical domain. This is in line with previous observations that the posterior striatum receives distinct DA inputs (Menegas et al., 2015) and bears a unique neuronal composition (Gangarossa et al., 2013). The importance of this fourth domain has been recently discussed elsewhere (Valjent and Gangarossa, 2020).

STRIATAL COMPARTMENTS

The second division of the striatum is the distinction of patches (or striosomes) and matrix (**Figure 1A**). The patches are like islands, constituting around 10–15% of the striatal volume. There are no anatomical demarcations separating the patches, but their existence can be revealed by histochemical markers, such as the μ-opioid receptor or acetylcholinesterase (Herkenham and Pert, 1981). Patch and matrix are associated with different behavioral functions. In rodents, for example, patches are involved in cost-benefit trade-off decisions (Friedman et al., 2015), and in humans, striatal patches play a certain role in cognitive control (Beste et al., 2018). Also, the neurons inside the two compartments differ, for example in their synaptic connectivity and neuromodulation (for a recent review, see Prager and Plotkin, 2019). Importantly, the patch and matrix compartmentalization can be found in all anatomical domains of the striatum.

SPINY PROJECTION NEURON POPULATIONS

The striatum hosts one type of projection neuron: the GABAergic spiny projection neuron (SPN), sometimes referred to as medium-spiny neuron (MSN). The SPNs form the backbone of the basal ganglia and are "classically" divided into two groups, forming the *direct* (dSPNs) and *indirect* pathway (iSPNs). The dSPNs project predominantly to the substantia nigra reticulata (SNr) and express the DA D1 receptor, whereas the iSPNS project to the globus pallidus pars externa (GPe) and express the D2 receptor. They also differ in a range of electrophysiological, morphological, and molecular parameters (Gertler et al., 2008; Heiman et al., 2008; Planert et al., 2013). Importantly, dSPNs and iSPNs are intermingled in the striatum. They are found in all anatomical domains, and both patches

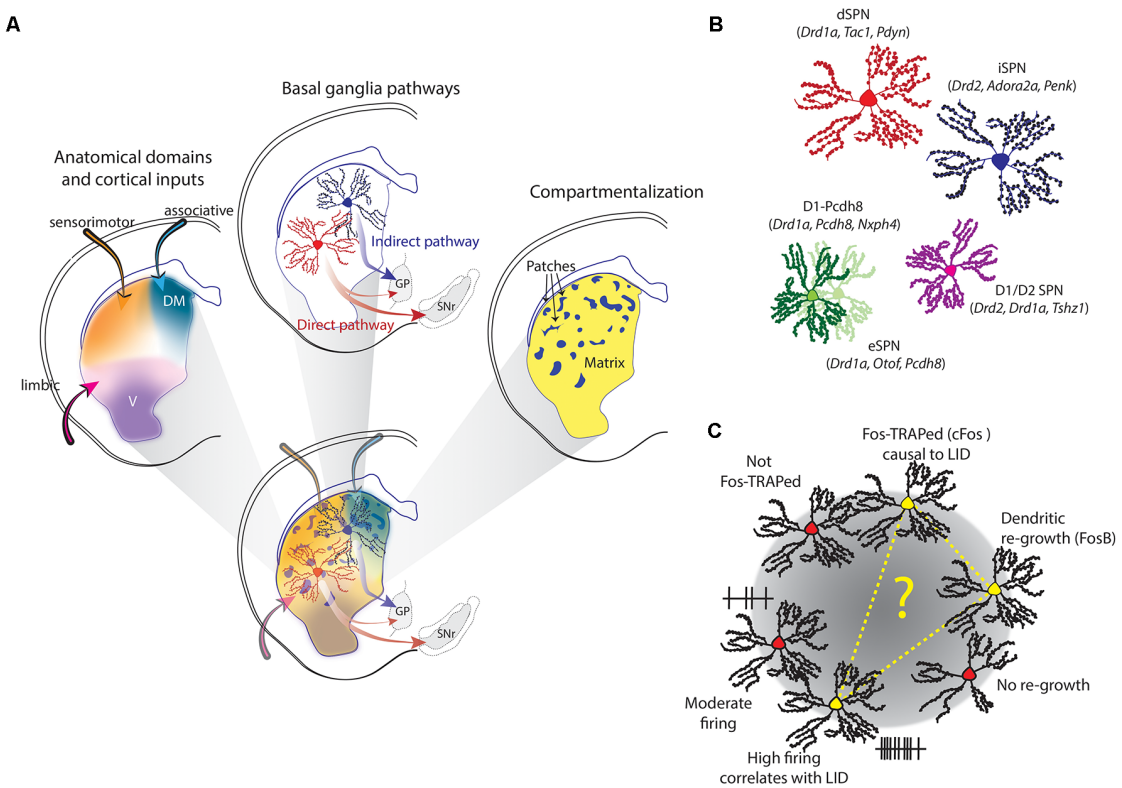

FIGURE 1 | Striatal heterogeneity, spiny projection neuron (SPN) (sub-) populations and L-DOPA-induced dyskinesia (LID)-associated dSPNs. **(A)** The rodent striatum constitutes a complex, overlapping field of heterogeneity. It combines anatomic-functional domains, patch/matrix compartmentalization, and the "classical" distinction of dSPNs and iSPNs, which anchor the *direct* and *indirect* pathway of the basal ganglia. **(B)** Apart from "classical" SPNs, also D1/D2-SPNs were described in scRNA-seq studies, as well as new sub-populations. Characteristic genes are given in parentheses. **(C)** Three different studies identified a sub-group of dSPNs specifically linked to LID. The sub-group was either identified by Fos-TRAP, high-firing activity that correlates with LID, or a specific cellular phenotype. It is tempting to speculate that these three markers identified the same LID-linked subgroup of dSPNs.

and matrix (**Figure 1A**). However, with regard to locomotor control, the *direct* and *indirect* pathways are classically associated with opposite functions. While the direct pathway is considered to promote motor behavior and initiation of locomotion, the indirect pathway has been associated with the opposite, i.e., inhibition of movement initiation and cessation of ongoing locomotion (Albin et al., 1989; DeLong, 1990; Kravitz et al., 2010).

Some distinctions between the "classical" SPN groups are however not simply "black-or-white" (but rather graded) and controversies prevail (see Calabresi et al., 2014). One point of debate is also a group of SPNs expressing both the D1 and D2 receptors. These constitute only a small fraction of all SPNs (about 2%) but show distinctive electrophysiological and morphological properties (Gagnon et al., 2017). If these D1/D2-SPNs project to the SNr and/or GPe is not yet established. It is also known that dSPN axons do not exclusively terminate in the SNr, but also make very plastic connections in the GPe (Cazorla et al., 2012; Cui et al., 2021). Another open question is whether patches are equally composed dSPNs and iSPNs, or preferentially enriched with one type (see Prager and Plotkin, 2019). Along this line, it has been noted that the most caudal part of the striatum (corresponding to the fourth anatomical division mentioned above) is largely devoid of iSPNs (Gangarossa et al., 2013). New experimental approaches, for example investigating single-cell information, may be useful for answering, at least in part, these open questions.

TRANSCRIPTIONAL PROFILES REVEAL A CODE FOR STRIATAL HETEROGENEITY AND NEW TYPES OF SPNs

Before the advent of single-cell sequencing technology, transcriptional analysis was at large limited to bulk measures from whole tissue or fluorescently labeled and sorted neuronal populations. Single-cell mRNA sequencing (scRNA-seq) provided a major advancement: it enabled the unbiased analysis of a single cell's transcriptome, for thousands of cells at a time, and thus revealed the individual and populational heterogeneity of SPNs.

One of the first scRNA-seq studies unearthed a range of interesting insights (Gokce et al., 2016). First, it confirmed that SPNs can be classified into dSPNs and iSPNs based on specific and largely known markers. The gene set to identify dSPNs includes, for example, *Drd1a* (the gene coding for the

D1 receptor), *Tac1* and *Isl1*, whereas the set to identify iSPNs includes *Drd2* (coding for the D2 receptor), *Adora2a*, *Penk*, *Gpr6*, *Gpr52*, and *SP9*. These sets enabled a discrete and robust separation of the "classical" SPNs, and similar ones were used in subsequent studies (Ho et al., 2018; Saunders et al., 2018; Martin et al., 2019; Malaiya et al., 2020; Stanley et al., 2020). Secondly, it also reported a small group of D1/D2 SPNs. Lastly, it revealed that SPNs within a given class have highly heterogeneous transcriptional profiles. This heterogeneity was used to characterize further subpopulations. For dSPNs a major subpopulation (D1-Foxp1) was identified, characterized by the expression of high levels of *Foxp1* and *Camk4*, as well as a minor subpopulation of dSPNs (D1-Pcdh8) characterized by *Pcdh8*, *Tacr1*, and *Adarb2*. The iSPNs similarly divide into subpopulations: a minor group marked by the unique expression of genes including *Htr7* and *Agtr1a*, and a major subpopulation characterized by a lack of *Cacnad2d3* and *Kcnip1* expression. Interestingly, it was observed that other genes form distinct gradients across all SPNs. The meaning of this gradient was, however, only examined in later studies (see below).

Another extensive scRNA-seq study, investigating several brain regions, confirmed the transcriptomic distinction of dSPNs and iSPNs in the striatum, based on more than 60 differentially expressed genes (Saunders et al., 2018). In contrast to the previous study, it additionally provided evidence for a third SPN population, which was neither a subpopulation of dSPNs nor iSPNs. These so-called "eccentric" eSPNs are only few in numbers, but transcriptionally distinct based on over 100 differentially expressed genes. Some of the eSPN markers encompass genes typically used to distinguish iSPNs and dSPNs, such as *Adora2a* and *Drd1*, which likely explains why this population was overlooked so far. *In situ* hybridization (ISH) further showed that eSPNs, dSPNs and iSPNs are intermingled in the striatum. Key marker genes for eSPNs include *Casz1*, *Otof*, *Cacng5*, and *Pcdh8*—of which the last was also a defining factor of the D1-Pcdh8 subpopulation described previously (Gokce et al., 2016), suggesting a possible relationship between these two groups. A later study, investigating the role of *Foxp1* in striatal neuron development, confirmed the transcriptional distinction of dSPNs and iSPNs in early postnatal mice, as well as the existence of D1/D2-SPNs and eSPNs, based on scRNA-seq (Anderson et al., 2020). *Foxp1* appears to be especially important for the segregation of different SPN populations during the development, as its deletion led to an enrichment of eSPN markers in both dSPNs and iSPNs.

Expanding the first report (Gokce et al., 2016), a subsequent study deeper investigation the transcriptional gradients in SPNs by combining scRNA-seq with ISH (Stanley et al., 2020). Apart from dSPNs and iSPNs two further main populations are defined: the SPNs of the Islands of Calleja (IcjSPNs) and the D1-Pcdh8 population. Key markers for IcjSPNs are the expression of *Drd1a* and *Rreb1*, and *Pcdh8* and *Nxph4* mark D1-Pcdh8. Upon closer examination, the study finds nine subgroups of dSPNs and seven subgroups of iSPNs, all of which were best defined by a combination of genetic markers. Several subgroups also showed a preferential anatomical location, as revealed by ISH. Most interestingly, this study reveals that the transcriptional gradients across all SPNs actually codes for the cells' anatomical position (along the dorsoventral axis), as well as their compartmental identity. Along the dorsoventral axis, the expression-ratio of *Cnr1* to *Crym* is lowest in the ventromedial, and highest in the DL striatum. This gradient has been recently confirmed in both mouse and marmoset striatum (Martin et al., 2019). It furthermore matched, at least to some extent, the cortical input patterns, as cortical regions enriched in *Cnr1* or *Crym* project to strong *Cnr1* or *Crym* expressing striatal regions. The transcriptional gradient thus nicely aligns with the anatomical domains (Hunnicutt et al., 2016).

Compartmental identity, i.e., whether an SPN belongs to the patches or matrix, was found to be coded by several genes (*Kremen1*, *Sema5b*, and *Id4*), forming a gradient orthogonal to the *Cnr1* to *Crym* ratio (Stanley et al., 2020). Overall, this study confirmed again that scRNA-seq can identify discrete neuron populations, which can both be spatially clustered (like icjSPNs) or intermingled (like dSPN and iSPNs). Furthermore, it showed that information about the anatomical location and compartmental identity is on the other hand not discretely coded, but lies on a continuous gradient, for both dimensions.

The transcriptional signatures of patches and matrix identity were recently further dissected (Martin et al., 2019). Characteristic genes for patches are *Oprm1* (coding for the μ-opioid receptor, a well-described immunohistochemical marker) and *Sema5B*, and *Id4* is a matrix-specific gene. But in addition to these, the authors also describe a curious population of SPNs that is enriched in both, *Oprm1* and *Id4*. These are the so-called exopatch SPNs. Exopatch SPNs are placed in the matrix but physiologically resemble SPNs of the patches (Smith et al., 2016). Based on scRNA-seq data it is concluded that most of the patch and exopatch neurons are dSPNs. Among all dSPNs, this study further identified a distinct subpopulation, characterized by *Col11a1*, *Otof*, *Cacng5*, and *Pcdh8*. This transcriptomic profile resembles closely the previously reported eSPNs (Saunders et al., 2018; Anderson et al., 2020) and/or D1-Pcdh8-SPNs (Gokce et al., 2016; Stanley et al., 2020). Adding to the characterization of this particular SPN group, the authors demonstrate that they project to the SNr, arguing for a close relationship with classical, striatonigral-projecting dSPNs (Martin et al., 2019). It is tempting to speculate that this newly identified SPN group therefore could be promoting locomotion as well.

ADVANCES AND LIMITATIONS

The scRNA-seq technology presents certain advantages over previous, population-based approaches such as BAC-TRAP, which is based on EGFP-tagging ribosomal subunits to investigate mRNA undergoing translation in specific cell types. This has been successfully used to describe transcriptome differences of striatal dSPNs and iSPNs (Heiman et al., 2008), and their changes in rodent models of disease (Heiman et al., 2014). However, not all genes that were identified as differentially expressed by BAC-TRAP were confirmed using scRNA-seq, with some apparently not being expressed in SPNs at all (Ho et al., 2018). Consulting complementary approaches (such as independent gene expression databases), it was concluded

that the BAC-TRAP results are likely false-positives caused by the sampling of interneurons and "contamination" by mRNA originating from cortical axons (Ho et al., 2018). This shows the utility of scRNA-seq in refining and advancing population-based findings.

On the other hand, the successful isolation of single-cells from a complex tissue is a major challenge for scRNA-seq studies. This is particularly true in a structure like the striatum, which receives a lot of short- and long-distance connections from various other brain areas. Even a simple variation of tissue thickness can be a major source of variability in cellular recovery (Ho et al., 2018). Differences in tissue extraction and cell isolation could therefore limit comparisons across different studies. The scRNA-seq studies reviewed here are however largely in line with each other, with a few minor discrepancies. For example, one study described *Otof* as a marker for eSPNs (Saunders et al., 2018), yet, others find that it also labels a class of GABAergic interneurons (Martin et al., 2019) or is co-expressed with *Penk* and *Tac1* in the ventral striatum (Stanley et al., 2020). Similarly, *Chrm4* was found to be a dSPN-specific gene in one (Ho et al., 2018), but not another study (Gokce et al., 2016). This is a particularly interesting point, because functionally, M4 muscarinic receptors (encoded by *Chrm4*) have been shown to selectively play a role in synaptic plasticity of dSPNs, but not iSPNs (Shen et al., 2015). These examples make the point that for the interpretation of scRNA-seq data validation through other experimental approaches is required. Since most of the neuronal (sub) types lack a single unique genetic marker but are rather defined by a combination of genes/markers, it still stands to question if these combinations (and resulting classifications) are functionally meaningful.

Nevertheless, scRNA-seq studies expanded our understanding of the heterogeneity in the striatum on several levels. First of all, they all confirm the clear distinction between dSPN and iSPNs. Secondly, they deciphered a transcriptional gradients coding for both the anatomical location of a given SPNs, as well as its compartmental identity. Additionally, most studies confirmed the existence of transcriptionally defined eSPNs or eSPN-like D1-Pcdh8-neurons (Gokce et al., 2016; Saunders et al., 2018; Anderson et al., 2020; Malaiya et al., 2020; Stanley et al., 2020), D1/D2-SPNs (Gokce et al., 2016; Martin et al., 2019; Anderson et al., 2020; Stanley et al., 2020) and exopatch neurons (Smith et al., 2016; Martin et al., 2019; **Figure 1B**).

But what is the importance of these newly defined SPN subpopulations? Their cellular physiology, intracellular signaling networks, morphology, and role in striatal behaviors have not been rigorously assessed, yet. However, clues about the importance of a dSPN subgroup in locomotor control have emerged from the study of PD and LID.

A NEW SUB-GROUP OF dSPNs CAUSES ABNORMAL MOVEMENTS?

L-DOPA treatment induces dyskinesia in PD patients and animal models. Strong evidence suggests that abnormal DA signaling and alteration of SPNs underlies aberrant movement control. Especially dSPNs seem to play a prominent role, even though iSPNs show dramatic alterations as well (Fieblinger et al., 2014; Suarez et al., 2014) and chemogenetic manipulation of both dSPNs and iSPNs proved necessary to elicit full LID symptoms in parkinonian mice (Alcacer et al., 2017). Interestingly, recent publications have now shown that not all (alleged) dSPNs react the same to L-DOPA in the parkinsonian brain, and furthermore, only some appear to be causally linked to abnormal involuntary movements.

A first study used targeted recombination in active populations (TRAP) to capture SPNs that express cFOS during dyskinetic episodes and found only a discrete subpopulation being TRAPed (Girasole et al., 2018). It largely, but not exclusively, consisted of dSPNs. Reactivation of this group—but not random dSPNs—using optogenetics induced dyskinetic behavior in the absence of L-DOPA. Inhibition of this TRAPed group conversely interrupts ongoing LID. In a follow-up article using *in vivo* single-cell recordings, it was shown that L-DOPA elicited high firing rates in a specific subset of dSPNs, whose firing rates also correlated with the severity of dyskinetic behavior (Ryan et al., 2018). This strongly suggests that not all dSPNs equally contribute to abnormal movements. What could be the reason for this? Using retroviral labeling of striatonigral SPNs in a rat model of PD we made a surprising finding: their response to L-DOPA was not uniform, but divided into two "clusters," with distinct morphological and electrophysiological characteristics (Fieblinger et al., 2018). While one subpopulation's morphological appearance resembled a typical dSPN in the parkinsonian striatum—with marked dendritic regression—the other showed signs of dendritic recovery. The latter were furthermore less excitable than their counterparts. It is known that L-DOPA treatment induces FosB in a subset of striatal neurons (Andersson et al., 1999; Pavon et al., 2006) and we observed that roughly half of the retrogradely labeled dSPNs showed FosB immunoreactivity. Interestingly, FosB staining was predominantly found in the dSPN subgroup that showed dendritic regrowth. Since FosB-expression has been causally linked to LIDs (Cao et al., 2010; Beck et al., 2019), it seems a plausible assumption that also this particular subgroup is specifically linked to LIDs. Each of these studies identified a subgroup of dSPNs through: (i) TRAP; (ii) firing activity; and (iii) cellular phenotype after L-DOPA treatment, that is specifically linked to LIDs (**Figure 1C**). Although lacking experimental evidence, it is tempting to speculate that this could be one and the same SPN group.

OUTLOOK

The scRNA-seq studies found evidence for distinct SPN groups outside the classical dSPNs and iSPNs, such as D1/D2-SPNs, eSPNs, and D1-Pcdh8-SPNs. They also demonstrate that transcriptomic heterogeneity plays an important role and differences (e.g., SPN sub-populations, anatomical location and compartmental identify) are coded through the combination of genes and along gradients, rather than in discrete steps.

As discussed, a current limitation to these scRNA-seq studies is that it has yet to be established if transcriptionally defined cell populations indeed have different functional properties, specific behavioral importance, or if they are particularly relevant in diseases like PD and LID. Previously, the generation of BAC transgenic mice and the restricted expression of fluorescent proteins or Cre-recombinase driven by a dSPN or iSPN specific promoter had provided an excellent tool to selectively investigate dSPN and iSPN functionality (Gong et al., 2003). Similar transgenic mouse lines targeting the new neuronal (sub-) groups identified by scRNA-seq would be highly useful to determine their function and advance our understanding of the striatal organization. However, since they are best defined not by a single, unique gene but rather by the combination of several genes, the development of such reporter mice will not be trivial. Until then, studies investigating the properties of these newly defined (sub-) groups will likely rely on anatomical allocation and/or *post hoc* identification e.g., using a combination of histological markers.

A noteworthy question is also how the different transcriptional gradients are created in SPNs. One potential way could be the differential use and regulation of transcription factors. Interestingly, it were also transcription factors (namely cFos and FosB) that guided the discovery of the LID-associated dSPN subgroup. It is tempting to speculate that this group could be identical, for example, with the newly identified SNr-projecting D1-Pcdh8-SPNs. However, this has to be established in future studies.

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A Novel Viewpoint on the Anticipatory Postural Adjustments During Gait Initiation

Veronica Farinelli[1], *Francesco Bolzoni*[1,2]*, *Silvia Maria Marchese*[1], *Roberto Esposti*[1] and *Paolo Cavallari*[1]

[1] Human Physiology Section of the Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy, [2] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

Anticipatory postural adjustments (APAs) are the coordinated muscular activities that precede the voluntary movements to counteract the associated postural perturbations. Many studies about gait initiation call APAs those activities that precede the heel-off of the leading foot, thus taking heel-off as the onset of voluntary movement. In particular, leg muscles drive the center of pressure (CoP) both laterally, to shift the body weight over the trailing foot and backward, to create a disequilibrium torque pushing forward the center of mass (CoM). However, since subjects want to propel their body rather than lift their foot, the onset of gait should be the CoM displacement, which starts with the backward CoP shift. If so, the leg muscles driving such a shift are the prime movers. Moreover, since the disequilibrium torque is mechanically equivalent to a forward force acting at the pelvis level, APAs should be required to link the body segments to the pelvis: distributing such concentrated force throughout the body would make all segments move homogeneously. In the aim of testing this hypothesis, we analyzed gait initiation in 15 right-footed healthy subjects, searching for activities in trunk muscles that precede the onset of the backward CoP shift. Subjects stood on a force plate for about 10 s and then started walking at their natural speed. A minimum of 10 trials were collected. A force plate measured the CoP position while wireless probes recorded the electromyographic activities. Recordings ascertained that at gait onset APAs develop in trunk muscles. On the right side, Rectus Abdominis and Obliquus Abdominis were activated in 11 and 13 subjects, respectively, starting on average 33 and 54 ms before the CoP shift; Erector Spinae (ES) at L2 and T3 levels was instead inhibited (9 and 7 subjects, 104 and 120 ms). On the contralateral side, the same muscles showed excitatory APAs (abdominals in 11 and 12 subjects, 27 and 82 ms; ES in 10 and 7 subjects, 75 and 32 ms). The results of this study provide a novel framework for distinguishing postural from voluntary actions, which may be relevant for the diagnosis and rehabilitation of gait disorders.

Keywords: APAs, trunk muscles, prime movers, ankle muscles, postural control, human

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***Correspondence:**
Francesco Bolzoni
francesco.bolzoni@unimi.it

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INTRODUCTION

Walking is one of the most common and natural motor actions performed in daily life. However, this naturalness requires a prolonged learning period in which the automatic stepping activity must be coupled with a postural control under development (Forssberg, 1999). The intrinsic complexity of this motor behavior is apparent when starting to walk (i.e., gait initiation), where the control of focal movement should be strictly coupled to a feedforward postural control. This has been described both in healthy children (Assaiante et al., 2000) and in patients suffering from different neurological conditions (Delval et al., 2014; Delafontaine et al., 2019; Farinelli et al., 2020; Palmisano et al., 2020). The "complexity of simplicity" becomes evident even to the walker when the physiological organization of the neural network underlying gait initiation is impaired, causing a dramatic deterioration of the self-confidence of the patient and increasing the risk of fall (Walton et al., 2015).

Before initiating a movement, throughout a top-down control, our brain shapes specific feedforward motor programs dispatched to the prime movers and to the postural muscles. The ensuing postural activities that precede the onset of the voluntary movement are called anticipatory postural adjustments (APAs). According to the literature (for a review, refer to Massion, 1992; Bouisset and Do, 2008; Cavallari et al., 2016), APAs are defined as muscular activities intended to prevent the mechanical perturbations caused by the focal movement, by building up fixation chains that link the body segments to the available support points. If not properly counterbalanced, these perturbations would affect, or even impede, the correct execution of the voluntary movement itself.

Gait initiation seemingly introduces an exception to this well-accepted definition of APAs. In fact, in this specific case, the literature calls APAs those muscular activities that produce a specific well-tailored perturbation of the equilibrium, i.e., the forward displacement of the center of mass (CoM) of a body, which is necessary to make the first step. This dichotomy in the definition of APA opens a question: are APAs involved in preserving the equilibrium or in disturbing it, or are they capable of both? What it may appear as a mere semantic issue becomes a crucial matter when studying gait initiation; in fact, the nervous system organizes the postural and voluntary component of the movements in different ways, and different involvements of these components may imply evident clinical repercussions (Takakusaki, 2017; de Lima-Pardini et al., 2020). For example, according to the hypotheses summarized in the review of Takakusaki, both the motor program for voluntary skilled movements and the program for the associated postural actions are processed with the contribution of the supplementary motor area (SMA) and premotor cortices. Then, the voluntary command is forwarded to the primary motor cortex (M1) and reaches the focal muscles through the lateral corticospinal tract, while the APA command follows the corticoreticular projections and reaches the postural muscles through the reticulospinal tract. This highlights how much the correct categorization of many muscular activities within a given action, distinguishing what is volitional and what regards postural control, would be relevant for a correct diagnosis of motor disturbances. Therefore, is it true that APAs play a different role in gait initiation than in other motor actions?

Approaching such "APA dualism" requires an insight into how the voluntary movement integrates with the postural actions. Prior to the onset of a voluntary movement, it is possible to identify changes in the activity of muscles directly responsible for the action (i.e., the prime movers) and that of muscles acting on the body support (i.e., postural muscles). The distinction between prime movers and postural muscles is apparent when considering upper limb movements in which postural muscles have a clear role in preserving the whole-body equilibrium (Bouisset and Zattara, 1981; Aruin and Latash, 1995). This distinction becomes less evident when a voluntary movement requires a change in the whole-body position, such as in gait initiation. In this case, the muscles acting on the body support surface produce mechanical actions that are fundamental for initiating the intended movement. It is also worth noting that while APAs preserving body equilibrium usually precede the voluntary movement by no more than about 200 ms, when initiating gait, the muscles acting on the support base are recruited much more in advance. Most of the literature agrees in identifying three phases in gait initiation: (i) the imbalance phase, which starts with the shift of the CoP backward and toward the future swing foot and ends with the heel-off; (ii) the unloading phase, from heel-off to toe-off of the swing foot, in which CoP shifts toward the future stance foot; and (iii) the swing phase, from toe-off to heel-strike, in which CoP moves forward (Crenna et al., 2006). Traditionally, the "APA" window coincides with the imbalance phase, lasting from the very first CoP shift to the onset of heel-off, thus covering a time period of around 500 ms for gait initiation at natural speed, down to 300 ms at maximal speed (Crenna and Frigo, 1991; Assaiante et al., 2000; for a review, refer to Yiou et al., 2017). This CoP movement is driven by the activities of ankle joint muscles: an inhibition of both Soleus (Sol) muscles, which are tonically active when standing, followed by the excitation of Tibialis Anterior (TA) muscles (about 100 ms later, for one of the first description, refer to Crenna and Frigo, 1991). Aiming at distinguishing these early activities, which alter the body equilibrium to ensure the adequate mechanical conditions for the planned action, from the classical APAs that preserve body equilibrium against the mechanical perturbation, Klous et al. (2012) called them early postural adjustments (EPAs) and also reported the different behavior of EPAs vs. APAs.

To solve such a question, we proposed to reconsider the subtle mechanical underpinnings of the action, so that to distinguish what is volitional and when the ensuing afferent information is generated: initiating gait means to project the CoM forward (Gélat et al., 2006). Such forward projection results from the misalignment between the center of pressure (CoP) and the vertical CoM projection onto the ground, so as to produce a disequilibrium torque that accelerates the CoM in the anterior direction (Brenière et al., 1987); therefore, such "loss of equilibrium" is the actual goal of prime mover activity. Moreover, the CoP movement is a remarkable source of afferent kinesthetic and cutaneous information (Meyer et al., 2004), thus what it may be called APA/EPA includes a time window in which this sensory

information can already lead to the feedback control of the motor command. However, this contrasts with the definition of APA/EPA as feedforward programmed motor activities. Thus, the motor activities planned in a merely feedforward manner should be looked for before the first CoP displacement. So far, Sol and TA activities have been indicated as APAs because their timing excludes any contribution of feedback afferent information. However, this single criterion is not sufficient to define Sol and TA activities as APAs. In fact, in view of their role in causing the initial CoM displacement, i.e., the gait initiation goal, TA and Sol should rather be the prime movers.

At this point, it becomes crucial to redefine what should it be the role of APAs in gait initiation. Arguing that the disequilibrium torque pushing the CoM forward is mechanically equivalent to a forward force acting at the pelvis level, it follows that such concentrated force should be distributed throughout the body so that all body segments move homogeneously. This requires "fixation chains" linking the various body segments to the pelvis, which now acts as the "support point." This leads the role of APAs in gait initiation back to the more general view, i.e., to prevent the perturbations caused by the focal movement.

According to this novel viewpoint, we would like to propose that (i) Sol and TA act as prime movers because they directly produce the intended forward displacement of the CoM, and (ii) APAs, in their literal acceptation, should be searched for before (or around) the backward CoP shift, in those muscles that link the various body segments to the pelvis. In this aim, we analyzed gait initiation in healthy subjects, searching for activities in upper and lower trunk muscles, accompanying in time the onset of the backward CoP shift.

MATERIALS AND METHODS

Participants and Experimental Protocol

We enrolled 15 healthy subjects (6 females) with the age of 23 ± 4 years (mean ± SD), the height of 1.73 ± 0.08 m, and the weight of 68.8 ± 12.7 kg. All participants were right-footed, as ascertained by asking them which leg they used for kicking a ball, stepping up on a chair, and leading off in the long jump, as well as by observing the limb they used to start walking.

All subjects were free of any musculoskeletal or neurological dysfunction and gave their written informed consent to the study. The experimental procedure was carried out in accordance with the standards laid down in the Declaration of Helsinki and approved by the "Comitato Etico di Ateneo dell'Università degli Studi di Milano" (counsel 6/19). Subjects were asked to perform a gait initiation task: standing on a force plate for 10 s and then begin walking at their natural speed in response to a vocal prompt. After collecting a minimum of 10 trials starting with the preferred right foot, subjects were asked to start walking with the contralateral non-preferred foot, for a minimum of 10 more trials.

Recordings

A dynamometric force plate (9286AA, KISTLER, Winterthur, Switzerland) was used to compute the CoP position. Wireless probes (FREEEMG 1000, BTS, Italy) were employed bilaterally to record the surface electromyographic (EMG) activity of TA, Sol, Rectus Abdominis (RA), Obliquus Abdominis (OA), Erector Spinae at L2 vertebra (ES-L), Erector Spinae at T3 (ES-T), Semispinalis Capitis (SC), and Deltoideus Anterior (DA). Electrodes were placed according to the Surface Electromyography for the Non-Invasive Assessment of Muscles (SENIAM) guidelines (Hermens et al., 2000). Body kinematics was recorded through an eight-camera optoelectronic system (SMART-DX, BTS, Milan, Italy) using a full-body marker set (Ferrari et al., 2008), which allowed estimating the CoM and the heel-off events. Synchronous data acquisition was accomplished by the SMART-DX workstation; the sampling rate being 100 Hz for optoelectronic cameras, 400 Hz for dynamometric signals, and 1,000 Hz for EMG.

Data Processing

The analysis aimed at highlighting APAs accompanying the first backward displacement of the CoP, which marks the onset of the afferent signals produced by the voluntary recruitment of the gait prime mover muscles. The data analysis approach replicated that used by Marchese et al. (2019). In brief, the raw EMG data were high-pass filtered with a zero-phase shift sixth-order elliptic filter and a cut-off frequency of 50 Hz, to remove movement artifacts. For abdominal muscles, the cut-off frequency was set to

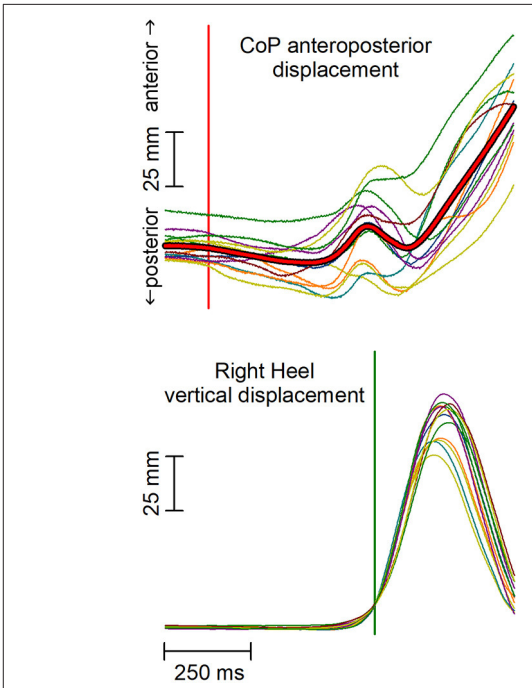

FIGURE 1 | Anterior-posterior (AP) displacement of the center of pressure (CoP) and vertical displacement of the leading heel in a representative subject. Thin traces represent single trials, which are time aligned to the heel-off (vertical green line). Red thick trace in the upper plot represents the average CoP displacement. Notably, the high trial-by-trial variability of CoP makes the automatic identification of the CoP onset difficult and error-prone in each single trial. The vertical red line marks the CoP shift onset as identified on the average CoP trace.

TABLE 1 | Mean latency of anticipatory postural adjustments (APAs) with SD (in parentheses) for each postural muscle when starting gait with the preferred limb.

Starting gait with the preferred right limb				
Muscle	**Leading side**		**Trailing side**	
	Mean latency (ms)	**Occurrence**	**Mean latency (ms)**	**Occurrence**
RA	−33 (101)	*N* = 11, 73% (45–92)	−27 (48)	*N* = 11, 73% (45–92)
OA	−54 (101)	*N* = 13, 87% (59–98)	−82 (95)	*N* = 12, 80% (52–96)
ES-L	−104 (89)	*N* = 9, 60% (32–84)	−75 (96)	*N* = 10, 67% (38–88)
ES-T	−120 (75)	*N* = 7, 47% (21–73)	−32 (69)	*N* = 7, 47% (21–73)
			−113	*N* = 1, 7% (0.2–32)
SC	−38 (85)	*N* = 5, 33% (12–62)	−112 (88)	*N* = 3, 20% (4–48)
	−75	*N* = 1, 7% (0.2–32)	−10 (123)	*N* = 2, 13% (1.7–40)
DA	−10 (48)	*N* = 6, 40% (16–68)	93 (88)	*N* = 2, 13% (1.7–40)

Latency was measured with respect to the onset of the backward center of pressure (CoP) shift, negative values indicate that the APA started before the CoP shift, and N is the number of subjects that showed the APA, also expressed as a percentage with 95% CI (in parentheses). The color shows the pattern: red for excitation and blue for inhibition.

TABLE 2 | Mean latency of APAs with SD (in parentheses) for each postural muscle when starting gait with the non-preferred limb.

Starting gait with the non-preferred left limb				
Muscle	**Leading side**		**Trailing side**	
	Mean latency (ms)	**Occurrence**	**Mean latency (ms)**	**Occurrence**
RA	−68 (74)	*N* = 6, 40% (16–68)	−79 (101)	*N* = 9, 60% (32–84)
OA	−51 (94)	*N* = 7, 47% (21–73)	−74 (83)	*N* = 8, 53% (27–79)
ES-L	−106 (44)	*N* = 6, 40% (16–68)	16 (70)	*N* = 5, 33% (12–62)
	24	*N* = 1, 7% (0.2–32)	−72 (39)	*N* = 2, 13% (2–40)
ES-T	−48 (82)	*N* = 6, 40% (16–68)	−17 (65)	*N* = 5, 33% (12–62)
SC	0.5 (68)	*N* = 4, 27% (8–55)	69 (35)	*N* = 2, 13% (2–40)
	83 (18)	*N* = 2, 13% (2–40)	−40	*N* = 1, 7% (0.2–32)
DA	−58 (54)	*N* = 3, 20% (4–48)	66 (13)	*N* = 2, 13% (2–40)

Latency was measured with respect to the onset of the backward CoP shift, negative values indicate that the APA started before the CoP shift, and N is the number of subjects that showed the APA, also expressed as a percentage with 95% CI (in parentheses). The color shows the pattern: red for excitation and blue for inhibition.

150 Hz to remove the cardiac artifacts. Traces were then full-wave rectified, without applying any smoothing, then time-aligned to the heel-off of the leading foot, and averaged across trials. The heel-off was automatically identified as the time in which the heel marker raised 10 mm above its quiet standing value; this signal was chosen for time alignment instead of the CoP shift due to the much higher trial-by-trial variability of the CoP traces (**Figure 1**). The same averaging procedure was applied to CoP and CoM traces. All subsequent measurements were taken by a software algorithm on the averaged traces and visually validated.

First, the onset of the backward CoP shift was extracted by seeking for the first point in which the trace fell below −2 SD with respect to the mean level recorded from 3 to 1 s prior to heel-off and remained below that value for at least 50 ms. When this criterion was met, the algorithm searched backward the point where the trace started deviating from such mean level. Time 0 was then assigned to CoP onset.

Thereafter, the same algorithm was applied to identify the EMG changes by (i) integrating the trace with a 25-ms running average window, (ii) measuring the mean level and SD of the trace from 3 to 1 s before the CoP shift (baseline time window), and (iii) setting the searching threshold to mean +2 SD for excitation and mean −2 SD for inhibition. The algorithm search was restrained into two time windows: from −300 to +100 ms with respect to CoP onset, in order to identify APAs, and from +100 ms to heel-off, in order to identify those later changes in EMG activity of postural muscles that precede the heel-off.

Statistical Analysis

Due to the lack of appreciable APAs and/or later EMG changes in one or more muscles of several subjects, it was not possible to fill up a complete repeated measures design on latency. Therefore, such values were not statistically compared but only reported as means and SD, together with the occurrence of such APAs. The occurrence was expressed both in terms of the number of subjects showing APAs and in percentage with the corresponding 95% CI (**Tables 1**–**4**), calculated according to the Clopper–Pearson "exact" method.

With regard to the APA occurrence data in each postural muscle and subject (i.e., 1 for presence and 0 for absence), the Aligned Rank Transformation Tool (Wobbrock et al., 2011) was applied to correct for the non-Gaussianity. The transformed

TABLE 3 | Mean latency of the change in electromyographic (EMG) activity occurring between CoP onset and heel-off, with SD (in parentheses), when starting gait with the preferred limb.

Starting gait with the preferred right limb				
Muscle	**Leading side**		**Trailing side**	
	Mean latency (ms)	**Occurrence**	**Mean latency (ms)**	**Occurrence**
RA	404 (108)	*N* = 13, 87% (59–98)	498 (131)	*N* = 12, 80% (52–96)
OA	397 (90)	*N* = 15, 100% (78–100)	425 (158)	*N* = 15, 100% (78–100)
ES-L	308 (159)	*N* = 15, 100% (78–100)	333 (119)	*N* = 14, 67% (38–88)
ES-T	258 (132)	*N* = 13, 87% (59–98)	380 (87)	*N* = 13, 87% (59–98)
SC	329 (145)	*N* = 13, 87% (59–98)	390 (114)	*N* = 10, 67% (38–88)
			371	*N* = 1, 7% (0.2–32)
DA	340 (117)	*N* = 13, 87% (59–98)	441 (84)	*N* = 11, 73% (45–92)

Latency was measured with respect to the onset of the backward CoP shift, all values are positive since these EMG changes started after the CoP shift, N is the number of subjects that showed the EMG change, also expressed as a percentage with 95% CI (in parentheses). The color shows the pattern: red for excitation and blue for inhibition.

TABLE 4 | Mean latency of the change in EMG activity occurring between CoP onset and heel-off, with SD (in parentheses), when starting gait with the non-preferred limb.

Starting gait with the non-preferred left limb				
Muscle	**Leading side**		**Trailing side**	
	Mean latency (ms)	**Occurrence**	**Mean latency (ms)**	**Occurrence**
RA	336 (106)	*N* = 12, 80% (52–96)	373 (144)	*N* = 12, 80% (52–96)
OA	375 (107)	*N* = 13, 87% (59–98)	392 (118)	*N* = 14, 67% (38–88)
ES-L	325 (98)	*N* = 12, 80% (52–96)	330 (79)	*N* = 13, 87% (59–98)
ES-T	341 (93)	*N* = 12, 80% (52–96)	384 (111)	*N* = 11, 73% (45–92)
SC	360 (143)	*N* = 12, 80% (52–96)	477 (94)	*N* = 6, 40% (16–68)
DA	386 (102)	*N* = 7, 47% (21–73)	402 (158)	*N* = 10, 67% (38–88)

Latency was measured with respect to the onset of the backward CoP shift, all values are positive since these EMG changes started after the CoP shift, and N is the number of subjects that showed the EMG change, also expressed as a percentage with 95% CI (in parentheses). Red color indicates excitation.

data were then analyzed by a three-way ANOVA with repeated measures. The factors were *Muscle* (RA vs. OA vs. ES-L vs. ES-T vs. SC vs. DA), *Starting limb* (right vs. left) and *Body side* (leading vs. trailing), Thereafter, Tukey *post-hoc* tests were run on significant effects. The significance threshold was set at $p < 0.05$.

RESULTS

EMG Activity Preceding the Backward CoP Shift

Starting Gait With the Preferred Limb

In the majority of the subjects, APAs were observed in the EMG activity of the dorsal and ventral muscles of the trunk. In particular, on the side of the leading limb (right), RA and OA were activated while ES-L and ES-T were inhibited before the backward CoP shift (**Figure 2**). Such shift was driven by the coordinated bilateral inhibition of Sol and activation of TA, which thus act as prime mover muscles (**Figures 2**, **3**). On the contralateral side, both abdominal and spinal muscles mainly showed excitatory APAs accompanying the CoP shift, while TA and Sol maintained the same pattern exhibited on the leading side (**Figure 3**). With regard to the SC muscles, APAs could be recorded in less than half of the subjects who mainly showed an inhibitory APA on the leading side. Instead, on the trailing side, three subjects showed excitatory APAs and two displayed inhibitory ones. Even fewer subjects showed APAs in DA muscles, who were excited on both body sides. **Table 1** reports the average latency of APAs for each postural muscle, the number of subjects that showed them, and the resulting percentage of occurrence with its 95% CI.

Starting Gait With the Non-preferred Limb

When subjects were asked to start gait with their non-preferred limb (left), overall, they showed the same APA pattern observed when starting with the right limb (**Table 2**). RA and OA developed excitatory APAs on both body sides while ES-L and ES-T mainly showed inhibitory APAs on the leading side (now the left one) and excitatory APAs on the trailing side. Considering SC, APAs were mainly inhibitory on the leading side and excitatory on the contralateral one, but such prevalence was less strong than when starting gait with the preferred limb (**Tables 1**, **2**). Finally, very few subjects showed APAs in DA, excitatory in all cases. It is apparent from **Tables 1** and **2** that the occurrence

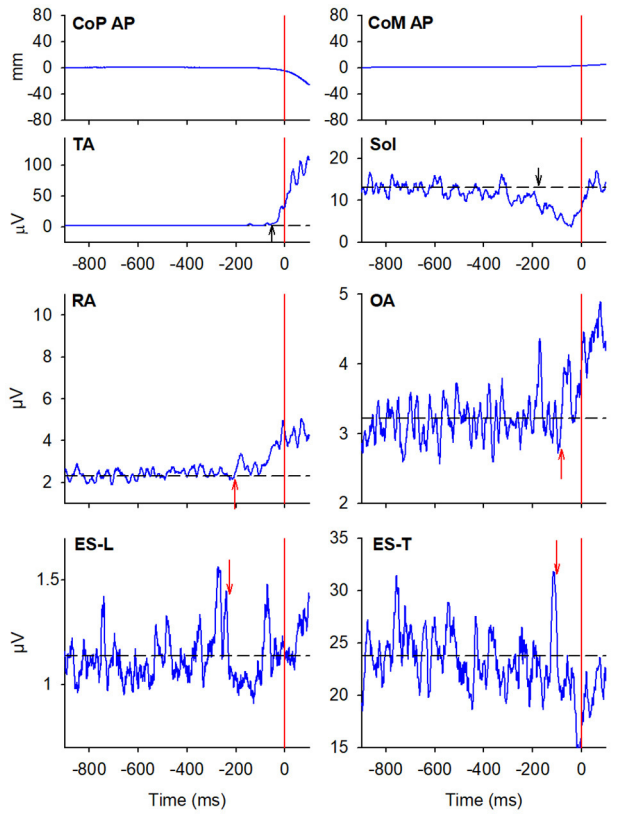

FIGURE 2 | The two uppermost plots display the AP displacements of CoP and center of mass (CoM) in a representative subject when starting gait. Vertical red lines at time 0 mark the onset of the backward CoP shift. The remaining plots show the EMG activity recorded in the prime movers Tibialis Anterior (TA) and Soleus (Sol), as well as in trunk postural muscles Rectus Abdominis (RA), Obliquus Abdominis (OA), Erector Spinae at L2 vertebra (ES-L), and Erector Spinae at T3 (ES-T) of the leading side (right). Arrows in each EMG plot mark the onset of excitation (upward arrow) or inhibition (downward arrow). Black dashed lines represent the average muscle activity in the baseline time window.

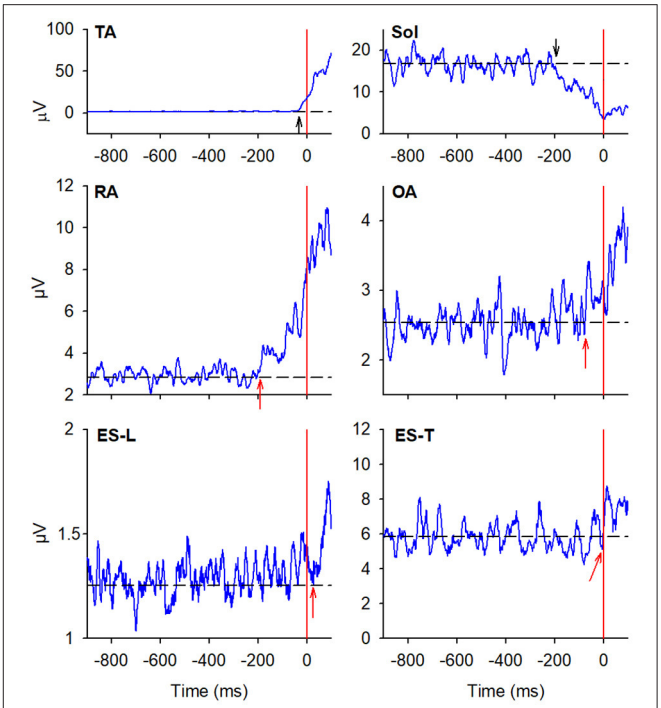

FIGURE 3 | EMG activity in the prime mover (TA and Sol) and trunk postural muscles (RA, OA, ES-L, and ES-T) recorded on the trailing side (left) of the same representative subject as in **Figure 2**. Vertical red lines at time 0 mark the onset of the backward CoP shift. Arrows in each EMG plot mark the onset of excitation (upward arrow) or inhibition (downward arrow). Black dashed lines represent the average muscle activity in the baseline time window.

of APAs, regardless of their sign, decreased when passing from abdominal (RA and OA) to dorsal (ES-L and ES-T) to upper trunk muscles (SC and DA). Moreover, APA occurrence was lower when starting gait with the non-preferred limb vs. the preferred one.

Statistics confirmed these observations by revealing a main effect of *Muscle* ($F_{5,70} = 5.75$, $p < 0.0002$) and *Starting limb* ($F_{1,14} = 14.07$, $p = 0.0021$), while the main effect of *Body side* and all *interactions* were non-significant (in all cases, $p > 0.48$). *Post hoc* on the *Muscle* effect discovered that APA occurrence was lower in DA than in RA, OA, and ES-L ($p < 0.013$) as well as in SC than in OA ($p = 0.025$). Similar conclusions were obtained if considering only those APAs whose sign was prevalent (e.g., only the three excitatory APAs in the SC of the trailing side when starting with the right limb). In this case, the APA occurrence in SC was significantly lower than in RA, OA, and ES-L ($p < 0.032$). In conclusion, a structured pattern of APAs was observed in trunk muscles before the first backward CoP shift. However, such APAs were less frequent than the muscular actions which current literature reports to occur during the imbalance phase (i.e., between CoP shift and heel-off).

EMG Activity Before Heel-Off

In general, EMG changes preceding the heel-off were larger than APAs preceding the CoP shift and could be easily observed in more subjects, especially in ES, SC, and DA muscles. Moreover, such changes were excitatory in all but one case.

Starting Gait With the Preferred Limb

In almost all the experimental subjects, another change in muscular activity preceded the heel-off event. On the leading right side, in RA and OA, a second EMG burst anticipated the heel-off and followed that linked to the CoP shift (see above). Instead, the inhibitory APA observed in ES-L and ES-T, shown in **Figure 2**, turned into excitation before heel-off (**Figure 4**; **Table 3**). Also on the contralateral side, almost all subjects showed a new burst after the excitatory APA, in both ventral (RA and OA) and dorsal (ES-L and ES-T) muscles (**Figure 5**; **Table 3**). With regard to the SC muscles, the new change in EMG activity was mainly excitatory on both body sides and was observed in more subjects than before the CoP shift (**Tables 1**, **3**). The increase in occurrence was also evident in DA muscles, in which the new EMG change was also excitatory.

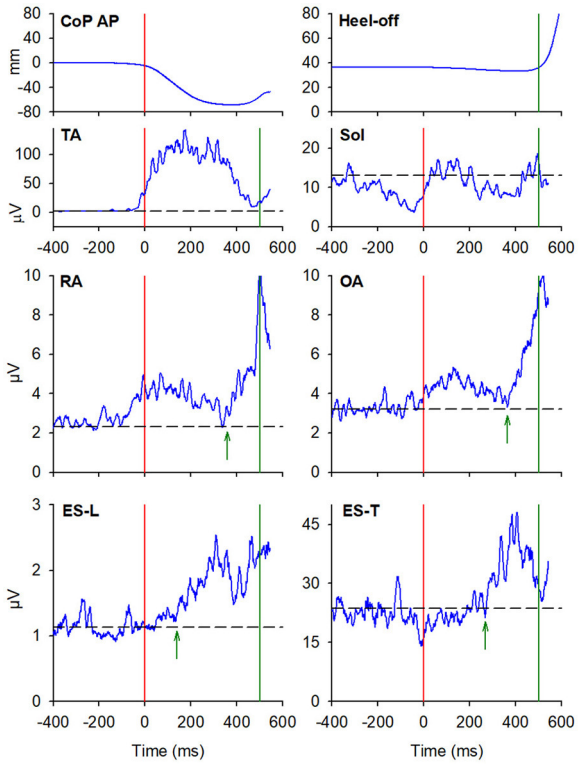

FIGURE 4 | The two uppermost plots display the AP displacements of CoP and the vertical displacement of the leading heel, in the same representative subject of **Figures 2**, **3**, when starting gait. Vertical red lines at time 0 mark the onset of the backward CoP shift while vertical green lines mark the heel-off. The remaining plots show the EMG activity recorded in the prime mover (TA, Sol) and trunk postural muscles (RA, OA, ES-L, ES-T) of the right leading side. Green arrows in each plot mark the onset of the changes in EMG activity that follow the CoP onset and precede the heel-off. Black dashed lines represent the average muscle activity in the baseline time window.

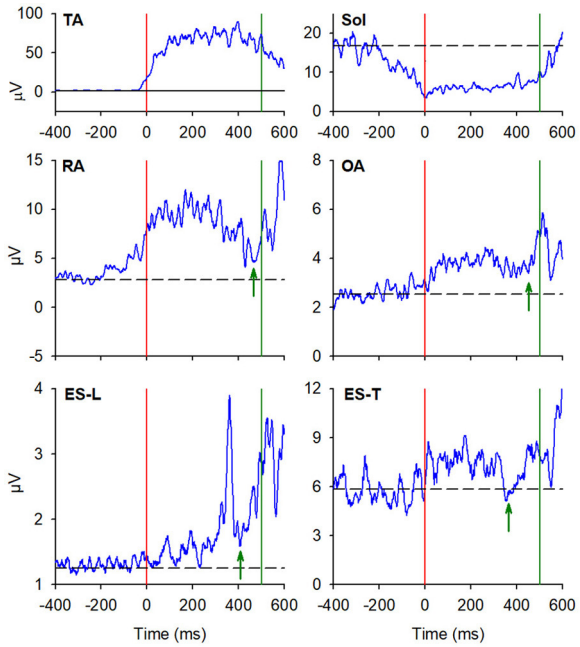

FIGURE 5 | EMG activity in the prime mover (TA and Sol) and trunk postural muscles (RA, OA, ES-L, and ES-T) recorded on the trailing left side of the same representative subject of **Figures 2**, **3**. Vertical red lines at time 0 mark the onset of the backward CoP shift while vertical green lines mark the heel-off. Green arrows in each plot mark the onset of the second changes in EMG activity that, once more, follow the CoP onset and precede the heel-off. Black dashed lines represent the average muscle activity in the baseline time window.

Starting Gait With the Non-preferred Limb

When starting gait with the Non-preferred left limb, subjects generally showed the same pattern of excitatory EMG changes preceding heel-off as that observed when starting with the preferred limb (**Table 4** vs. **Table 3**). However, the occurrence of such EMG changes was somewhat lower, replicating what happened for the APAs accompanying the CoP shift (**Table 2** vs. **Table 1**).

DISCUSSION

To the best of our knowledge, this is the first study that systematically describes changes in trunk muscle activities preceding the backward CoP shift. Based on these observations, we reconsidered the organization of the posturo-kinetic chain related to gait initiation, in which the Sol and TA activity should no longer be considered APAs but rather as the expression of the motor command to prime movers.

A possible limitation of this study is that we did not apply EMG amplitude normalization, which prevented us from showing average traces from the entire population. Our choice was supported by the difficulty of obtaining reliable standard recordings from which to extract normalization factors. In fact, maximal voluntary contraction is particularly difficult in trunk muscles due to complex muscle synergies. Furthermore, considering that some of the recorded muscles are silent in quiet standing, using activity during that period as a normalization factor would actually be misleading.

Nevertheless, the results of this study not only confirmed the known postural activity preceding heel-off but also showed the existence of a structured pattern of anticipatory activities linked to the CoP shift, i.e., well before (about 400 ms) the muscular activity preceding heel-off. Taking into account that no gait-related afferent signals should precede the CoP shift, the first EMG changes observed in trunk muscles should be the expression of feedforward postural adjustments, i.e., APAs. Furthermore, these activities are also consistent with gait initiation mechanics. As stated in the "Introduction" section, the backward CoP shift exploits the body weight to produce a disequilibrium torque that pushes the pelvis forward and the feet backward. If this action occurred on a low friction surface, such as on ice, all the body would rotate forward around the pelvis (where CoM lies) and fall, without a net horizontal shift of the CoM. On the ground, instead, the frictional reaction force supports a forward CoM shift, promoting the first step. The force acting at the pelvis is then distributed throughout the body so that all segments move forward homogeneously. This requires

APAs to build up "fixation chains" between the various body segments and the pelvis, which now acts as the "support point." In fact, the bilateral activation of RA and OA, coupled to the reciprocal antagonist action of ES-L and ES-T on the trailing vs. leading side, stiffen the trunk to follow the forward pelvis displacement and its simultaneous rotation toward the trailing side. Thus, in view of their timings and mechanical actions, the trunk muscle activities linked to the CoP shift should be the actual APAs of gait initiation, a view that leads back such APAs to the more general definition, i.e., APAs aim at preventing the perturbations acting on the body. The same stiffening action may also be observed in the DA muscles: their activity observed in the earliest phase of gait is seemingly aimed at contrasting the arm inertia and at transmitting the forward motion of the trunk also to the upper limb. In fact, during gait initiation, the arm swing does not yet occur; it will become apparent only during walking. In this view, DA acts as a postural muscle, in the same way as the trunk muscles.

So far, only a few studies have searched for activities in trunk muscles linked to gait initiation. Despite the recordings reported in some of those studies (Assaiante et al., 2000; Wang et al., 2005, 2017; Ceccato et al., 2009; Rum et al., 2021) encompassed the initial backward shift of CoP, no description was provided for EMG activities preceding such shift, while changes occurring between CoP shift and heel-off were systematically reported. Assaiante et al. (2000) studied the development of postural chains in children, showing an excitation occurring in both extensor and flexor muscles of the trunk, only on the swing side, about 200 ms before heel-off, i.e., 300 ms after the CoP shift. Ceccato et al. (2009) later confirmed this finding in adults, by bilaterally recording ES muscles at several spinal levels and reporting that, in a comparable time window, excitatory EMG changes occurred on the swing side. Instead, Maslivec et al. (2018) reported a bilateral excitation in sternocleidomastoid and ES muscles (at T9 and L3 level), again after the backward CoP shift, with a larger delay in sternocleidomastoid in older subjects. The bilateral activation of cervical and thoracic ES in elder subjects is appreciable also in the study by Rum et al. (2021), again about 200 ms after the CoP shift. Wang et al. (2005, 2006, 2017) dedicated several studies to this topic. In some studies, they considered a time window including the first CoP shift and recorded activities in trunk muscles on the right side (Wang et al., 2005, 2006, 2017). Illustrations in these reports confirmed that dorsal and ventral muscles are excited before heel-off, both when starting with the dominant right limb and with the contralateral one.

Notably, all the above mentioned studies described muscular activities occurring before heel-off but after the CoP shift; none of them explicitly reported pre-CoP shift activities similar to those we described in this study. However, considering that the pre-heel-off activities reported in the literature are comparable to what we have shown in **Figures 4**, **5**, we feel confident that our methodological approach and data analysis provided reliable results. Since we observed that APAs before the CoP shift are apparently smaller, less frequent, and less systematic than the excitations preceding heel-off (compare **Tables 3**, **4** with **Tables 1**, **2**), maybe the above cited authors simply neglected them.

In our experiments, the occurrence of APAs in trunk muscles was significantly lower when starting gait with the non-preferred limb and decreased when passing from abdominal to dorsal and then to upper trunk muscles. In this regard, the higher APA occurrence when starting gait with the preferred foot agrees with studies showing a relationship between APA pattern and lateral dominance (Teyssèdre et al., 2000; Bruttini et al., 2016). Being the result of the feedforward control, APAs should be based on the previous motor learning processes (Massion, 1998); from this perspective, starting gait with the preferred foot is seemingly the most trained motor plan, also from a postural point of view.

Finally, a specific comment deserves TA and Sol activities, which are repeatedly reported in the literature as anticipatory adjustments preceding the CoP shift (Brenière and Do, 1991; Crenna and Frigo, 1991; refer to Yiou et al., 2017 for a review). As already stated in the "Introduction" section, initiating gait means to project the CoM forward (Gélat et al., 2006). In this regard, the bilateral inhibition of the tonic Sol activity followed by the excitation of both TAs actually drives the backward CoP shift and the ensuing CoM displacement. Therefore, TA and Sol act as prime movers, not as postural muscles. In fact, the anticipation of muscle recruitment with respect to the onset of afferent signals (i.e., CoP shift) and the fact that such recruitment scales with the intended gait velocity (Crenna and Frigo, 1991; Lepers and Brenière, 1995) are two shared properties of both APAs and prime mover activities. Thus, such properties do not allow distinguishing between the two categories. Instead, the functional differences should be searched for in their mechanical roles: counterbalancing the perturbation (APAs) vs. driving the focal movement (prime movers).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico di Ateneo dell'Università degli Studi di Milano (counsel 6/19). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PC: conceptualization, funding acquisition, and supervision. VF, FB, SM, and RE: investigation and formal analysis. VF and FB: writing—original draft preparation. VF, FB, SM, RE, and PC: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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SYSTEMATIC REVIEW
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Repeated Gait Perturbation Training in Parkinson's Disease and Healthy Older Adults: A Systematic Review and Meta-Analysis

Femke Hulzinga[1], Veerle de Rond[1], Britt Vandendoorent[1], Moran Gilat[1], Pieter Ginis[1], Nicholas D'Cruz[1], Christian Schlenstedt[2,3] and Alice Nieuwboer[1]*

[1] Neuromotor Rehabilitation Research Group, Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium,
[2] Department of Neurology, University Hospital Schleswig-Holstein, Christian-Albrechts-University Kiel, Kiel, Germany,
[3] Institute of Interdisciplinary Exercise Science and Sports Medicine, Department Performance, Neuroscience, Therapy and Health, Medical School Hamburg, Hamburg, Germany

Background: Gait impairments are common in healthy older adults (HOA) and people with Parkinson's disease (PwPD), especially when adaptations to the environment are required. Traditional rehabilitation programs do not typically address these adaptive gait demands in contrast to repeated gait perturbation training (RGPT). RGPT is a novel reactive form of gait training with potential for both short and long-term consolidation in HOA and PwPD. The aim of this systematic review with meta-analysis is to determine whether RGPT is more effective than non-RGPT gait training in improving gait and balance in HOA and PwPD in the short and longer term.

Methods: This review was conducted according to the PRISMA-guidelines and pre-registered in the PROSPERO database (CRD42020183273). Included studies tested the effects of any form of repeated perturbations during gait in HOA and PwPD on gait speed, step or stride length. Studies using balance scales or sway measures as outcomes were included in a secondary analysis. Effects of randomized controlled trials (RCT) on RGPT were pooled using a meta-analysis of final measures.

Results: Of the 4421 studies, eight studies were deemed eligible for review, of which six could be included in the meta-analysis, totaling 209 participants (159 PwPD and 50 HOA). The studies were all of moderate quality. The meta-analysis revealed no significant effects of RGPT over non-RGPT training on gait performance (SMD = 0.16; 95% CI = −0.18, 0.49; $Z = 0.92$; $P = 0.36$). Yet, in some individual studies, favorable effects on gait speed, step length and stride length were observed immediately after the intervention as well as after a retention period. Gait variability and asymmetry, signifying more direct outcomes of gait adaptation, also indicated favorable RGPT effects in some individual studies.

Conclusion: Despite some promising results, the pooled effects of RGPT on gait and balance were not significantly greater as compared to non-RGPT gait training in PwPD and HOA. However, these findings could have been driven by low statistical power. Therefore, the present review points to the imperative to conduct sufficiently powered RCT's to verify the true effects of RGPT on gait and balance in HOA and PwPD.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php? Identifier: CRD42020183273.

Keywords: gait adaptation, split-belt, treadmill, rehabilitation, consolidation, Parkinson's disease

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****Correspondence:***
Femke Hulzinga
femke.hulzinga@kuleuven.be

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INTRODUCTION

Gait impairments in the aging population are related to falls and have other serious repercussions, such as that they are associated with reduced physical activity levels (Campbell et al., 1989; Seematter-Bagnoud et al., 2006). Gait impairments and their negative consequences are further exacerbated in people with Parkinson's disease (PwPD) (Bouça-Machado et al., 2020). The neuropathology of PD progressively affects the locomotor network, particularly the striatal circuitry and alters the cerebellar involvement in adapting gait to environmental changes (la Fougère et al., 2010; Bohnen and Jahn, 2013; Hinton et al., 2019). Gait adaptation is required when the gait pattern needs to be adjusted, for instance, during the transition from straight walking to a turn. Adjusting one's gait to unexpected environmental changes additionally involves reactive postural control, which is also compromised in older adults and especially in PwPD (Benatru et al., 2008; Süptitz et al., 2013). Impairments to adjust gait become more and more apparent in PwPD with disease progression. These impairments also frequently trigger episodes of freezing of gait (FOG) in PwPD (Nutt et al., 2011), thereby further increasing the risk of falling (Deandrea et al., 2010; Weaver et al., 2016). Falls are a major burden for the aging population and more so in PwPD, where approximately 60% experience repeated falls (Wood et al., 2002; Balash et al., 2005). This poses one of the most important hurdles for clinical management of PwPD, as falls and FOG are largely refractory to medication (Curtze et al., 2015; McKay et al., 2019). All of the above stresses the need for training interventions to safely improve adaptive mobility in PwPD and healthy older adults (HOA).

Several training modalities can improve ambulation and thereby decrease the risk of falling (Canning et al., 2015; Sherrington et al., 2017). Regular treadmill training has been shown to be effective in improving gait parameters, such as speed and stride length in both HOA and PwPD (Tomlinson et al., 2012; Mehrholz et al., 2016), especially when a cognitive challenge is added to the motor training (Mirelman et al., 2016). Moreover, combining balance and strength training has shown to bring benefits for mobility and falls (Sherrington et al., 2020). However, these traditional rehabilitation programs do not directly address the typical demands of ambulation in natural environments, particularly with regard to adapting to asymmetrical demands induced by the need to make turns and directional changes (Mehrholz et al., 2016).

Repeated gait perturbation training (RGPT) is a relatively novel training concept that addresses gait adaptation and reactive balance. RGPT consists of unexpected perturbations, such as push and pulls, applied by a trainer or a cable system during walking. Additionally, novel concepts of treadmill training have emerged under the impetus of technological advances. These modalities include the ability to offer translations of the walking surface (Mansfield et al., 2010), acceleration and deceleration of the treadmill or changes in gait asymmetry imposed by split-belt-treadmills, whereby the gait speed of each leg can be controlled independently (Seuthe et al., 2019). Repeated exposure to such perturbations may have lasting effects on the ability to modulate walking and reduce falls (Gerards et al., 2017). Encouragingly, our group recently evaluated a single session of split-belt training in HOA and PwPD, showing beneficial effects on gait adaptation and turning performance that were retained for at least 24 hours (D'Cruz et al., 2020; Seuthe et al., 2020).

Apart from mimicking daily life mobility, RGPT may prove beneficial by tapping into a more reactive and subconscious way of motor learning. Indeed, PwPD and HOA to a lesser degree, rely heavily on attentional strategies during gait performance as a result of reduced motor automaticity (Montero-Odasso et al., 2012; Wu et al., 2015). Consequently, they become less able to deal with consecutive attention-requiring environmental demands (Hausdorff et al., 2006). A reactive training strategy, such as RGPT, whereby participants need to adapt their gait to sudden perturbations without prior awareness of the precise timing of perturbations is thought to modulate gait automatically via cerebellar locomotor circuits, rather than overloading the cortical frontal and anterior-basal ganglia (BG) attentional reserves (Hausdorff et al., 2006; Sarter et al., 2014). In line with this notion, Marinelli et al. (2017) proposed that training, which is not relying on attentional strategies or conscious awareness of the learning process, may still be preserved in PwPD (in some paradigms) due to cerebellar compensatory contributions (Marinelli et al., 2017). As such, RGPT training may boost the compensatory cerebellar circuits, reducing attentional demand during adaptive gait in PwPD and HOA.

Following the initial reactive response to the perturbation, conscious awareness of the perturbation likely becomes involved to some degree in the control of the subsequent gait cycles. This goal-directed aspect of RGPT likely taps into the anterior BG circuits that are relatively spared in PwPD and may assist in the acquisition of new adaptive gait strategies (Marinelli et al., 2017). Unfortunately, consolidation of new motor engrams is rather impaired in PwPD due to altered processing in the posterior BG circuits (Marinelli et al., 2017), and it therefore remains to be determined how well PwPD can retain the beneficial effects of RGPT training. All in all, the training of both reactive and goal-directed processing of gait via RGPT has potential to herald larger effects on gait in PwPD than non-RGPT types of gait training. In the present review, we therefore reviewed the literature to explore the notion that RGPT may lead to improved gait and retention in PwPD and HOA by boosting "adaptive learning" pathways (Jayaram et al., 2011; Marinelli et al., 2017).

Previous reviews summarizing the effects of perturbation training focused mainly on young and older healthy adults and a combination of neurological populations (e.g., stroke, Parkinson's disease) (Mansfield et al., 2015; Gerards et al., 2017; Papadimitriou and Perry, 2017). The meta-analysis conducted by Mansfield et al. (2015), including both older adults and patients with varying neurological disorders, showed that perturbation training could significantly reduce falls when compared to control interventions without perturbation training (RR = 0.54; 95% CI = 0.34,0.85; $P = 0.007$) (Mansfield et al., 2015). These results were corroborated by Gerards et al. (2017) who concluded in their review that perturbation training is effective

in reducing falls, and that treadmill-based systems and therapist-applied perturbations are likely the most feasible approaches for perturbation training (Gerards et al., 2017). The meta-analysis by Papadimitriou and Perry (2017) further showed that perturbation training reduced falls in the laboratory for both older and younger adults 6-fold compared to the non-perturbation control groups (Papadimitriou and Perry, 2017). Taken together, prior reviews indicated beneficial effects of perturbation training for reducing falls. However, no review has focused specifically on gait perturbation training in PwPD. Given that PD is a complex multi-system disorder affecting both motor and non-motor symptoms that respond variably to therapy, generalizability of findings from prior reviews on healthy adults or other neurological disorders to PD is limited. As such, in this systematic review we set out to evaluate the evidence for immediate and long-term effects of repeated gait perturbation training (i.e., RGPT) on gait outcomes in PwPD and HOA. Therefore, the aim of this systematic review with meta-analysis is to ascertain whether RGPT is more effective in improving gait performance, expressed here as improvements in gait speed, step or stride length, in HOA and PwPD, as compared to other non-perturbation-based gait interventions. In addition, we aim to assess the impact of RGPT on balance performance as a secondary endpoint. We hypothesized that, via the modulation of "adaptive learning" circuits and eventually reduced needs for attentional processing, RGPT would prove more efficacious for improving gait performance (i.e., gait speed, step length or stride length), and balance (i.e., MiniBESTest, Berg Balance Scale or postural sway) than non-RGPT gait training in both HOA and PwPD.

METHODS

Search Strategy and Included Databases

A systematic search of the literature was conducted on 27 April 2020 in the PubMed, Embase, Medline, Web of Science and Google Scholar databases without date restriction (Bramer et al., 2017). A final screening for eligible studies was performed on 10 February 2021. The following search syntax was used (Google Scholar example): *(gait OR locomotion OR walk OR walking)* AND *(split-belt OR split belt OR splitbelt OR balance loss OR dynamic balance OR dynamic stability OR surface translation OR trip OR tripping OR slip OR slipping OR pull OR push OR perturbation OR perturbations OR perturbed OR perturb)* AND *(rehabilitation OR repeated OR repetition OR training OR program)* AND *(Parkinson's Disease OR aging OR elderly OR older adults)*. The exact search syntax used for each of the other databases is presented in the **Supplementary Materials**. As no consensus exists in the current literature on how to describe "perturbation" and "training," we used a broad range of terms in our search syntax to avoid missing eligible studies (McCrum et al., 2017). The review protocol was prospectively registered in PROSPERO (CRD42020183273) and the review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009).

STUDY SELECTION

The inclusion criteria for the selected studies were: (1) written in the English or Dutch language; (2) intervention study (RCT and non-RCT) assessing the effect of any type of repeated, and unexpected, perturbations during walking, hereafter called RGPT; (3) presenting outcomes on HOA (mean age ≥65 years) and/or PwPD; (4) measurement of effects right after the last training session and/or retention of effects (≥24 h after the last training session); and (5) gait speed, step length or stride length obtained as either the primary or secondary outcome. Exclusion criteria were: (1) not peer-reviewed; (2) conference abstracts; (3) reviews of the literature, with or without meta-analysis or commentaries without original data; (4) perturbations not given during gait (e.g., static or optical); (5) gait only assessed during the baseline assessment without a retest after the last training session; (6) effect of training on gait speed, step length or stride length only measured during the intervention, not in separate assessment after the last training session. Since this review focuses on the effects of perturbations during gait, all other forms of perturbation training, such as perturbations in a static context or optical instead of mechanical perturbations were excluded. Studies without a randomized controlled design (RCT) were excluded from the meta-analysis. However, because of the novelty of this field, studies with repeated measures designs with or without a control group but without randomization were included in the qualitative (i.e., descriptive) analysis. This enables the evaluation of promising paradigms not yet tested in a RCT. Two reviewers independently and sequentially screened titles and abstracts (FH, BV) and full texts (FH, VR) for eligibility. Any disagreements regarding eligibility were discussed amongst the reviewers after screening, until mutual agreement was achieved and verified by a third independent reviewer (MG).

Data Extraction and Quality Assessment

A standardized form for data extraction was used (Microsoft Excel, version 2019, Microsoft Corp. Redmond, WA) to record information about: the study population, participant demographics, details of the intervention and control conditions, study design, primary outcome measures (e.g., gait speed, step length, stride length), secondary outcome measures (e.g., balance or postural sway), and main conclusions by the study authors. In addition, information was collated to assess the studies' internal validity using the NIH National Heart, Lung, and Blood Institute's Quality Assessment Tool for Controlled Intervention Studies. This tool uses 14 criteria for assessing internal validity and potential risk of bias (National Institutes of Health, 2019). Two reviewers independently scored the internal validity (FH, VR).

Data Synthesis and Analysis

The primary outcome measure was gait performance, expressed as the pooled outcomes of the following gait measures: gait speed, step length or stride length. When several of the outcome measures were present, only one was included in the meta-analysis based on the following predefined prioritization: (1) gait speed, (2) step length and (3) stride length. Secondary outcomes included other gait measures (i.e., asymmetry, variability),

Center of Mass (CoM) measures (i.e., sway speed) and balance performance [i.e., Mini-BESTest and the Berg Balance Scale (BBS)]. If included studies had these data available in secondary analyses, these were also included in the analysis. Three secondary analyses were performed: (1) including only studies that used regular treadmill training as an active comparator to RGPT; (2) including only studies that assessed PwPD; and finally (3) including only balance outcomes. Additional data were

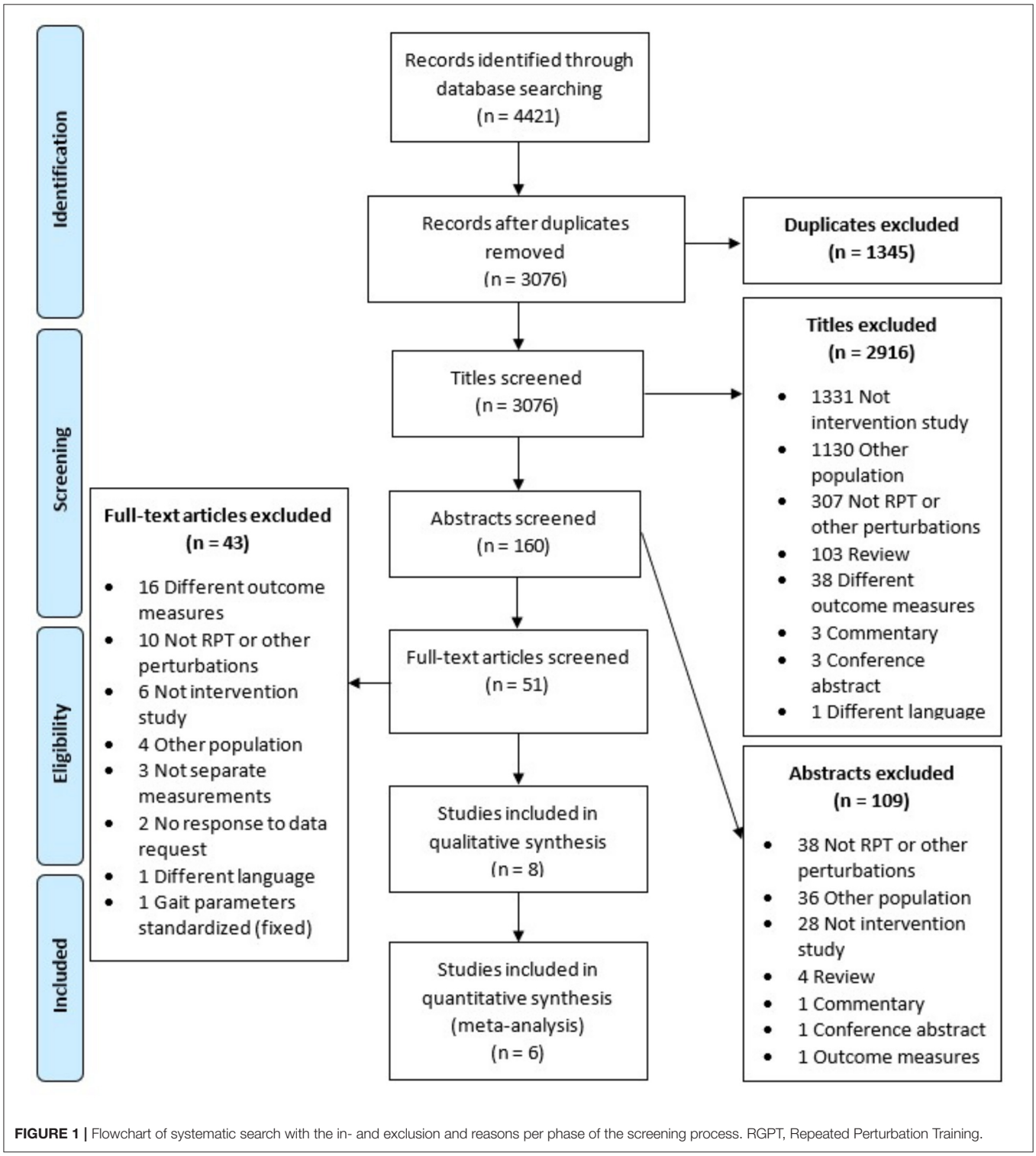

FIGURE 1 | Flowchart of systematic search with the in- and exclusion and reasons per phase of the screening process. RGPT, Repeated Perturbation Training.

requested from the corresponding authors if not reported in the original publication. Authors were given at least 2 weeks' time to respond to this request before the data was labeled as missing. A meta-analysis of final measures was conducted for the post and retention scores separately, in which the means and standard deviations of the scores were used to compare the pooled effects of the different interventions in the pooled population (PwPD and HOA). If only change scores were reported and the corresponding authors did not respond to the data request, the mean was determined based on the baseline mean added to the change score of the post and/or retention timepoint. This was the case for one study (Shen and Mak, 2015). Here, the standard deviation at baseline was entered as the estimate of the standard deviation at post and/or retention.

The standardized mean difference (SMD) between the intervention and control group was calculated with a random effects model using Reference Manager (RevMan, v5.4), which accounts for inter-study variance in the methods and outcome measures. Based on the SMD corresponding 95% confidence intervals, two-sided *P*-values and the main effect sizes (Z-scores) were calculated. *P*-values < 0.05 were considered statistically significant. Heterogeneity between study effects was assessed using both the χ^2 test and I^2 statistic (Higgins et al., 2003). I^2 values $< 25\%$, between 50 and 75%, and $> 75\%$ were considered as low, moderate or large heterogeneity, respectively (Higgins et al., 2003). The results were displayed in forest plots. Possible publication and selection bias were assessed using funnel plots. Where possible, effect sizes (ES) were calculated using Cohen's d.

RESULTS

Study Selection

The search and selection procedure are outlined in **Figure 1**. The systematic search identified 4421 potential records. After duplicate removal, 3,076 titles were screened and 2,916 records excluded. A total of 160 abstracts were screened for eligibility, resulting in the exclusion of 109 records. Of the remaining 51 full-text records, ten met the inclusion criteria (Cakit et al., 2007; Bhatt and Yang, 2012; Yang and Pai, 2013; Harro et al., 2014a; Shen and Mak, 2015; Klamroth et al., 2016; Martelli et al., 2017; Steib et al., 2017; Gimmon et al., 2018; Rieger et al., 2020), of which two were not included as we received no response to our data requests (Bhatt and Yang, 2012; Yang and Pai, 2013). Consequently, eight studies were included in the qualitative review and six could be included in the meta-analysis for having applied an RCT design and providing useable data (Cakit et al., 2007; Shen and Mak, 2015; Klamroth et al., 2016; Steib et al., 2017; Gimmon et al., 2018; Rieger et al., 2020). Reasons for exclusions are described in **Figure 1**. Two out of the eight included studies (Harro et al., 2014a; Gimmon et al., 2018) had additional data available on balance outcomes in other secondary analyses papers, which were also considered in this review (Harro et al., 2014b; Kurz et al., 2016). A summary of characteristics of the included studies can be found in **Table 1**.

Summary of Study Characteristics

A total of eight studies were considered eligible for qualitative review (Cakit et al., 2007; Harro et al., 2014a; Shen and Mak, 2015; Klamroth et al., 2016; Martelli et al., 2017; Steib et al., 2017; Gimmon et al., 2018; Rieger et al., 2020), of which six could be included in the meta-analysis (Cakit et al., 2007; Shen and Mak, 2015; Klamroth et al., 2016; Steib et al., 2017; Gimmon et al., 2018; Rieger et al., 2020). Information about participants, modes of RGPT, training design, control groups, retention periods and main gait outcomes are presented in **Table 1**. **Table 1** also illustrates the different forms of perturbations delivered while walking, including 3D tilting (Klamroth et al., 2016; Steib et al., 2017) or sudden translations of the treadmill (Steib et al., 2017; Gimmon et al., 2018), sudden acceleration or deceleration of the treadmill (Cakit et al., 2007; Harro et al., 2014a; Shen and Mak, 2015; Rieger et al., 2020), manual perturbations by the trainer (Shen and Mak, 2015), and push and pulls from a cable system during treadmill walking (Martelli et al., 2017). Six out of the eight studies compared RGPT with an active control intervention in an RCT design (Harro et al., 2014a; Shen and Mak, 2015; Klamroth et al., 2016; Steib et al., 2017; Gimmon et al., 2018; Rieger et al., 2020). Five studies used regular treadmill training (Harro et al., 2014a; Klamroth et al., 2016; Steib et al., 2017; Gimmon et al., 2018; Rieger et al., 2020) and one used strength training (Shen and Mak, 2015) as comparison. The study of Cakit et al. (2007) did not specify their control intervention.

Duration of the training sessions differed between studies. Three studies consisted of a single session (Klamroth et al., 2016; Martelli et al., 2017; Rieger et al., 2020), two studies had 16 sessions (Cakit et al., 2007; Steib et al., 2017), and the other studies provided 18 (Harro et al., 2014a), 24 (Gimmon et al., 2018) and 44 sessions, respectively (Shen and Mak, 2015), with an average of 2-3 sessions per week. The total length of the intervention period ranged from 1 day to 4 months. Retention of training effects was acquired in three studies. These studies measured retention after 1 week (Rieger et al., 2020) and 3 months (Harro et al., 2014a; Steib et al., 2017). The study of Shen and Mak (2015) measured retention effects at 3 different time points: 3, 6 and 12 months after training. To reduce heterogeneity, we included the data obtained at the 3-month time point into the retention, as this matches the retention period in two of the three studies. Five studies included PwPD (Cakit et al., 2007; Harro et al., 2014a; Shen and Mak, 2015; Klamroth et al., 2016; Steib et al., 2017), two studies included HOA (Gimmon et al., 2018; Rieger et al., 2020), and one study compared PwPD and HOA (Martelli et al., 2017). Data of both groups were pooled in the current primary meta-analysis including a total of 209 participants (159 PwPD and 50 HOA). The mean ages of PwPD and HOA differed significantly across studies [PwPD 66.4 (3.6) and HOA 76.2 (5.1), $t = -2.807$, $P = 0.048$]. The gait parameters most frequently used as an outcome were comfortable gait speed in four studies (Harro et al., 2014a; Shen and Mak, 2015; Klamroth et al., 2016; Steib et al., 2017), followed by fast gait speed in three studies

TABLE 1 | Characteristics of included studies.

References	Participants age (SD)	Perturbation training	Control intervention	Retention	Gait outcome	Balance outcome
Cakit et al. (2007)	*N* = 31 PwPD 71,8 (6,4) HY: 2–3 UPDRSII: 18.14 (9.32)	16 sessions, 30 min for 8 wks speed dependent treadmill training with unexpected speed increments or decrements (0.6 km/h)	Control group mentioned but content not specified	None	Max gait speed on treadmill	Berg Balance Scale
Gimmon et al. (2018)	*N* = 53 HOA IG: 78.2 (5.6) CG: 81.4 (4.3)	24 sessions, 20 min for 3 mo of treadmill at comfortable speed with unexpected perturbations of platform in random directions	24 sessions, 20 min for 3 mo of treadmill walking at comfortable speed	None	Stride length on treadmill (1.9 mph speed)	Postural sway (EC)
Klamroth et al. (2016)	*N* = 39 PwPD IG: 64.8 (10.3) HY: 2.4 (0.6) UPDRSIII: 16.7 (5.5) CG: 64.2 (8.5) HY: 2.2 (0.9) UPDRSIII: 17.7 (8.7)	1 session, 20 min of treadmill walking with small 3D tilting movements of the walking surface	1 session, 20 min of regular treadmill walking at comfortable speed	10 min	Comfortable overground gait speed, *CoV and asymm of stride length*	Postural sway (EO)
Rieger et al. (2020)	*N* = 30 HOA 72.6 (5.4)	1 session, 16 perturbations of treadmill walking with sudden acceleration or decelerations	1 session, 8 min of conventional treadmill walking	1 week	Step length on treadmill	None
Shen and Mak (2015)	*N* = 45 PwPD IG: 63.3 (8.0) HY: 2.43 (0.47) UPDRSIII: 24.0 (8.3) CG: 65.3 (8.5) HY: 2.48 (0.49) UPDRSIII: 23.2 (6.5)	44 sessions, 20–60 min, 12 wks total, 2 × 4wks 60 min of lab technology-assisted gait and balance training with volitional stepping, leaning, unexpected treadmill deceleration or manual perturbations and 1wk 20min self-supervised training.	44 sessions, 20–60 min of strength training of the lower extremity with dynamometers/leg press machines, rowing, cuff weight	3 mo (6 mo/12 mo)*	Comfortable overground gait speed	None
Steib et al. (2017)	*N* = 38 PwPD IG: 67.6 (8.2) HY: 2.43 (0.47) UDRSIII: 24.0 (8.3) CG: 62.5 (7.9) HY: 2.48 (0.49) UPDRSIII: 23.2 (6.5)	16 sessions, 30min for 8 wks of treadmill walking with 3D movements of tilting platform	16 sessions, 30 min for 8 wks of conventional treadmill walking	3 months	Comfortable and fast overground gait speed	Mini-BESTest, Postural sway (EO and EC)
Paradigms without RCT design or control group						
Harro et al. (2014a,b)**	*N* = 20 PwPD IG: 67.3 (11.47) HY: 1.9 (0.57) UPDRSIII: / CG: 64 (9.58) HY: 2.0 (0.67) UPDRSIII: /	18 sessions, 30 min for 6 wks of rhythmic auditory cued over-ground walking, walking to the beat of music with incremental BPM to increase gait speed	18 sessions, 30 min for 6 wks of speed dependent treadmill training, unexpected increase of speed every +/- 2.5-5 min and decreases to comfortable speed	3 months	Comfortable and fast overground gait speed	Berg Balance Scale
Martelli et al. (2017)	*N* = 18, 9 PwPD + 9 HOA PwPD: 64,3 (7,4) HY: 1.78 (0.44) UPDRSIII: 14.44 (6.44) HOA: 64,7 (7,3)	1 session, 30 min, 9 blocks of 8 AP or ML pull or push perturbations by external cables during walking on a treadmill	None	None	Step length of walking on treadmill	None

*RCT, Randomized Controlled Trial; CC, Case Control Study; IG, Intervention Group; CG, Control Group; PwPD, People with Parkinson's Disease; HOA, Healthy Older Adults; HY, Hoehn and Yahr stage; UPDRSIII, Movement Disorder Society Unified Disease Rating Scale part III; Mo, months; Wks, weeks; CoM, Center of Mass; EO, Eyes Open; EC, Eyes Closed; BPM, Beats Per Minute; AP, Anterior-Posterior; ML, Medio-Lateral; CoV, Coefficient of Variance; Asymm, asymmetry. *These timepoints were also collected but not used in this meta-analysis, **only control group was suitable for inclusion in qualitative analysis.*

(Cakit et al., 2007; Harro et al., 2014a; Steib et al., 2017), step length in two studies (Martelli et al., 2017; Rieger et al., 2020), and stride length in one study (Gimmon et al., 2018). The study of Klamroth et al. (2016) also included measures of gait variability and asymmetry (see **Table 1**).

Results of the Individual Studies - Qualitative Review

Cakit et al. (2007) found a significant improvement of 0.20 m/s in maximum tolerated walking speed on the treadmill in PwPD compared to the control group (unspecified), immediately after a

TABLE 2 | Qualitative description of studies not included in meta-analysis.

References	Main finding on gait outcome pre-post	Main finding on gait outcome pre-ret
Harro et al. (2014a)	Comfortable gait speed (m/s) did improve with 4.53% after training 1.30 (0.19) vs. 1.36 (0.21), however non-significantly ($p = 0.13$). Fast gait speed (m/s) did significantly improve by 7.45% after training 1.69 (0.27) vs. 1.82 (0.30), $p = 0.01$.	Comfortable gait speed (m/s) remained increased at retention, 1.39 (0.24) vs. 1.30 (0.19), however these improvements were non-significant ($p = 0.12$). Improvements in fast gait speed retained after 3 months, 1.69 (0.27) vs. 1.80 (0.33), $p = 0.05$.
Martelli et al. (2017)	Step length (mm) increased over time in the pooled groups [HOA 14.59 (23.70), PwPD 21.78 (17.09)] ($p = 0.003$) after 30 min of perturbation training, but no group x time effect was observed ($p = 0.497$)	Not measured

HOA, Healthy Older Adults; PwPD, People with Parkinson's Disease.

training with sudden accelerations and decelerations (ES = 2.15, $p < 0.01$). In addition, an improvement in balance, measured with the Dynamic Balance Scale (ES = 6.21, $p < 0.01$) and the Berg Balance scale (ES = 9.32, $p < 0.01$), and a reduction in fear of falling ($p < 0.01$) were observed (Cakit et al., 2007). Shen and Mak (2015) did not find an improvement in over-ground gait speed, but did find a significant increase in stride length in PwPD immediately (ES = 0.968, $p = 0.003$), 6 months (ES = 0.643, $p = 0.038$) and 12 months (ES = 0.783, $p = 0.013$) after their technology-assisted balance and gait training including sudden decelerations during treadmill walking (Shen and Mak, 2015). Moreover, they reported a significantly lower number of fallers after RGPT compared to the control intervention, which was retained for 12 months ($p = 0.047$) (Shen and Mak, 2015). Klamroth et al. (2016) compared 3D tilting perturbations of the treadmill platform during treadmill walking to regular treadmill walking and found a group (RGPT vs. control) by time (pre, post, retention) effect for over-ground walking speed in PwPD (ES = 0.41, $p = 0.014$). In addition, they reported a decrease in gait variability in the intervention group (ES = −0.34, $p = 0.048$), suggesting a more stable gait pattern (Klamroth et al., 2016). The studies of Steib et al. (2017), Gimmon et al. (2018), and Rieger et al. (2020) found no improvement in gait (i.e., gait speed, stride length and step length respectively) after RGPT compared to regular treadmill walking.

Two studies were not suitable for inclusion in the meta-analyses. One did not have a RCT design (Martelli et al., 2017), and the other compared two interventions of which only the control intervention matched our RGPT criteria. Here, the intervention group was focused on cueing and therefore not suitable as comparison in the meta-analysis (Harro et al., 2014a). Regardless, both studies showed a positive effect of RGPT on gait outcomes when comparing pre-post results (see **Table 2**). Harro et al. (2014a) found an improvement in fast gait speed directly after a training with sudden accelerations and decelerations, compared to the pre-measurement (ES = 0.46, $p = 0.01$), which was retained after 3 months (ES = 0.36, $p = 0.05$). Martelli et al. (2017) found an effect over time in step length after training participants with a push/pull cable system (ES = 0.17, $p = 0.003$), but no difference in effects between PwPD and HOA groups was demonstrated (ES = 0.33, $p = 0.497$) (Martelli et al., 2017). Retention of these effects was not measured in this study.

Effects of RGPT on Gait

Immediate Effects – Meta-Analysis

Figure 2A shows the outcomes of the meta-analysis of the standardized mean difference (SMD), from six studies demonstrating no improvement of gait after RGPT training compared to the control training (SMD = 0.16; 95% CI = −0.18, 0.49; $Z = 0.92$; $P = 0.36$). When pooling the data of the four studies that compared RGPT with regular treadmill training (**Figure 2B**), the SMD and significance level did not change considerably (SMD = 0.10; 95% CI = −0.25, 0.45; $Z = 0.55$; $P = 0.58$), although heterogeneity measures decreased (from $I^2 = 30\%$ to $I^2 = 0\%$). When pooling the four studies including only PwPD, the effect size and SMD remained the same (SMD = 0.17; 95% CI = −0.31, 0.64; $Z = 0.69$; $P = 0.49$) (**Figure 2C**). Heterogeneity increased from 30 to 54%, reducing the robustness of these results.

Retention Effects – Meta-Analysis

Three studies reported the retention effects of RGPT on gait. Overall, no gait improvements were retained (SMD = 0.22; 95% CI = −0.42, 0.85; $Z = 0.67$; $P = 0.50$) (**Figure 3**).

Effects of RGPT on Balance and Postural Sway

Immediate Effects on Balance Scales

Two studies reported the effect of RGPT on balance assessments. Cakit et al. (2007) assessed the Berg Balance Scale and Steib et al. (2017) the Mini-BESTest. Overall, RGPT showed a non-significant effect on balance assessments immediately after the training (SMD = 0.09; 95% CI = −0.40, 0.58; $Z = 0.36$; $P = 0.72$, see **Supplementary Figures**). These results are in line with the study of Harro et al. (2014b) that could not be included in this meta-analysis, while also showing no significant improvement on the Berg Balance Scale after RGPT at the individual study level.

Immediate Effects on Postural Sway

Three studies assessed velocity of postural sway during quiet stance (Klamroth et al., 2016; Steib et al., 2017; Gimmon et al., 2018). Sway was assessed with eyes open and eyes closed in one study (Steib et al., 2017) and two either assessed with eyes open (Klamroth et al., 2016) or closed (Gimmon et al., 2018). A decrease in postural sway velocity points toward better

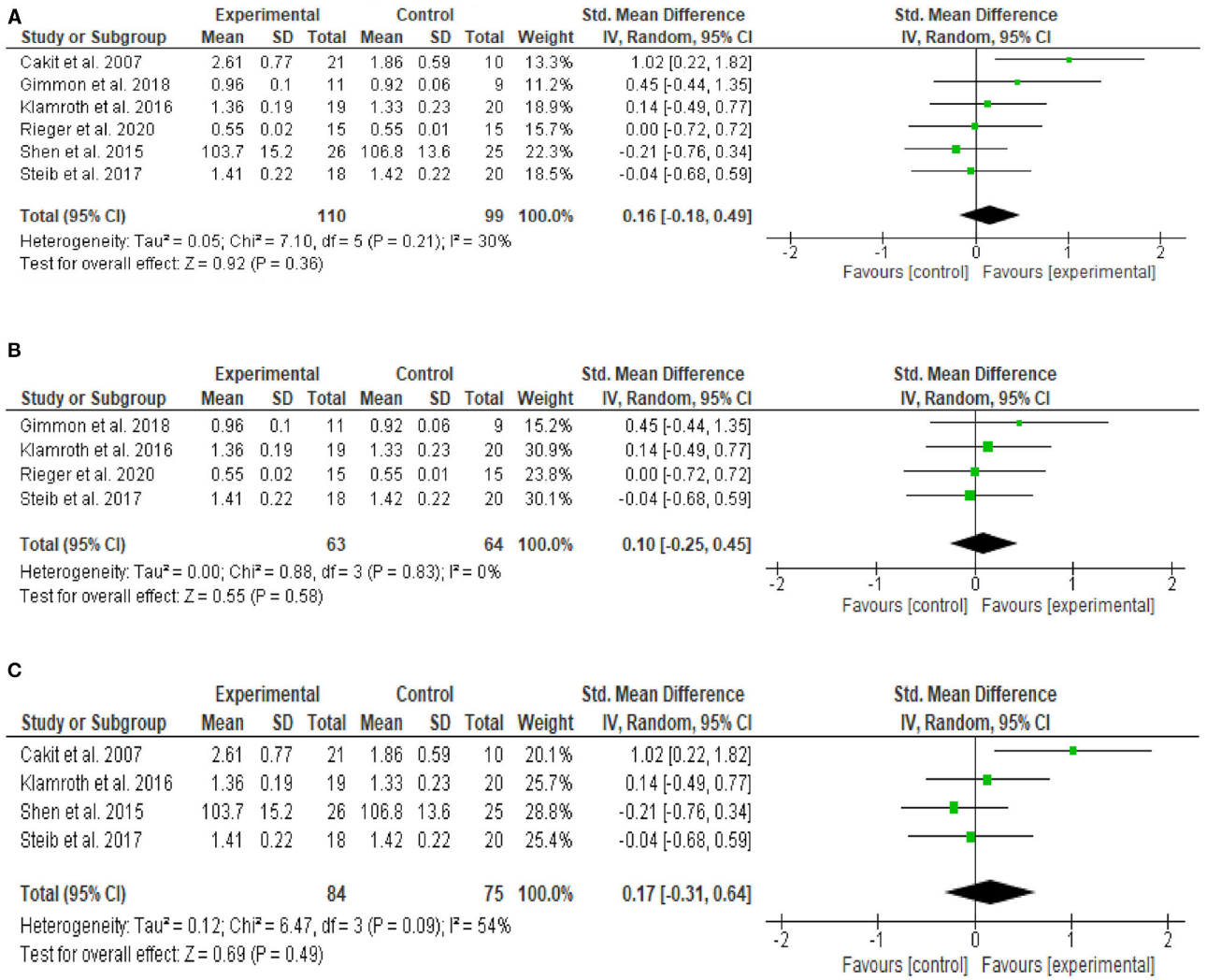

FIGURE 2 | (A) Meta-analysis of the effect of RGPT (experimental) vs. non-RGPT (control) training on gait outcomes (i.e., gait speed, step length, or stride length) in PwPW and HOA immediately after the intervention. **(B)** Meta-analysis of the effect of RGPT (experimental) vs. regular treadmill training (control) on gait outcomes (i.e., gait speed, step length, or stride length) in PwPD and HOA immediately after training. **(C)** Meta-analysis of the effect of RGPT (experimental) vs. non-RGPT (control) training on gait outcomes (i.e., gait speed, step length, or stride length) immediately after training in PwPD only.

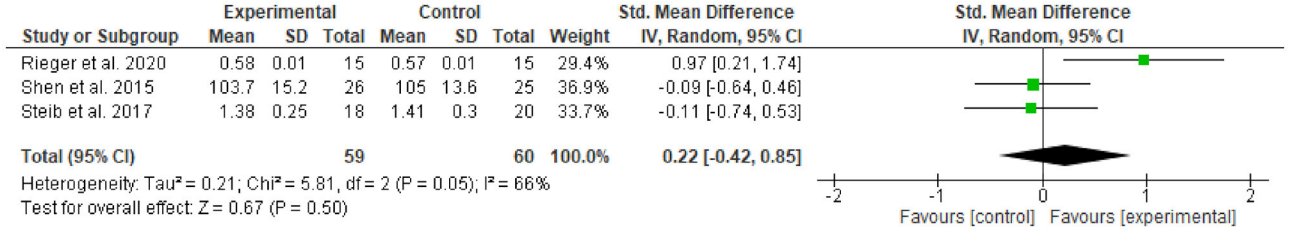

FIGURE 3 | Meta-analysis of the effects of RGPT (experimental) vs. non-RGPT (control) training on gait outcomes (i.e., gait speed, step length, or stride length) in PwPD and HOA at retention.

postural control. RGPT significantly decreased postural sway with eyes open (MD = −1.74; 95% CI = −3.18, −0.29; Z = 2.35; P = 0.02). Sway with eyes closed did not reduce in both studies resulting in a non-significant effect of RGPT (SMD = −1.43; 95% CI = −5.33, 2.48; Z = 0.72; P = 0.47, see **Supplementary Figures**).

TABLE 3 | Quality assessment of included studies.

Item / study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Klamroth et al. (2016)	1	1	1	0	0	1	1	1	1	?	1	0	1	1
Shen and Mak (2015)	1	1	1	0	1	1	0	1	1	?	1	1	?	0
Cakit et al. (2007)	1	?	?	?	1	1	0	0	1	?	1	0	?	0
Gimmon et al. (2018)	1	1	?	?	?	0	0	1	?	?	1	1	1	?
Steib et al. (2017)	1	1	1	0	1	1	0	1	1	1	1	0	1	0
Rieger et al. (2020)	1	?	?	?	?	1	1	1	?	?	1	0	?	1
Harro et al. (2014a)	1	?	?	0	1	1	1	1	1	?	1	1	?	1
Martelli et al. (2017)				?	?	1			1	?	1	0	?	1
Sum score	7/7	4/7	3/7	0/8	4/8	7/8	3/7	6/7	6/8	1/8	8/8	3/8	3/8	4/8

Green color: low risk of bias, Red color: high risk of bias, Orange color: not reported, Dark gray color: not applicable. Q1: RCT, no/RCT, Q2: randomization quality, Q3: concealed allocation, Q4: participant blinding, Q5: blinded testers, Q6: similar groups, Q7: drop-out <20%, Q8: differential drop-out rate <15%, Q9: adherence >75%, Q10: similar background treatments, Q11: valid outcome measures, Q12: power >80%, Q13: preregistration, Q14: intention-to-treat.

Retention Effects on Balance Scales and Postural Sway

Only Steib et al. (2017) assessed 3-month retention of balance scales and postural sway. They found a slight, but statistically non-significant, decrease in Mini-BESTest scores after both the RGPT interventions in PwPD [mean difference (post-pre) = −0.1] and non-RGPT control [mean difference (post-pre) = −0.9], with lower scores indicating better performance (range from 0 to 28). The decrease in scores appears larger for the control group over the RGPT group, but no significant group by time interaction effect was found ($P = 0.441$), nor a main effect of time ($P = 0.340$). In addition, no significant improvements in postural sway with either eyes open (within group $P = 0.862$, between group $P = 0.626$), or eyes closed (within group $P = 0.446$, between group $P = 0.626$) were observed after RGPT.

Risk of Bias in Included Studies

Selection Bias

Funnel plots were generated for the primary outcomes of this review immediately after the intervention and at retention and are presented in the **Supplementary Materials**. Both plots showed balanced heterogeneous results, pointing toward a low risk of selection bias. However, the low number of studies included may have clouded interpretation of the funnel plots.

Within-Study Bias

Table 3 presents the internal validity of the included studies. All studies had some risk of bias. In particular, blinding of treatment allocation (Q4) was insufficient or not reported in all studies. Four of the eight studies did blind the assessors (Q5). Nearly half of the studies reached 20% or more dropout rates (Q7), though it should be noted that these rates were often similar between intervention arms (Q8). Most importantly, only few studies justified the sample size using an a-priori power calculation (Q12). Several studies preregistered their protocols (Q13), but for most studies this was not reported. All studies assessed their outcomes using valid and reliable measures (Q11).

DISCUSSION

The aim of the present systematic review was to investigate the short and long-term effects of repeated gait perturbation training (RGPT) vs. non-RGPT training on gait performance in healthy older adults and people with Parkinson's disease. Overall, no significant additional beneficial effects of RGPT on gait performance were found when contrasted to regular treadmill training, especially for retention. Some individual studies did show favorable pre-post and between-group effects for gait speed, step length, stride length, gait variability and asymmetry measures, immediately after RGPT and after a retention period (Cakit et al., 2007; Harro et al., 2014a; Shen and Mak, 2015; Klamroth et al., 2016; Martelli et al., 2017).

Our findings are in contrast to our hypothesis and diverge from previous reviews showing a beneficial effect of repeated balance and/or gait perturbations in HOA and PwPD on reducing fall risk and increasing reactive recovery (Mansfield et al., 2015; McCrum et al., 2017), though these prior reviews did not assess gait performance. We propose three complementary explanations for the lack of significant results in the present review.

First, most of the included studies in this review contrasted RGPT with regular treadmill training (Klamroth et al., 2016; Steib et al., 2017; Gimmon et al., 2018; Rieger et al., 2020). Treadmill training alone has shown strong positive effects on gait speed and stride length in several populations, including frail older adults and PwPD (Van Ooijen et al., 2013; Mehrholz et al., 2016; Ni et al., 2018; Pereira et al., 2020). The Cochrane review conducted by Mehrholz et al. (2016) showed substantial effects of treadmill training in PwPD when compared to other interventions (e.g., stretching, dancing, resistance training, conventional therapy) on both gait speed [Mean difference (post-pre) = 0.09 m/s; 95% CI = 0.03, 0.14; $p = 0.001$] and stride length [Mean difference (post-pre) = 0.05 m; 95% CI = 0.01, 0.09; $p = 0.01$] without increased drop-out rates or adverse events. Ni et al. (2018) found similar results on exercise interventions including treadmill for PwPD. Given the positive effects of regular treadmill training, it would require large sample sizes to

detect a modest effect on gait outcomes in response to RGPT when contrasted to regular treadmill training. This is supported by the results of the individual studies included in this review, showing improvements on gait, however often less than the regular treadmill control group. As a result, most included studies were probably underpowered to detect between-group differences on gait outcomes. Moreover, only 3 out of 8 included studies determined their sample sizes based on a-priori power calculation. The outcomes of the present review might help researchers to perform a power-based sample size calculation for future intervention trials on RGPT.

Second, the effectiveness of RGPT, as for most training-based interventions, is likely dependent on the dosage and task-specificity of the training. Since the dosage of the training paradigms included in this review varied greatly, this may have influenced the results and clouded the potential of some specific perturbation paradigms. Work from Karamanidis et al. (2020) showed that RGPT could improve balance recovery responses in HOA with and without neuropathology, as long as the amount of perturbations reached a certain critical threshold. This threshold theory implies that even in neurological populations such as PwPD, retention and transfer can be achieved as long as there is sufficient training exposure to reach the optimal dose-response relationship. Future studies should conduct a meta-regression analysis to delineate the impact of intervention dosage on RGPT effectiveness, once the body of work in this domain has grown. With regard to task-specificity of RGPT, the type of perturbations may have contributed to the effectiveness of RGPT on some gait measures. Optimally, the mode of perturbation should resemble complex gait as performed in daily life, such as turns and other maneuvers. Moreover, translation should be tested in over-ground as well as experimental conditions. Seuthe et al. (2020) compared several split-belt to regular treadmill walking speeds (i.e., contrasts) in HOA and PwPD gait to see which split-belt contrasts elicited the largest improvements in step length asymmetry, which were relevant for turning. They found that changing the speed ratios between the belts during one session repeatedly led to a quicker adaptation back to symmetry in step length, compared to static ratios (i.e., a constant speed reduction of one treadmill belt with either 25% or 50%). D'Cruz et al. (2020) also found that specific split-belt perturbations, especially the "changing ratios" and steady reduction by 50%, led to improved dual-task gait speed during over-ground walking and turning in place, when compared to regular treadmill training in PwPD and HOA. In addition, in both the studies of D'Cruz et al. (2020) and Seuthe et al. (2020) these improvements in turning and asymmetry were retained for 24 h. These results suggest that split-belt training with changing ratio's, when offered at optimal dosage and form, could lead to retention and transfer effects to daily gait challenges. Furthermore, the speed or contrast at which the perturbation is introduced, appears to play a role in how people learn to cope with the perturbation, and how well-they can retain learning effects (D'Cruz et al., 2020; Seuthe et al., 2020).

Third, valid outcomes that are responsive to gait adaptation, need to be adopted to capture the potential of RGPT on gait function. Gait speed, step and stride length are gait outcome measures that also improve with regular treadmill walking. One study included in this review reported additional outcomes, that could be more indicative of gait adaptation and flexibility. Klamroth et al. (2016) reported on the coefficient of variation and asymmetry of several gait parameters, including stride length and step time. Significant reductions in stride length variability and significant increases of step time symmetry were observed compared to the control group, who received regular treadmill training (Klamroth et al., 2016). These results are corroborated by another study not included in this review from Seuthe et al. (2020), who reported a significant reduction in asymmetry following split-belt perturbations after RGPT compared to regular treadmill training, whereas no improvements in gait speed were observed. These results suggest that to quantify gait adaptation, future studies should consider incorporating gait adaptation tasks and testing the validity of asymmetry and other variability/adaptation measures of gait as outcomes of interest. In addition, validity studies are needed to test whether outcomes, which capture change immediately after imposing perturbations and after retention, are correlated with ecological gait measures.

Finally, previous results of RGPT on balance are also in sharp contradiction to our secondary analysis on balance outcomes, in which we overall found non-significant results for both sway and balance scales. However, this is likely caused by the limited number of studies, as we only included papers that primarily focused on gait perturbation and outcomes. Careful interpretation of the secondary analyses is also warranted, given that these included some of the same study participants.

The present results challenged our hypothesis that exposing people to RGPT would lead to additional gait improvements that were better retained compared to non-RGPT. Gait adaptation is likely governed by cerebellum-motor cortex connectivity (Jayaram et al., 2011; Spampinato et al., 2017). When a discrepancy occurs between the expected and experienced situation (i.e., sensory prediction error), sensory integration is facilitated by the cerebellum, allowing adaptation of motor control (Krakauer et al., 2019). Because the cerebellum is intact in HOA and not severely affected in the early disease stages of PwPD (Wu and Hallett, 2013), the functional circuits related to this structure may still have some capacity to induce learning effects relevant for gait adaptation training (Gilat et al., 2019). A recent ALE meta-analysis on fMRI findings showed that PwPD consistently activate the cerebellar locomotor region more than HOA during gait, supporting the view that the cerebellum plays an important compensatory role in gait processing for PwPD (Gilat et al., 2019). In patients with cerebellar lesions, Morton and Bastian (2006) showed that an intact cerebellum is essential for adaptive gait control during split-belt walking. Moreover, a recent PET imaging study showed increased lateral cerebellar activity while adjusting gait during split-belt walking in healthy young adults (Hinton et al., 2019). These imaging studies further endorse that PwPD may still be able to train gait adaptation through RGPT, constituting promising gait rehabilitation strategies for these fall-prone patients.

Clinical Implications

Although, the results of this review were negative, it is interesting to see that five RGPT paradigms resulted in significant within-group, and sometimes between-group improvements in gait, albeit in different outcomes. Of these five interventions, three consisted of sudden accelerations or decelerations of the treadmill, either at once or in a split-belt context, requiring an immediate response (Cakit et al., 2007; Harro et al., 2014b; Shen and Mak, 2015). The similarities in these programs suggest, that also in regular clinical practice, even without specific instrumentation, it may be useful to offer training conditions that require speed changes to improve steady gait and gait flexibility. In addition, the only study that tested long-term effects showed retention of up to 12 months following RGPT (Shen and Mak, 2015) and split-belt training (D'Cruz et al., 2020; Seuthe et al., 2020) demonstrated transfer to an over-ground adaptive task, namely turning. However, the experiments included were still at the proof-of-concept stage, as our quality assessment indicated largely underpowered samples and other potential risks of bias. Inherently, the present review could thus only include few studies and with small samples, limiting the statistical power of our meta-analyses. In addition, for the main meta-analysis, data of PwPD and HOA were pooled although there was a difference in mean age, which could have biased the results. This methodology was based on an a-priory decision (see pre-registration) to not arbitrarily restrict age for PwPD and allow for optimal power in the meta-analysis. Taken together, the present review points to the need for more well-designed, adequately powered RCTs, as well as, to gap in knowledge on the impact of RGPT on daily-life ambulation, before wide implementation in the clinical field can be recommended. Future studies should also elucidate the specific type of perturbations and dosage for use in rehabilitation, to improve flexibility of gait and balance performance in older and neurological populations.

CONCLUSION

This systematic review with meta-analysis on RGPT showed that despite the promising effects reported in individual studies, their pooled effects were not helpful in improving gait outcomes when compared to other training interventions. The limited number of studies, methodological heterogeneity in the type and dosage of training and the varying outcome measures further clouded possible intervention effects. However, this review also revealed the potential of RGPT, providing a rationale for conducting future effect studies in this training concept in HOA and in PwPD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

FH: conception, organization, and execution of the research project, acquisition and processing of the data, design and execution of the statistical analysis, writing of the first draft of the manuscript. VR and BV: execution of the research project, acquisition and processing of the data, review and critique of the manuscript. MG: execution of the research project, processing of the data, review and critique of the statistical analysis, review and critique of the manuscript. PG: execution of the research project, review and critique of the statistical analysis, review and critique of the manuscript. ND'C and CS: execution of the research project, review and critique of the manuscript. AN: conception, organization, and execution of the research project, design and review and critique of the statistical analysis, review and critique of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.732648/full#supplementary-material

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REVIEW
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Future Therapeutic Strategies for Freezing of Gait in Parkinson's Disease

*Cathy K. Cui and Simon J. G. Lewis**

ForeFront Parkinson's Disease Research Clinic, Brain and Mind Centre, School of Medical Sciences, The University of Sydney, Camperdown, NSW, Australia

Freezing of gait (FOG) is a common and challenging clinical symptom in Parkinson's disease. In this review, we summarise the recent insights into freezing of gait and highlight the strategies that should be considered to improve future treatment. There is a need to develop individualised and on-demand therapies, through improved detection and wearable technologies. Whilst there already exist a number of pharmacological (e.g., dopaminergic and beyond dopamine), non-pharmacological (physiotherapy and cueing, cognitive training, and non-invasive brain stimulation) and surgical approaches to freezing (i.e., dual-site deep brain stimulation, closed-loop programming), an integrated collaborative approach to future research in this complex area will be necessary to systematically investigate new therapeutic avenues. A review of the literature suggests standardising how gait freezing is measured, enriching patient cohorts for preventative studies, and harnessing the power of existing data, could help lead to more effective treatments for freezing of gait and offer relief to many patients.

Keywords: gait disorders, dopamine agents, deep brain stimulation, non-invasive stimulation, physical therapy, repurposing, problem solving, humans

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Christian Schlenstedt, Medical School Hamburg, Germany

***Correspondence:**
Simon J. G. Lewis
simon.lewis@sydney.edu.au

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INTRODUCTION

Freezing of gait (FOG) is a disabling symptom that affects more than half of all advanced Parkinson's disease (PD) patients (Giladi et al., 2001b; Forsaa et al., 2015; Zhang et al., 2021). It profoundly reduces quality of life (Perez-Lloret et al., 2014; Walton et al., 2015b), leading to falls (Okuma et al., 2018; Lieberman et al., 2019) and a loss of independence. Patients who develop gait freezing fare poorly: falls related to gait freezing occur during walking, rather than standing, resulting in more severe injuries and increased hospitalisation (Lieberman et al., 2019). Gait freezing is also associated with a higher burden of non-motor symptoms (Choi et al., 2019) and femoral neck osteoporosis (Choi et al., 2021), independent of disease duration and stage of disease, which has implications for the broader treatment of such patients. Our understanding about the pathophysiology underpinning FOG is improving to appreciate its episodic features, heterogeneous phenotypes (Schaafsma et al., 2003) and the variety of modulators that can both trigger and relieve attacks (Ehgoetz Martens et al., 2018b). However, the symptom remains a treatment challenge. Whilst several established approaches, such as physiotherapy and optimising

dopaminergic therapy, have long formed the cornerstones of management, FOG appears more difficult to treat compared to other Parkinsonian symptoms. Specific triggers of FOG differ between individuals, and successful treatment is likely to require the identification and targeting of these features at the level of the individual. However, intervention studies tend not to stratify participants by phenotype (Ehgoetz Martens et al., 2018b). Even more foundational, the first hurdle in identifying better treatments is of accurately and objectively measuring FOG itself. This review will highlight where future strategies need to be directed in our pursuit of more effective therapies (**Figure 1**).

PATHOPHYSIOLOGY OF GAIT FREEZING

Unfortunately, FOG has a complex pathophysiology that is only somewhat understood. Critical anatomical areas involved in locomotion are the pontomedullary reticular formation (PMRF), mesencephalic locomotor region (MLR) including the pedunculopontine nucleus (PPN), basal ganglia and frontal cortical regions (Nutt et al., 2011). These supraspinal structures act on central pattern generators in spinal segments, which are involved in basic rhythmical stepping (Guertin, 2009). Transient disruption of this locomotor circuitry is thought to be responsible for FOG: Nieuwboer and Giladi (2013) have summarised four current models in the literature seeking to explain its episodic nature. Firstly, the "threshold" model suggests FOG manifests when multiple motor gait abnormalities accumulate to a critical threshold of instability, leading to gait breakdown (Plotnik et al., 2005). Secondly, the "interference" model proposes FOG arises from cross-talk between parallel cognitive and limbic circuits passing through the basal ganglia inducing temporary inhibition of the PPN (Lewis and Barker, 2009). The third "cognitive" model is conceptualised as a conflict-resolution deficit, related to executive dysfunction, where freezers are unable to compensate in complex situations for deficits in automaticity by switching to increased cognitive control, resulting in gait breakdown (D'Ostilio and Garraux, 2012). Lastly, the "decoupling" model refers to a discrepancy between perceived intention to move, and failure of a pre-planned motor program that then propagates motor arrest (Jacobs et al., 2009). Each model is likely to contribute to FOG, with various degrees of interplay in an individual patient, and resulting in its heterogeneity (Nieuwboer and Giladi, 2013). Situational factors such as anxiety and dual-tasking (Hackney and Earhart, 2010; Ehgoetz Martens et al., 2018b) may trigger FOG through a combination of models. In the background, the likelihood of a FOG episode occurring will increase with progression of disease, as cognitive and motor reserve is eroded and the response to levodopa becomes more variable (Giladi et al., 2001b; Nonnekes et al., 2020). Despite the complexity of these mechanisms, models such as these provide a theoretical framework for current and future treatment strategies such as reducing neural overload or improving motor gait parameters.

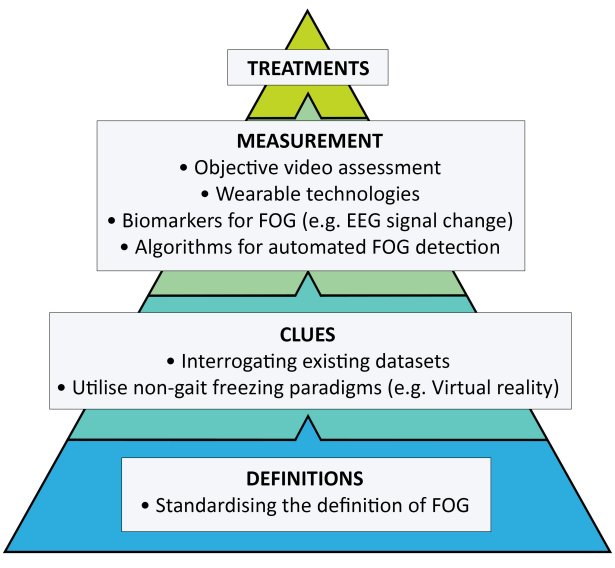

FIGURE 1 | Key steps toward developing effective therapies for freezing of gait.

HOW WOULD WE CONFIRM AN EFFECTIVE TREATMENT?

One of the first considerations when thinking about the development of an effective therapy for FOG, is just how to go about measuring the symptom itself. The current consensus statement defines FOG as the "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (Nutt et al., 2011). This definition followed on from an earlier proposal that FOG represents "an episodic inability (lasting seconds) to generate effective stepping" (Giladi and Nieuwboer, 2008). However, these definitions whilst helpful in the clinic do not reflect the complexity of FOG (Nutt et al., 2011) and do little to establish objective criteria that can be generalised for objective trial work. For example, a variety of FOG phenotypes (Schaafsma et al., 2003) have been described, along with typical phenomena including start hesitation and target freezing (Giladi et al., 1992). There are three phenotypes based on leg movement: (i) shuffling with small steps, (ii) trembling in place, and (iii) complete akinesia (Schaafsma et al., 2003), with complete akinesia occurring much less frequently than the others (Schaafsma et al., 2003). Whilst most FOG is "off" FOG, which is relieved by dopaminergic medication, less common types include "pseudo-on" FOG which is seen during a seemingly "on" state but improves with additional dopamine, and true "on" FOG, which appears induced by dopaminergic stimulation (Espay et al., 2012). We would like to highlight that there is very little evidence to explain the pathophysiology underpinning these sub-types and we would like to avoid being too speculative. Thus, we have focused on the pragmatic basis for treating the broader issue. It is unclear as to whether these different manifestations of FOG share the same underlying mechanisms (Ehgoetz Martens et al., 2018b; Mancini et al., 2019), and therefore, it is difficult to know if they are comparable for scoring purposes in an intervention

study. Furthermore, most patients exhibit mixed patterns of FOG (Giladi et al., 1992) and it is not clear if the most appropriate measure would be to compare the impact of any novel treatment on the total amount of time spent freezing or if each component of FOG (e.g., periods of start hesitation, festination) should be compared separately.

Confirming any effective treatment would also require an accurate and objective measurement of FOG (Mancini et al., 2019; **Table 1**). This is surprisingly difficult as FOG is most commonly experienced unpredictably at home where gait is more automatic or natural. In the clinic, gait becomes more goal directed and it can become difficult to trigger episodes (Mancini et al., 2019). Two questionnaires for the assessment of FOG have previously been developed, namely the Freezing of Gait Questionnaire (FOG-Q; Giladi et al., 2000) and the New Freezing of Gait Questionnaire (NFOG-Q; Nieuwboer et al., 2009). Whilst these were both validated in sizeable cohorts against subjective carer and clinician ratings, there was no gold standard measure or definition of FOG at the time the instruments were constructed (Nieuwboer et al., 2009). Indeed, subsequent work has demonstrated that self-perceived ratings of FOG severity using the FOG-Q and NFOG-Q do not correlate well with the actual number or duration of objective freezing episodes when scored from video recordings of Timed Up and Go (TUG) walking tasks (Shine et al., 2012). Furthermore, it is only recently that the authors of the NFOG-Q examined its test-retest reliability, as well as its ability to detect minimal change. This work found that the NFOG-Q is not sufficiently reliable or responsive to detect small effect sizes (Hulzinga et al., 2020).

In an effort to generate more objective measures, some researchers have developed standardised FOG assessments, such as the FOG Score (Ziegler et al., 2010), freezing indices based on accelerometer data (Moore et al., 2008; Mancini et al., 2012), and Stepping in Place on a pressure mat (Nantel et al., 2011).

TABLE 1 | Assessment methods in use for FOG measurement, and their advantages and disadvantages.

Assessment method	Advantages	Disadvantages
Self-reported FOG FOG-Q (Giladi et al., 2000) NFOG-Q (Nieuwboer et al., 2009)	▪ Records FOG over different environments including at home ▪ Assesses impact on quality of life ▪ Ease and speed of administration	▪ Relying on patient or carer recognition of FOG, though the NFOG-Q comes with accompanying video demonstrating FOG, making it easier to improve its recognition ▪ May not detect small effect sizes (Hulzinga et al., 2020) ▪ Scores do not correlate with frequency or duration of observed freezing (Shine et al., 2012)
Gait parameters Timed up and Go (Podsiadlo and Richardson, 1991) Walking biometrics (cadence, step length, step variability)	▪ Measures functional mobility ▪ Simple to perform	▪ Not specific to FOG ▪ Step biometrics require specialised equipment (gait pressure-mat)
FOG-provoking tasks Stepping in place (Nantel et al., 2011) Walking course (Ziegler et al., 2010) Virtual reality walking course (Shine et al., 2013a)	▪ Set walking course or task standardises FOG triggers across subjects ▪ FOG provoking tasks (e.g., dual tasking, turning, doorway walking, approaching target) can be incorporated to more reliably elicit FOG in laboratory settings ▪ Virtual reality walking allows manipulation of the walking environment (e.g., increase threat and anxiety) to assess their impacts on FOG (Ehgoetz Martens et al., 2015)	▪ Could be less sensitive to FOG as gait becomes more goal directed and less automatic ▪ Subjects requiring gait aids or those likely to fall may not be safe to complete the tasks
Visual scoring of FOG Video (Morris et al., 2012) Live rater	▪ Facilitates quantification of FOG (e.g., FOG duration, number of episodes, % time frozen) ▪ Video data is easily shared between multiple raters ▪ Ability to adjust play-back speed and replay video to identify short FOG	▪ Less sensitive to FOG as gait becomes more goal directed ▪ Time-intensive processing by human raters ▪ Variability between clinicians' ratings across centres, more so in the live setting ▪ Algorithms for automatic video processing not yet at high accuracy
Instrument-based freezing indices Accelerometer [Freezing Ratio (Mancini et al., 2017)] Pressure mat Electromyography Smart phone Combination	▪ Allows for faster processing speed if using automated algorithm	▪ Requires specialised and often bulky equipment, again limiting assessment in the home ▪ Body-worn sensors may interfere with normal gait
Home-based wearable devices	▪ Captures more automatic gait in the everyday environment ▪ Allows for long-term monitoring ▪ Could deliver a therapeutic intervention (e.g., cue)	▪ Artefact and interference ▪ Devices need to operate at a patient or carer level of expertise, which may limit complex or bulky set-ups

The FOG score is a clinical rating tool that scores freezing episodes as a subject completes four tasks aimed to elicit freezing (gait initiation, turning clockwise, turning counter-clockwise, and passing through a doorway), with and without two types of dual task (Ziegler et al., 2010). This method can objectively measure FOG severity, is sensitive to On and Off-medication states, and correlates well with patient self-evaluation of FOG. However, the duration of FOG episodes is not considered and the FOG Score assumes that akinetic freezing is of greater severity than the festination phenotype (Ziegler et al., 2010).

Instruments such as accelerometers (Moore et al., 2008; Mancini et al., 2012, 2017), force plates under the feet (Nantel et al., 2011), and lower limb surface electromyography (Nieuwboer et al., 2004) have all been used in the gait laboratory setting to quantify freezing along with a range of algorithms to produce an automated FOG detection mechanism. Previously, researchers have shown that body-worn inertial sensors can record a Freezing Ratio during a 2-min turning in place protocol that correlated well with clinical ratings of FOG (Mancini et al., 2017). However, these instrumented algorithms have not been widely validated for FOG assessment outside of their specific research purpose.

Visually scoring FOG from video by independent raters is still currently recognised as the gold-standard for assessing FOG severity in PD (Morris et al., 2012; Shine et al., 2012; Walton et al., 2018). This approach can be used to calculate the percentage of time spent frozen during a TUG task and has demonstrated excellent inter-rater correlations (Morris et al., 2012; Walton et al., 2018). However, this approach is time consuming to score and does not reflect what might be occurring outside of the clinic. In future, automated video scoring (Hu et al., 2020) could make this approach more viable at scale for comparing between assessment centres in the setting of a clinical trial. Obviously, there is a need for reliable, portable home based sensors or wearable technologies (Silva de Lima et al., 2017) that could identify even brief episodes of FOG during everyday activities and this is becoming a more focused area of FOG research (Marcante et al., 2020; Mancini et al., 2021).

WHAT SHOULD WE FOCUS ON TREATING?

Not surprisingly, most current research trials are focused on symptomatic therapies for patients with established FOG (see below), rather than exploring approaches to delay or prevent the onset of freezing. However, some data does exist about these "at risk" groups (Gao et al., 2020) and identifying those patients who will go on to develop FOG is of great interest given that they may benefit from specific intervention approaches, such as physiotherapy (Cosentino et al., 2020) or cognitive behavioural therapy (Moonen et al., 2021).

There are only a limited number of longitudinal studies that have followed patients without freezing to explore those characteristics that are associated with the future emergence of FOG, and whilst highlighting some of the potential risk factors for developing FOG, more integrated studies looking across further potential variables are probably required to understand the pathophysiological mechanisms by which they might be operating (Giladi et al., 2001a; Forsaa et al., 2015; Zhang et al., 2016; Ehgoetz Martens et al., 2018a; Kim et al., 2018; Kim R. et al., 2019; Gallea et al., 2021). These studies have identified that whilst patients with FOG have higher depression scores earlier in their disease course (Giladi et al., 2001a), the presence of anxiety may be more predictive of FOG onset within the next 12 months (Ehgoetz Martens et al., 2018a). More generally, a higher burden of neuropsychiatric symptoms predicted earlier onset of freezing of gait in a 2-year prospective study of 329 drug-naïve patients with PD, after adjusting for age of onset, disease duration, Unified PD Rating Scale (UPDRS) motor score, and dopamine transporter (DAT) activity (Jeong et al., 2021). Other clinical factors such as non-tremor predominance, early gait disturbance, cognitive impairment, left-sided disease onset and higher daily levodopa have also been associated with the development of FOG (Giladi et al., 2001a; Forsaa et al., 2015; Zhang et al., 2016; Kim et al., 2018; Lichter et al., 2021).

Other novel approaches for identifying those patients at risk of developing FOG are also being described. One recent study found that compared to a non-freezer group, patients who developed freezing within 5 years demonstrated increased baseline anti-saccade latencies (>300 ms), whilst having equivalent motor and cognitive deficits (Gallea et al., 2021). Indeed, this parameter alone was also strongly predictive for the presence of FOG and correctly classified 88% of non-freezers and 76% of eventual freezers (Gallea et al., 2021), which is broadly consistent with earlier work showing anti-saccade errors in PD patients with FOG (Walton et al., 2015a). Increased anti-saccade latencies were also correlated with decreased connectivity in the mesencephalic locomotor region-supplementary motor area (MRL-SMA) network, one of the networks involved in gait control, and a compensatory increase in other networks years before onset of freezing, which might provide a potential neurobiological explanation for these associations (Walton et al., 2015a).

It is also possible that biomarkers might prove useful in identifying those non-freezers at greatest risk of transitioning to FOG. Severe reduction in DAT activity in the caudate and putamen is associated with significantly higher incidence of FOG (Kim et al., 2018). Previous neuroimaging studies have identified the potential contribution of cholinergic deficits to FOG (Mancini et al., 2019), and amongst CSF biomarkers, low β-amyloid 1–42 has been associated with the future development of FOG in early stage PD patients (Kim R. et al., 2019). Obviously, it is not known whether this finding represents the role of concomitant Alzheimer-type pathology and it is well known that FOG is associated with cognitive decline (Irwin et al., 2012). Furthermore, combining β-amyloid 1–42 levels in a model integrating caudate DaTscan uptake and the postural instability gait difficulty (PIGD) motor phenotype score performed even better in identifying future freezers (Kim R. et al., 2019).

Thus, mechanisms already exist for enriching patients at risk of developing FOG who might be suitable for intervention studies. Such enriched cohorts would not only be a target group for early treatments, but may also reduce costs of recruitment

and follow-up if accelerated FOG development is accounted for in a trial design.

PHARMACOLOGICAL APPROACHES

It is well known that FOG occurs more frequently in the Off-state (Schaafsma et al., 2003) and thus, the first line treatment for Off-freezing is manipulating dopaminergic therapies to reduce Off time (Fietzek et al., 2013; Nonnekes et al., 2015). Studies evaluating that adjunct use of the monoamine oxidase B (MAO-B) inhibitors selegiline (Iijima et al., 2017) and rasagiline (Rascol et al., 2005; Cibulcik et al., 2016; Rahimi et al., 2016) have reported reductions in FOG, presumably through this mechanism. There is no available data yet to confirm whether the newest agent in this class, namely safinamide, may also be helpful in this regard. Freezing of gait was not an endpoint in the major randomised controlled trial of safinamide for wearing Off symptoms (Borgohain et al., 2014), but interestingly FOG-Q scores did not improve in a smaller recent uncontrolled study of 50 patients (Garcia et al., 2021).

The phenomenon of On-freezing is less common and much more difficult to manage as its relationship to dopamine levels is not fully understood (Espay et al., 2012; Cossu et al., 2015; Morales-Briceno et al., 2020). A recent proposal has suggested that levodopa may trigger FOG, hypothesising that maladaptive plasticity might in fact be induced by levodopa, which disproportionally increases the mismatch between motor and non-motor (cognitive and limbic) loops (Nonnekes et al., 2020). Obviously, the need by most patients for levodopa may limit meaningful investigation of this phenomenon but one approach might be through a large prospective delayed start design to see whether the earlier use of levodopa may drive the development of FOG. However, it should be highlighted that maladaptive plasticity may only occur with severe levels of striatal dopamine depletion and much of the literature supporting the paradox was recorded in the pre-levodopa era. Interestingly, a recent case series of five PD patients treated with 24-h levodopa carbidopa intestinal gel (LCIG) infusion, has reported a reduction in levodopa-unresponsive freezing and falls, when compared to conventional 16-h LCIG (Chang et al., 2015). The mechanisms underpinning such a finding are unclear, although improvements in sleep were proposed by the authors.

Though degeneration of dopaminergic neurons is the pathological hallmark of PD, non-dopaminergic neurons are also lost in the disease (Kalia et al., 2013). Cholinergic deficits related to cholinergic neuronal loss in the pedunculopontine nucleus (PPN) and nucleus basalis of Meynert (Karachi et al., 2010; Yarnall et al., 2011) have been reported as contributing to gait (Rochester et al., 2012) and attentional disturbance (Bohnen et al., 2006). Furthermore, antimuscarinic use has been found to be more frequent in the FOG group compared to non-FOG, in a cross-sectional study of 672 PD patients (Perez-Lloret et al., 2014). More recently, a phase 2 placebo-controlled trial of 130 PD patients found that the acetylcholinesterase inhibitor rivastigmine, improved step time variability, falls per month, gait speed whilst dual-tasking and freezing during the last month of a 32-week trial (Henderson et al., 2016). However, FOG was not a primary endpoint of this trial and a larger phase 3 trial aiming to recruit 600 patients is currently underway (ClinicalTrials.gov, 2021a).

Drugs that enhance noradrenergic transmission have also been investigated for FOG, given its possible association with noradrenergic neuron loss in the locus coeruleus (Rommelfanger and Weinshenker, 2007; Ono et al., 2016). However, current trials have been disappointing including two small, randomised studies of Atomoxetine, a selective noradrenaline reuptake inhibitor, which failed to improve dopamine-resistant FOG (Jankovic, 2009; Revuelta et al., 2015). Limited open-label data for droxidopa (L-threo-3,4-dihydroxyphenylserine), a noradrenaline precursor licensed for use for orthostatic hypotension, has suggested that it may be useful in combination with entacapone for treating dopamine-resistant FOG (Fukada et al., 2013). However, it is difficult to know how much of this response related specifically to stimulation of the noradrenergic pathways. Similarly, methylphenidate is a drug that increases both synaptic noradrenaline, as well as dopamine levels. Previous trials of methylphenidate have reported mixed results where FOG-Q scores were improved in patients with advanced disease who had undergone STN-DBS (Devos et al., 2007; Moreau et al., 2012), but no improvements were observed in patients with moderate gait impairment without DBS (Espay et al., 2011). These differences could in part reflect differential pathologies in heterogeneous patient groups or selective medication effects. Future studies assessing noradrenergic stimulation could be complimented by specific imaging techniques that could relate any changes in neurotransmitter signal to clinical efficacy or lack thereof, such as 11C-MeNER PET, a highly selective noradrenaline transporter radioligand, and/or neuromelanin imaging, to assess the integrity of the locus coeruleus (Sommerauer et al., 2018).

Drugs already established in improving anxiety and depression (Takahashi et al., 2019) may also have beneficial effects on FOG. Both selective serotonin reuptake inhibitor (SSRI) and serotonin noradrenaline reuptake inhibitor (SNRI) treatment improved the FOG-Q after 10 weeks in a small group of Japanese PD patients with depression (Takahashi et al., 2019). Short-term administration of paroxetine (an SSRI) interestingly improved baseline walking speed in a small group of PD patients who were not premorbidly depressed, but did not augment the motor response to levodopa (Chung et al., 2005). Whilst anxiety and depression have been associated with FOG, it is not clear whether any symptomatic benefits of these agents may extend beyond their effects on mood. Similarly, cannabidiol (CBD) is also known to modulate brain areas involved with mood (Fusar-Poli et al., 2010; de Faria et al., 2020) and some work has reported reduced falls, pain, depression, and tremor in PD (Balash et al., 2017). The endocannabinoid system is linked to motor control and dopaminergic signalling, with the highest densities of cannabinoid type 1 (CB1) receptors located in the globus pallidus and substantia nigra (Babayeva et al., 2016). A double-blind phase II randomised controlled trial is ongoing to assess the efficacy of cannabidiol (CBD) on motor symptoms (UPDRS part III score) in 75 PD patients (ClinicalTrials.gov, 2021b). Whether

these novel non-dopaminergic targets will benefit FOG will need further study.

SURGICAL APPROACHES

Deep brain stimulation (DBS) provides access to deep brain structures and the ability to directly modulate networks implicated in the pathogenesis of FOG (Fasano et al., 2012). Conventional bilateral DBS of the subthalamic nucleus (STN-DBS) is generally considered to reduce Off-state FOG (Fasano et al., 2012; Vercruysse et al., 2014; Schlenstedt et al., 2017; Barbe et al., 2020) in addition to its robust effects on other motor symptoms (Fasano et al., 2012). STN-DBS appears to be effective for at least 3–5 years post implantation (Schlenstedt et al., 2017), but after this time it has been recognised that there is often worsening of gait and balance (Moro et al., 2010; Schlenstedt et al., 2017). A small proportion of patients who typically have longer disease duration (Barbe et al., 2020), less pre-operative dopamine responsiveness (Schlenstedt et al., 2017) and greater putamen grey matter atrophy (Karachi et al., 2019) have also been identified as experiencing increased FOG and falls shortly after STN-DBS and careful pre-operative screening is recommended (Karachi et al., 2019). Lowering the STN-DBS frequency to 60–80 Hz from the more conventional >100 Hz has been another approach that has been pursued with mixed success (Moreau et al., 2008). Meta-analysis data suggests low frequency stimulation induces greater reduction in observed FOG and FOG-Q scores compared to high frequency stimulation (Su et al., 2018), possibly relating to differential effects of stimulation frequency on pathological alpha and beta-band oscillations (Blumenfeld et al., 2015). These benefits are, however, commonly lost over a few weeks (Ricchi et al., 2012; Zibetti et al., 2016). Gait improvements with low frequency STN-DBS stimulation may also come at the cost of reduced tremor control in the off-medication state (Phibbs et al., 2014; Conway et al., 2021) though arguably this limitation is less of a concern in most patients who will continue to be titrated on levodopa.

Alternative stimulation strategies targeting non-STN structures, such as the pedunculopontine (PPN) area (Thevathasan et al., 2011) and the substantia nigra pars reticulata (SNr; Weiss et al., 2013) have also been investigated as potentially offering benefits to specifically improve FOG. The PPN is thought to play an important role in automatic gait through the release of pre-prepared movement (Garcia-Rill et al., 2019), whilst the SNr influences the PPN through efferent monosynaptic GABAergic transmission (Nandi et al., 2008). Typically, stimulation of the SNr has been interleaved with STN-DBS and studies with relatively small patient numbers have reported some alleviation of resistant gait impairment in PD (Weiss et al., 2013; Valldeoriola et al., 2019; Golfre Andreasi et al., 2020). Exactly where and how to best stimulate the PPN remains unclear with meta-analyses (Golestanirad et al., 2016; Wang et al., 2017; Yu et al., 2020) and collaborative efforts between expert centres revealing significant heterogeneity in the studies conducted to date (Hamani et al., 2016; Garcia-Rill et al., 2019).

It is well recognised that the traditional "open loop" DBS approach for PD requires external input to adjust stimulation parameters with the stimulation being delivered continuously without regard for fluctuating clinical or electrophysiological states. In contrast, "closed loop" DBS is now being explored with bidirectional devices that can both sense neural signals and deliver stimulation in response to specific electrophysiological changes, thus acting in real time. Such neural signals include prolonged beta (13–30 Hz) bursts (Anidi et al., 2018), and low beta (15–21 Hz) and theta (5–8 Hz) band oscillations (Chen et al., 2019) in the STN associated with FOG episodes, which have now been shown to attenuate with stimulation, strengthening their place as biomarkers for gait freezing. Recent work utilising this technological advance has shown that this approach may be feasible, demonstrating that in a single patient, closed-loop bilateral STN-DBS responding to STN beta band power was superior to conventional open-loop DBS in reducing the percentage of time spent freezing during a Stepping in Place task (Petrucci et al., 2020). Furthermore, work using a validated Virtual Reality gait paradigm in patients during STN-DBS lead implantation has identified an increase in pathological beta and theta rhythms just prior to freezing episodes that could provide a specific trigger signal for adjusting closed-loop systems on demand (Georgiades et al., 2019). Closed-loop work incorporating PPN-DBS have also begun but appear more problematic. One recent study implanted five medication-refractory FOG PD patients with two closed-loop PPN leads in addition to bilateral globus pallidus interna (GPi) leads (Molina et al., 2021). However, due to surgical complications, two of these patients needed explantation of the leads. Results from the remaining subjects were heterogeneous and may have been impacted by GPi co-stimulation.

These findings suggest that whilst DBS for FOG does offer potential, more studies with homogenous patient populations undergoing standardised procedures and assessments will be required to progress the field. In addition, it is likely that patients will need close monitoring over extended periods of careful treatment titration to optimise their clinical benefits (Bronte-Stewart et al., 2020).

NON-PHARMACOLOGICAL APPROACHES

Physical Rehabilitation

Whilst a number of guidelines for physiotherapy in PD exist (e.g., Keus et al., 2014), there is little specific guidance for addressing FOG. Physical rehabilitation is acknowledged to be crucial (Cosentino et al., 2020) and there are a number of approaches that have been applied to FOG in the research setting. These include action observation training (Pelosin et al., 2010, 2018; Agosta et al., 2017; Mezzarobba et al., 2020), treadmill training (Hong and Earhart, 2008; Frazzitta et al., 2009; Lo et al., 2010; Barbe et al., 2013; Picelli et al., 2016; Baizabal-Carvallo et al., 2020; Bekkers et al., 2020; Seuthe et al., 2020), aquatic obstacle training (Zhu et al., 2018), curved walking training (Cheng et al., 2017), supervised slackline training (Santos et al., 2017), as well as

home based exercises (Canning et al., 2015). In contrast, general exercises and standard physiotherapy do not seem to be effective for the treatment of FOG (Miller et al., 2020). Behavioural strategies, such as cueing (Nieuwboer et al., 2007; Fietzek et al., 2014; Ginis et al., 2018), have also been extensively applied, as have dual-task situations (Geroin et al., 2018), which are designed to increase the complexity and recognise the association of FOG and selective cognitive deficits in attention (Naismith et al., 2010). Various types of cues (auditory, visual, somatosensory) and delivery systems (e.g., self-cueing, augmented reality) have been shown to positively modulate FOG (Fischer et al., 2018; Braunlich et al., 2019; Chang et al., 2019), though again the optimal way to target FOG is yet to be determined (Nieuwboer et al., 2007; Donovan et al., 2011; Spaulding et al., 2013; Young et al., 2016; Fischer et al., 2018; Braunlich et al., 2019; Chang et al., 2019). One meta-analysis comparing auditory to visual cues found that auditory cues appeared more effective, improving speed-related gait parameters in PD patients such as cadence and velocity as well as increasing step length whilst visual cues only improved step length (Spaulding et al., 2013). Auditory cues appear to make use of almost instantaneous motor entrainment to an external beat, activating the frontoparietal control and motor-cerebellar networks to bypass internal rhythm deficits of the basal ganglia (Braunlich et al., 2019). Somatosensory stimulation has historically been limited by the sophistication of the delivery technology, however, smaller wearable vibrotactile devices are emerging with early positive benefits on FOG (Tan et al., 2021), though their effects require validation. Long-term effects and the out-of-laboratory benefits of cueing training are to be confirmed (Chang et al., 2019). Methods to reduce cue habituation, including on-demand cueing, require further development before they can be deployed routinely (Ginis et al., 2018).

A recent meta-analysis of 19 studies involving 913 patients showed that interventions tended to have similar duration of each session (45–60 min) and number of sessions per week. Prolonged home based interventions (median 4 months) showed more promise of efficacy, whilst in terms of intervention categories, action observation and treadmill training had the most significant effect sizes (Cosentino et al., 2020). Common to these studies is the difficulty of creating a suitable control condition given the issues in blinding or finding a matched activity (e.g., cueing). In addition, only a limited number of studies have sought to correlate improvements in intervention with neurobiological changes through approaches such as fMRI (Silva-Batista et al., 2020). This can provide useful insights, such as a recent study that found increased activation in the mesencephalic locomotor region (MLR) post training in the intervention group of individual strength training with instability, but not in the control group of traditional strength training alone (Silva-Batista et al., 2020). The authors of this study also reported that these changes in MLR activation correlated with improvements in the NFOG-Q. It is likely that high-complexity exercises involving a combination of visual, cognitive, balance, and strength training have greater potential to modulate the network underlying FOG (Cosentino et al., 2020). Further larger trials investigating the long-term effects of therapy, the differences between On and Off-state training, and the comparison of multiple active intervention arms are desperately needed. Given that group training achieves similar positive effects to individual training (Pelosin et al., 2018), it is possible that such approaches could allow such programs to be delivered at scale.

Neuropsychiatric Approaches

Cognitive and affective deficits certainly modulate FOG (Heremans et al., 2013; Shine et al., 2013c,d; Ehgoetz Martens et al., 2014; Walton et al., 2014; Muralidharan et al., 2016; Witt et al., 2019) and it should be appreciated that approaches like cognitive training, cognitive behavioural therapy and meditation all have the potential to improve FOG and a wider range of symptoms with no risk of harm. A small number of studies have been completed in this space and offer insights into future approaches. One recent randomised double-blinded study of 38 PD patients with FOG evaluated cognitive training specifically targeting those neuropsychological processes most strongly associated with the symptom, including inhibitory control, attentional set-shifting, working memory, processing speed and visuospatial skills (Walton et al., 2018). This intervention was provided over 12 weeks and resulted in a statistically significant reduction in actual FOG severity in patients during their On-state (Walton et al., 2018). A smaller randomised cross-over trial of 15 patients comparing cognitive training, cognitive behavioural therapy (CBT) and proprioceptive training replicated the positive effect of cognitive training on observed FOG severity but not NFOG-Q scores (Chow et al., 2021). Of interest, the anxiety-targeting CBT intervention exacerbated FOG whilst showing a trend toward improving the Parkinson Anxiety Scale (PAS; Chow et al., 2021). Proprioception training appeared to have the greatest effect, though it should be noted that the effects of each intervention were lost at 2 weeks after the 4-week training program (Chow et al., 2021).

Less standardised interventions are yet to be investigated for FOG. However, it has been reported that meditation may protect against grey matter atrophy (Last et al., 2017) and is already well accepted by PD patients with high perceived efficacy for alleviating affective and motor symptoms (Fitzpatrick et al., 2010; Donley et al., 2019). Though there are no trials examining the impact of mindfulness meditation on FOG, it does improve attention (Malinowski et al., 2017) and emotional regulation (Tang et al., 2015), which have both been recognised as important modulators of freezing. A recent randomised controlled trial in 138 PD patients found a yoga-mindfulness program significantly improved anxiety and depression scores over a stretching and resistance training control, in addition to their Unified Parkinson's Disease Rating Scale Part III (motor) score (Kwok et al., 2019). A smaller study of just 30 PD patients participating in a yoga-meditation intervention experienced marked improvements in their FOG-Q, whereas a control group of no intervention did not change their freezing scores (Van Puymbroeck et al., 2018). It is unclear if these benefits were related to the meditation or physical rehabilitation component of the intervention (Van Puymbroeck et al., 2018).

Larger trials specifically investigating neuropsychiatric intervention strategies for FOG are now needed. These studies could potentially target both those with established FOG and an

enriched population of at-risk patients. These studies will need to have much larger numbers than those already conducted, which will probably necessitate coordinated international multi-centre approaches where cross-over designs with multiple active arms may be the most efficient method to compare different techniques. These would ideally be conducted in combination with standardised objective measures of FOG and mechanisms for interpreting neurobiological changes such as functional neuroimaging [e.g., MRI (Silva-Batista et al., 2020)] or neurophysiological [e.g., EEG (Malinowski et al., 2017)] parameters.

Non-invasive Brain Stimulation

Methods to modulate neuronal activity non-invasively also represent an attractive approach to access the distributed cortical and subcortical areas involved in FOG. Repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and more recently, non-invasive vagal nerve stimulation (nVNS), have all been explored as potential options.

Non-invasive brain stimulation is thought to improve motor symptoms of PD by inducing focal release of endogenous striatal dopamine following stimulation of the ipsilateral cortex (Strafella et al., 2001, 2003), as well as increasing cortical excitability of motor and cognitive cortical areas involved in the upstream regulation of gait. Though there have been several sham-controlled studies investigating rTMS and tDCS for FOG (El-Tamawy et al., 2013; Lee et al., 2014; Valentino et al., 2014; Kim et al., 2015; Chang et al., 2017; Dagan et al., 2017; Lu et al., 2018; Ma et al., 2019; Mi et al., 2019), the optimal target, stimulation intensity and duration of treatment are yet to be confirmed. To illustrate the heterogeneity of the literature, though the majority of rTMS studies used high-frequency stimulation ($\geq$10 Hz), the number of pulses and sessions varied significantly (450–3,000 pulses, delivered over 1–24 sessions) as well as treatment duration (3 days to 3 months) (Kim Y.W. et al., 2019; Xie et al., 2020). Indeed, two separate meta-analyses examining the benefits of prefrontal or primary motor cortical (M1) rTMS on FOG arrived at conflicting conclusions, though both noted heterogeneity amongst the included trials that may have masked a more positive outcome (Kim Y.W. et al., 2019; Xie et al., 2020). However, these studies do add to our understanding of brain networks involved in freezing. One resting-state functional MRI study with 10 sessions of rTMS delivered over an alternate target, the supplementary motor area (SMA), reported significant improvements in clinical freezing on the FOG-Q, as well as normalising functional connectivity patterns associated with FOG (Mi et al., 2020). Stimulation of a key cortical modulator confers effects on remote subcortical regions and demonstrates the related neural network with FOG (Mi et al., 2020). Previously, the SMA had not been thought to have a modulatory role on FOG based on single-session stimulation studies (Lee et al., 2014; Lu et al., 2018), suggesting that repeated sessions may be necessary to amplify the benefits of this type of intervention. Stimulation effects on FOG are likely transient rather than long-term, with a subgroup meta-analysis (Xie et al., 2020) of four rTMS studies with follow-up at $\geq$4 weeks (El-Tamawy et al., 2013; Ma et al., 2019; Mi et al., 2019, 2020) showing no significant difference in outcome by this time point. The effects of non-invasive stimulation may also be additive, as there appears to be a potential beneficial effect from multi-target compared to single target stimulation (Chang et al., 2017; Dagan et al., 2018; Manor et al., 2021). For example, simultaneous tDCS to the M1 and the left dorsolateral prefrontal cortex (DLPFC) improved freezing parameters immediately after the combined session, but not following primary motor cortex stimulation alone (Dagan et al., 2018). There is no additional benefit of simultaneous rTMS and rDCS stimulation compared to rTMS alone (Chang et al., 2017). Limitations of non-invasive stimulation are largely related to the need to remain within certain energy and pulse settings for safety, which reduces its access to deeper brain structures, but also contraindicates its use in PD patients with concomitant DBS (Magsood et al., 2020). However, taken altogether, these findings give cause for cautious excitement regarding the ability to modulate pathophysiological networks in FOG as techniques are further refined.

Vagus nerve stimulation (VNS) is an approved treatment for refractory epilepsy and depression that is also being investigated as a novel treatment for FOG in PD, especially following the availability of non-invasive transcutaneous stimulators (nVNS) (Farrand et al., 2017; Morris et al., 2019). It has been suggested that VNS may indirectly activate noradrenergic projections from the *locus coeruleus*, a region implicated in the pathogenesis of FOG, as well as exerting anti-inflammatory properties that may be important in halting disease progression. Recently, the first randomised, double-blind trial to investigate nVNS administered stimulation to the cervical vagus for 12 min each for 4 weeks in 33 PD patients with FOG (Mondal et al., 2021). The authors reported positive effects on gait velocity and step length, as well as reduced duration of freezing episodes in the laboratory gait assessment circuit, though interestingly patients' perception of their FOG-related disability (FOG-Q score) did not improve (Mondal et al., 2021). Excitingly there was a significant reduction in biomarkers of inflammation [TNF-α, reduced-glutathione, and brain-derived neurotrophic factor (BDNF)] which may have implications for future disease modification trials.

Spinal cord stimulation (SCS) for FOG is also under investigation targeting spinal afferents to modulate cortical motor circuits (Reis Menezes et al., 2020). Despite several publications arising over the past decade using percutaneously inserted epidural spinal stimulators (Thevathasan et al., 2010; Agari and Date, 2012; Pinto de Souza et al., 2017; de Lima-Pardini et al., 2018; Fonoff et al., 2019; Hubsch et al., 2019), this approach has yet to find its place in routine clinical practice. This may relate to difficulty delivering long pulse width and high-frequency stimulation to reach deep spinal tissue, which drains battery life and increases unpleasant sensations in the patient, as well as limited scope for a sham device (Fonoff et al., 2019). More recently, the first non-invasive SCS study was published exploring transcutaneous magnetic stimulation to the fifth thoracic vertebra level in five PD patients (three sessions of 400 pulses at 5 Hz) (Reis Menezes et al., 2020). The authors reported significant improvements in NFOG-Q and UPDRS-III motor scores at 7 days following stimulation

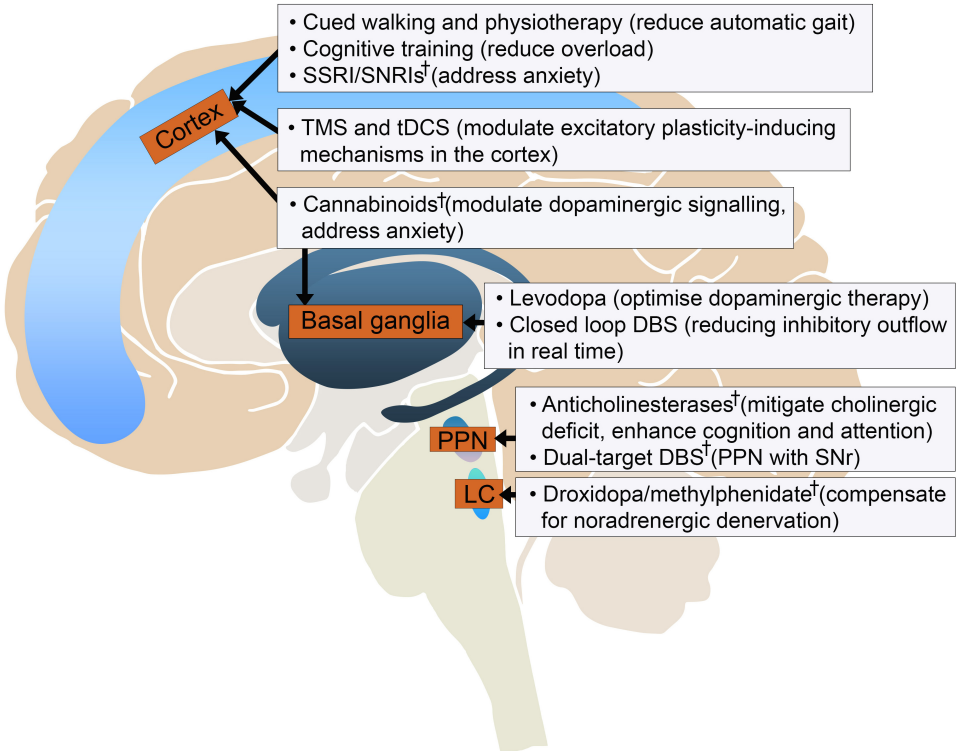

FIGURE 2 | Current and experimental† developments in treating gait freezing based on their potential targets in the locomotor circuit. DBS, deep brain stimulation; LC, locus coeruleus; PPN, pedunculopontine nucleus; SNr, substantia nigra pars reticulata; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin noradrenaline reuptake inhibitor; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

(Reis Menezes et al., 2020). Larger, sham-controlled studies are needed to establish if there is true benefit.

WHAT APPROACHES COULD HELP US IDENTIFY A NEW TREATMENT?

To date, methods in randomised controlled trials to improve FOG are heterogeneous in timing, duration, type of intervention (single target vs. multitarget), and outcome measures. Most studies aim to improve FOG symptoms once they have developed, which may be too late in the disease process. There are, as yet, no studies using population enrichment strategies (age, biomarker characterisation, motor phenotype) to examine interventions in participants at high risk of developing FOG. Designing future trials in FOG might also require matching the candidate intervention to the subpopulation most likely to benefit. For example, a trial testing cognitive behavioural therapy might require a cohort of anxious freezers (Ehgoetz Martens et al., 2018b).

To inform such trials, exploratory studies to clarify the neurobiological components of freezing (e.g., imaging, neurophysiology, epidemiology) and to identify the most accurate ways to gather this data will be important. Objective non-gait freezing paradigms that quantify freezing frequency and duration such as Virtual Reality (VR) gait (Shine et al., 2013a), Stepping in Place (Nantel et al., 2011) and alternate finger tapping (D'Cruz et al., 2020; Trager et al., 2020) or handwriting (Heremans et al., 2019) for upper limb freezing correlate well with observed freezing behaviour and can also be combined with functional neuroimaging (Shine et al., 2013b). Studies to compare such models side-by-side to determine their sensitivity in distinct subgroups could then be used to inform the design of larger trials. Objective biomarkers for FOG, such as electrophysiological changes in beta-band power (Handojoseno et al., 2015; Marquez et al., 2020; Molina et al., 2020), could also be used to inform larger trials. Indeed, whilst DBS provides a unique opportunity to record continuously from deep brain structures, this would potentially interfere with other measurement modalities including MRI and EEG. Other dynamic imaging techniques, such as functional near infra-red spectroscopy (fNIRS; Maidan et al., 2015; Vitorio et al., 2020) or magnetoencephalography (MEG; Boto et al., 2018), need to be explored for use in FOG and may provide helpful insights into the phenomenon.

Wearable technology or home-based "smart" systems to non-invasively measure FOG in the community should become a priority. This would allow for long-term recording, providing the large number of training events needed for algorithms to learn freezing signals in the individual patient in order to subsequently predict FOG in real time. Deep learning has already been deployed to automatically detect gait freezing in video recorded walks (Hu et al., 2020) and also using real-time

inertial measurements from wearable devices (Bikias et al., 2021). One group has recently developed an algorithm for use in patients without any previous anomalous gait data, trained on reference accelerometer data from a small group of reference normal and anomalous gaits, identifying 87.4% of FOG onsets (Bikias et al., 2021). Multi-modal measurements combining accelerometer and EEG readings are more accurate than single-modality measurement in detecting FOG events (Wang et al., 2020), suggesting future systems may require integration of different inputs. To create a multi-modal wearable system that is also comfortable to wear, it is likely that only the most robust signals from each modality will be included. Some progress has been made in identifying specific gait parameters that are the best for recognising abnormal steps (O'Day et al., 2020), and also in minimising intrusiveness of such devices, for example, the use of pressure-sensing insoles that were able to detect FOG in high agreement with clinical ratings (Pardoel et al., 2020).

There are also opportunities to make better use of already collected data. In a cross-sectional study of 172 PD patients, longer duration of treatment with dopamine agonists trended toward increased FOG, whilst longer duration of amantadine use trended against FOG, though these results did not reach significance in multiple regression (Giladi et al., 2001b). Collaboration between PD research groups to pool such data could prove useful. Interrogation of patient-level data in completed drug trials for potential candidate drugs for repurposing (e.g., if there was incidental reduction in fall frequency) could also provide a shortlist of already approved medications that can be investigated more cost-effectively. Efforts to follow large cohorts of PD patients prospectively with standardised biochemical, genetic and clinical assessments, such as in the Parkinson's Progression Markers Initiative 2.0 (NCT04477785), are already underway. The addition of FOG-specific gait assessments to this dedicated study would greatly add to our understanding of how FOG develops and progresses, as well as allowing for an examination of triggering or protective factors.

CONCLUSION

This review summarises the major difficulties in understanding and treating FOG. What is apparent is that a multimodal approach will be crucial to tackle this problem (**Figure 2**). Collaboration between research centres to standardise FOG measurement and share patient datasets will be necessary to scale studies, in tandem with development of novel techniques to better understand its pathophysiology.

AUTHOR CONTRIBUTIONS

CC performed the literature search and manuscript writing. SL was responsible for project conception, structuring, and editing. Both authors contributed to the article and approved the submitted version.

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REVIEW
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A Review of the Potential of Virtual Walking Techniques for Gait Rehabilitation

Omar Janeh[1*†] *and Frank Steinicke*[2†]

[1] Department of Computer Engineering, University of Technology, Baghdad, Iraq, [2] Human-Computer Interaction, Department of Informatics, Universität Hamburg, Hamburg, Germany

Virtual reality (VR) technology has emerged as a promising tool for studying and rehabilitating gait disturbances in different cohorts of patients (such as Parkinson's disease, post-stroke, or other neurological disorders) as it allows patients to be engaged in an immersive and artificial environment, which can be designed to address the particular needs of each individual. This review demonstrates the state of the art in applications of virtual walking techniques and related technologies for gait therapy and rehabilitation of people with movement disorders makes recommendations for future research and discusses the use of VR in the clinic. However, the potential for using these techniques in gait rehabilitation is to provide a more personalized approach by simulate the experience of natural walking, while patients with neurological disorders are maintained localized in the real world. The goal of our work is to investigate how the human nervous system controls movement in health and neurodegenerative disease.

Keywords: virtual locomotion techniques, virtual reality, gait disorders, therapeutic advances, rehabilitation

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****Correspondence:***
Omar Janeh
120049@uotechnology.edu.iq

†These authors have contributed equally to this work and share first authorship

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1. INTRODUCTION

The emergence of virtual reality (VR) as a therapeutic tool has provided important insights for developing potential movement therapies for patients with neurological conditions, such as Parkinson's disease (Lei et al., 2019), stroke (Huygelier et al., 2021) or other nervous system iseases (Liu et al., 2018). Although, its research in rehabilitation is becoming more widespread as technology becomes more accessible and affordable, the utilization of VR is not yet regularly used in clinical rehabilitation settings. However, VR provides a novel platform for the development of unique and customizable interventions, which enables new interventions by manipulating training duration or intensity as well as multi-sensory feedback to satisfy clinical demands for intensive and repetitive patients training (Deutsch and Mirelman, 2007; Kiefer et al., 2013), and increase their interest in the rehabilitation process by letting patients experience immersion [e.g., using head mounted displays (HMD)] or non-immersion (e.g., using 2D displays with a limited field of view) virtual environments (VEs), so that patients' treatment compliance is effectively improved (Peñasco-Martín et al., 2010; Gallagher et al., 2016). Thus, more immersive displays have a higher opportunity to present a fully artificial digital environment that results in a high sense of presence (Milgram and Kishino, 1994). Slater (2003) has defined presence as the feeling of being in an environment even when the person is not physically present and leading to behavior that resembles the subject's situation in the environment.

Rehabilitation interventions in VEs can manipulate practice conditions to engage motivation, motor control, cognitive processes and sensory feedback-based learning mechanisms

(Levin et al., 2015). Porras et al. (2018) suggested that implementation of patient-tailored motor learning strategies into the design and planning of VR interventions may enhance the efficiency and improve the therapeutic outcome. To this end, the general principles of motor learning can be well applied and integrated in VR training by providing goal-oriented, repetitive and varied practice that is adjusted to the abilities of the user (Deutsch and Mirelman, 2007; Langhorne et al., 2011). Therefore, when developing VR interventions, it is important to consider both the construction of the VE and the interfaces for measurement and feedback that accompany them (Weiss et al., 2006). Together, novel forms of therapeutic interventions can be used to evaluate and treat specific aspects of the human gait (Martens et al., 2017). Recent research has increasingly focused on the use of VR in rehabilitation, including to enhance walking (Mirelman et al., 2011, 2013; de Rooij et al., 2016, 2019).

Virtual walking (i.e., based on real walking) is considered the most intuitive way of navigation in VEs and is also found to be more presence-enhancing compared to other navigation techniques (Usoh et al., 1999). Furthermore, it is proven to be superior over other techniques across users' navigational tasks (Ruddle and Lessels, 2009), cognitive map buildings (Ruddle et al., 2011), and cognitive demands (Marsh et al., 2013). Therefore, a variety of virtual walking techniques have been proposed (see section 3), including walking in place (Slater et al., 1995a,b), redirected walking (Razzaque et al., 2001) or omnidirectional treadmill (Darken et al., 1997). However, there is an increased number of recent studies that use virtual walking techniques for medical and rehabilitative purposes, which provide insights into the future of gait rehabilitation in VR. For instance, Martelli et al. (2018), Janeh et al. (2019b), and Rockstroh et al. (2020) have used a real walking technique, which allows the user to walk about the space in a controlled VE. Other researchers have used new technologies of locomotion devices, such as Strider (Freiwald et al., 2020), 360° VR video-based immersive cycling training system (Lee et al., 2021) and KatWalk omnidirectional treadmill (Cherni et al., 2021). In addition, a recent study by Cai et al. (2021) has shown that WIP is feasible on gait rehabilitation of stroke patients, which translates the viewpoint when the user marches in a stationary location.

The goal of this review is to summarize insights from studies on locomotion techniques in VEs that illuminate the role of movement variability for gait therapy and discuss options for VEs to manipulate task attributes to provide novel forms of feedback and guidance. However, it can inform clinical decision-making and future practice about how to best apply virtual walking techniques in gait rehabilitation, and identify the walking task delivery under the different interface conditions, to demonstrate that the acquired skills from VE practice can be transferred to the real world. We summarize the state of the art of virtual walking techniques for gait rehabilitation in terms of technical, perceptual, cognitive aspects, as well as simulator sickness aspects that must be components of VEs for transfer to occur.

2. HUMAN GAIT

Human gait refers to the repetitive locomotion pattern of how a person walks. Although, the process appears automatic and easy, gait is actually a complex and high-level motor function (Mansfield and Neumann, 2009). In order to analyze and evaluate how a person walks, it is necessary to isolate the shortest, unique, repeatable task during gait. This task is called the (bipedal) gait cycle that requires movements from the right and left sides of the body. In normal gait, the average duration of a gait cycle will be very similar for the left and right sides. In pathological (i.e., abnormal) gait, there may be a pronounced difference between the two sides, leading to arrhythmic gait patterns (Uchytil et al., 2017).

2.1. Phases of the Gait Cycle

A gait cycle begins when the heel of one foot touches the ground and ends after the leg and body have advanced through space and time and the heel of that same foot hits the ground again. Realizing aspects of the gait cycle such as phasic, time, spatial and pressure measures, which can be measured an utilized to determine the quality of a person's gait. The cycle includes a period when the leg is in contact with the ground, which is followed by a period when it is advancing through space. Because of the dynamic and continuous nature of walking, the gait cycle is described as occurring between 0 and 100% (**Figure 1**). It can be distinguished into two primary phases: (i) the stance and (ii) swing phases, which alternate for right and left lower limbs.

- *Stance phase* describes the portion of the gait cycle when the foot is in contact with the ground, which makes up to 60% of the gait cycle. Within a stance phase, the double support represents approximately 20% and single support represents approximately 40% of the gait cycle (Inman et al., 1981). Therefore, when a foot is in a swing phase the other foot should be in a single support phase. When a foot is in a stance phase, it goes through a double support phase 10% of the initial stance phase, a single support phase 40%, and another double support phase 10% of the end of stance.
- *Double support* denotes the amount of time that a participant spends with both feet on the ground during one gait cycle.
- *Single support* describes the time elapsed between the last contact of the current footfall to the first contact of the next footfall of the same foot. It is equivalent to the swing time.
- *Swing phase* is the portion of the gait cycle when one foot is in the air. It is equivalent to the single support time of the opposite foot.

The phases of swing and stance are further divided into eight events during the gait cycle (Perry and Davids, 1992); five of which occur in the stance phase, when the foot is on the ground, and three in the swing phase, when the foot is moving forward through the air (**Figure 1**).

1. *Heel contact:* the heel or another part of the foot contacts the ground (at 0% of the gait cycle).
2. *Foot flat* the period that the entire plantar aspect of the foot is on the ground (at 8% of the gait cycle).

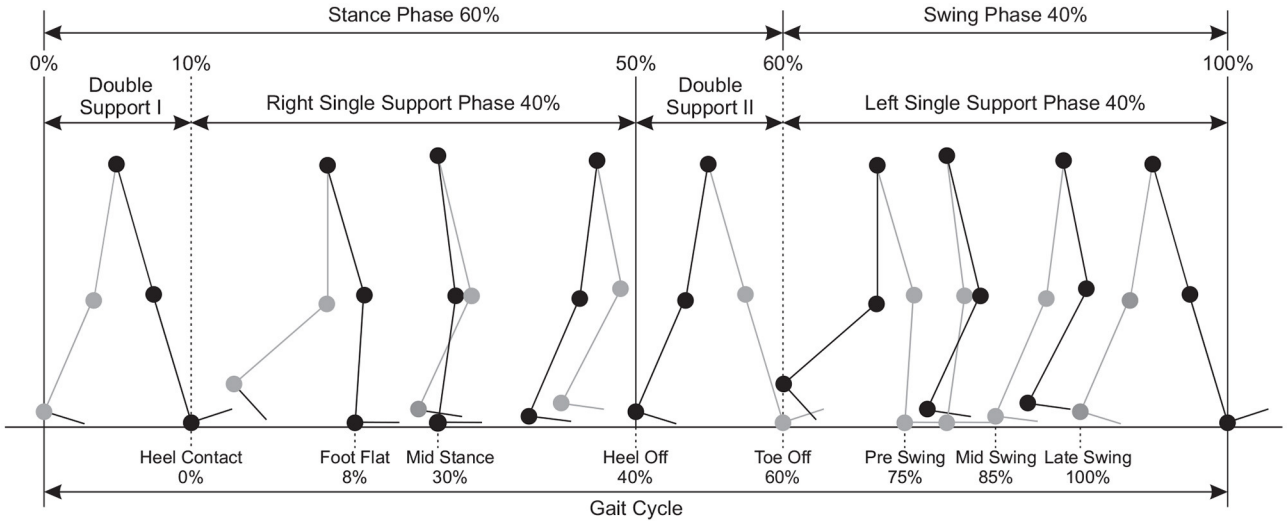

FIGURE 1 | Phases of gait cycle defined for rhythmic natural walking and their proportions as percentages.

3. *Mid stance* is the point where the body weight passes directly over the supporting lower extremity (at 30% of the gait cycle).
4. *Heel off* describes the instant the heel leaves the ground (at 40% of the gait cycle).
5. *Toe off* describes the instant the toe leaves the ground (at 60% of the gait cycle).
6. *Pre swing* describes the period from toe off to mid swing (at 75% of the gait cycle).
7. *Mid swing* is the period when the foot of the swing leg passes next to the foot of the stance leg (at 85% of the gait cycle). This corresponds to the mid stance phase of the opposite lower extremity.
8. *Late swing* the period ranging from mid swing until heel contact (at 100% of the gait cycle).

2.2. Control of the Gait Cycle

Bipedal locomotion is accomplished through a complex and coordinated pattern of nerve signals, sent to the muscles, which in turn move the joints, the limbs and the remainder of the body (Duysens and Van de Crommert, 1998; Whittle, 2014). During walking in the real world, vestibular, proprioceptive, and efferent copy signals, as well as visual information create a consistent multi-sensory representation of a person's self-motion, i.e., acceleration, velocity and walking direction (Dietz, 2002; Takakusaki, 2013). Modifying the sensory information during the movement can come from either proprioceptive information or efference copies of the motor command during the preparation for motor output (Pynn and DeSouza, 2013). The control of locomotion involves the use of afferent information from a variety of sources in the visual, auditory, vestibular and proprioceptive systems (Dietz, 2002). Efference copies are those neural representations of motor outputs that predict reafferent sensory feedback and modulate the response of the corresponding sensory modalities. Also, accessing a copy of the efferent command allows the brain to prepare for the consequences of an intended motion before it has occurred (Harris et al., 2002).

The voluntary control of movement and high-level modulation of gait patterns is originated at the supraspinal level. The latter regulates both the central pattern generator and reflex mechanisms (Dietz, 2002). Also at the supraspinal level, information from vestibular and visual systems are incorporated, which are crucial for the maintenance of balance, orientation, and control of precise movement (Dietz, 2002). Efferent stimulation is transmitted through motor neurons to individual muscle groups, which are recruited to affect the movement. Afferent feedback, including that from proprioceptors of the muscles and joints and mechanoreceptors of the skin, is used to directly modulate motor commands via mono- and polysynaptic reflex arcs, thus contributing to the efficiency of gait under normal conditions and stability of gait in the face of unexpected perturbations (Tucker et al., 2015).

2.3. Gait in Older Adults

The gait of the older adults is subject to two influences (Whittle, 2014): the effects of age itself and the effects of pathological conditions, such as osteoarthritis and parkinsonism, which become more common with advancing age. The gait of the older adults appears to be simply a slowed down version of the gait of younger adults. Furthermore, the differences between the gait of the younger and the older adults are described by Murray et al. (1969), which suggested that the purpose of gait changes in the elderly is characterized by a cautious attitude of walking, which is essentially an exaggeration of the gait changes which normally occur with age. For instance, decreasing the step length and increasing the step width make it easier to maintain balance while walking. Increasing the cycle time leads to a reduction in the percentage of the gait cycle for which there is only single support, since the increase in cycle length is largely achieved by lengthening the stance phase and hence the double support time.

A comprehensive review of the changes in gait with advancing age was given by Prince et al. (1997).

Given biological aspects of walking, gait performance is determined by continuous, ongoing postural adjustments by several types of control mechanisms. Stereotypical patterns of synergic muscle group activation (Diener et al., 1988) need to be scaled appropriately by peripheral sensory feedback (Diener et al., 1988) and centrally generated, anticipatory motor programs (Horak and Macpherson, 1996). It has proposed that postural alignment requires three different processes (Horak et al., 1992): (i) sensory organization and weighting of the orientation senses such as somatosensory proprioceptive, visual and vestibular information, (ii) motor adjustment processes involved with executing coordinated and properly scaled neuromuscular responses and (iii) background tone of muscles through which balance changes are compensated. The process of sensory organization seems to be hierarchically organized at different levels, these systems should be coherent, any conflicting orientation inputs must be quickly suppressed in favor of those congruent with the internal reference, otherwise postural and gait performance worsens (Massion, 1998; Mergner and Rosemeier, 1998).

3. VIRTUAL WALKING TECHNIQUES

As in the real world, most immersive virtual environments are usually suitable to be explored by walking. However, allowing VR users unconstrained walking requires huge free-space areas in which the movements of the user can be tracked. In particular, in a VE the space may have infinite size and the user should be able to walk and explore that space freely. However, in real physical spaces users have constrained space. If the virtual space and the real space have similar sizes, a one-to-one mapping can be used for navigation, but if the virtual space is larger than the real space, the users may eventually walk outside the real tracking space. This interrupts the tracking and may breaks in presence and lead to reduce user experience. To overcome this limitation, some techniques have been developed to enable users to explore larger VEs with real walking. In this section, we summarize some of these most fundamental approaches:

3.1. Walking in Place

In *walking-in-place* (WIP) interfaces, users perform stepping-like movements without forward motion of the body, but a virtual forward motion is induced instead. The diagram in **Figure 2** shows the gait cycle of WIP technique; the significant difference is that the single support periods of normal walking are replaced by foot off, maximum height and foot contact. In this technique, users make body gestures similar to real world walking, without actually moving with respect to the physical environment. This way, users can walk virtually and explore a larger virtual environment. Important advantages of WIP technique include: cost effectiveness (Feasel et al., 2008), naturalness (Usoh et al., 1999), stronger feeling of presence and easier to learn compared to other approaches (Slater et al., 1995b; Templeman et al., 1999), and proprioceptive feedback similar to real walking (Slater et al., 1994). However, since displacement in the real world is prevented with WIP technique, vestibular feedback as in real walking is not possible. One of the first scientific implementations of the walking in place technique was published by Slater et al. (1995b) and Slater et al. (1995a). In that work, head movements were analyzed while performing WIP gesture **Figure 4A**, and virtual walking was triggered by the movement of the head. The latency was substantial; the system required four steps in place to start the virtual walking, since false-positive steps (moving viewpoint when the user is not walking in place) were considered more confusing than a late start. Similarly, the system looked for no steps for two cycles to stop the virtual walking. Since then, different aspects of the walking in place technique have been examined, such as step detection, start and stop latency (Feasel et al., 2008), and smooth motion (Whitton and Peck, 2013).

Wendt et al. (2010) proposed system used a biomechanical state machine to control the virtual walking, and found more consistent output speeds compared to a study by Feasel et al. (2008). A similar study by Kim et al. (2012) have proposed a technique that triggers WIP technique using the inertial sensors embedded within two smart phones attached to the user's ankles in order to track leg movement in real time. Usually, most WIP techniques rely on gestures for walking input and control, for instance, a so-called stepping gesture, similar to soldiers marching in place. Nilsson et al. (2013a) performed a study comparing this gesture to two alternative gestural inputs: (i) a gesture where the user alternately bends each knee, thus moving the lower leg backwards, and (ii) a gesture where the user in turn taps each heel against the ground without breaking contact with the toes. Furthermore, the perceived required physical effort for the tapping gesture (**Figure 4B**) was closer to real walking. In another study by Nilsson et al. (2013b), some of those authors examined two more input gestures (i.e., hip movement and arm swinging). The results showed that arm swinging (**Figure 4C**) was perceived as natural as the original WIP technique. Moreover, Langbehn et al. (2015) have proposed WIP technique (**Figure 4D**) that involves a novel way of scaling the speed derived from the steps in place (i.e., the user is able to increase the speed by leaning the torso forward).

3.2. Redirected Walking

Redirected Walking (RDW) enables users to explore a virtual world that is considerably larger than the real world (Steinicke et al., 2009b). The idea is that users walk on different paths in the real world, which may vary from the paths they perceive in the VE (Bruder et al., 2013; Vasylevska and Kaufmann, 2017; Nilsson et al., 2018). For instance, using curvature gains the user effectively starts walking in small circles in the physical space while having the illusion of being able to walk straight in the VE (Razzaque et al., 2001). More particularly, (**Figure 3**) illustrates redirection of gait in a VE where the change of direction (i.e., redirected leg) is opposite to the contact leg, such as turning left while the right leg is in contact with the ground (Hase and Stein, 1999). This turning strategy is very similar to the one used in normal straight walking and tends to enlarge the step width, which minimizes the risk of falling, maximizes the possibility of fast change of directions, and ensures continuity of the walking path (Patla et al., 1999).

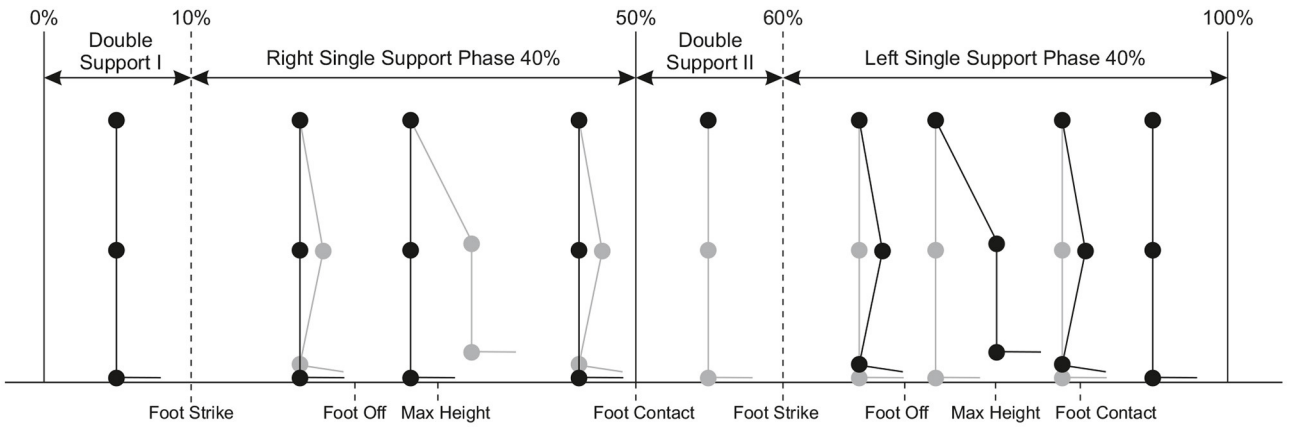

FIGURE 2 | Phases of gait cycle defined for rhythmic walking in place and their proportions as percentages.

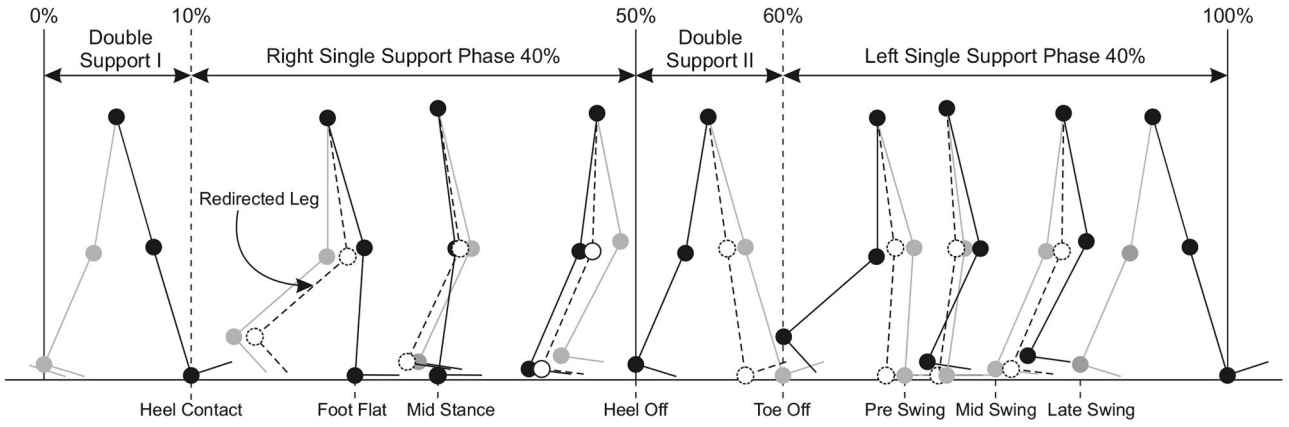

FIGURE 3 | Phases of gait cycle defined for redirected walking and their proportions as percentages.

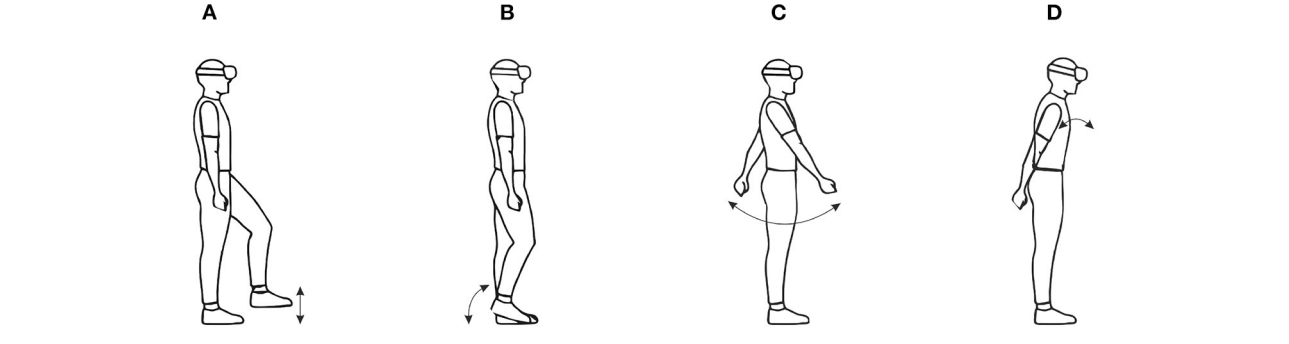

FIGURE 4 | Images for WIP technique gestures: **(A)** traditional WIP, **(B)** tapping in place **(C)** arm swinging, and **(D)** forward leaning. Arrows illustrate the movement of body parts used to perform the gesture.

However, redirection causes a sensory mismatch between the visual and bodily feedback elicited by the rotating VE during walking (Rothacher et al., 2018). It is found that, when only visual input is supplied, people can successfully estimate the amount of change in direction but not the path they followed (Lappe et al., 1999). This makes it possible to manipulate the visual flow to keep the users in the tracking area without being able to notice the manipulations if a physical space of at least $45m^2$

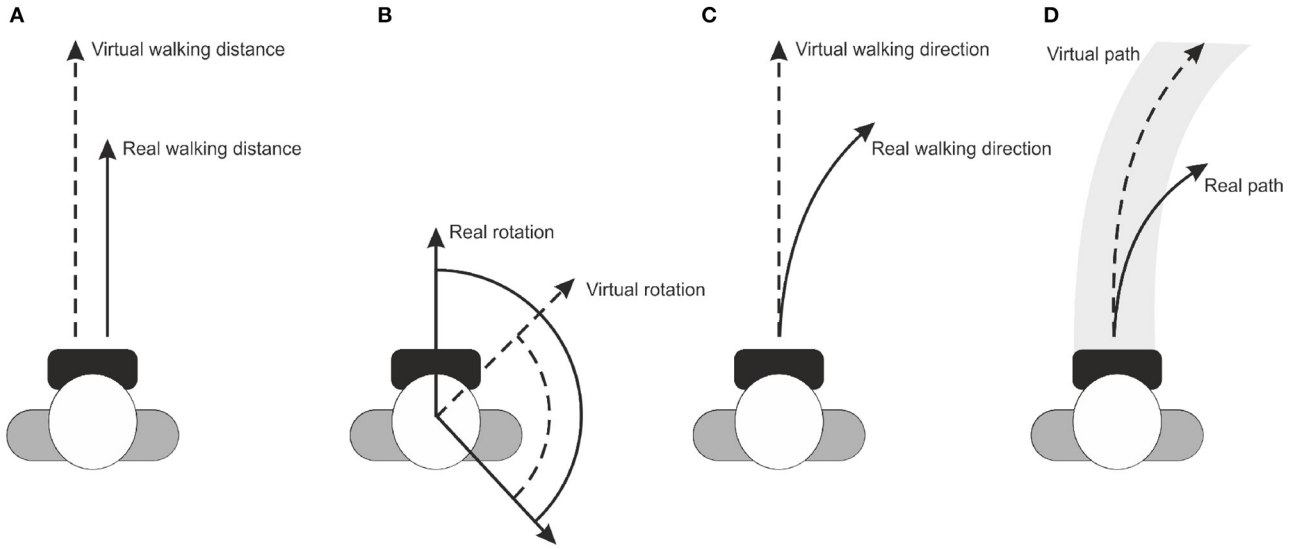

FIGURE 5 | Images for RDW technique manipulations: **(A)** translation gain, **(B)** rotation gain **(C)** curvature gain, and **(D)** bending gain. Lines indicate the real and virtual transformations.

is available (Steinicke et al., 2009b). These experiments have been replicated with different settings and extended several times (Kopper et al., 2011; Bruder et al., 2012; Freitag et al., 2016). For instance, Grechkin et al. (2016) found that an area of approximately $25m^2$ can be sufficient for unlimited straight walking in a VE.

However, with RDW techniques large-scale VEs can be explored within a smaller tracking area. There are some variations of RDW techniques, and different taxonomies have been proposed. Steinicke et al. (2009b) proposed a classification based on the types of gains applied: translation (**Figure 5A**), rotation (**Figure 5B**) or curvature (**Figure 5C**). Suma et al. (2012) proposed a different classification based on the geometric flexibility, the detectability of the technique and the continuity. In this taxonomy, the repositioning and reorientation techniques can either be overt or subtle according to the detectability, and either continuous or discrete according to the gain application. Bruder et al. (2012) examined the limits of the gains for individuals using an electric wheelchair controlled by a joystick. The possible range for the gain values was found to be larger for such redirected driving. Recent work by Zhang et al. (2018) has examined motion detection thresholds in a large VE for the purposes of improving a 360° camera telepresence robot by real walking. They found that participants could not discriminate between real and telepresence movements (i.e., translation and rotation) when translation gains are down-scaled by 6% and up-scaled by 10%, and rotation gains are about 12% less or 9% more than the actual physical rotations. This indicates that observers in this particular setup were indeed sensitive to motion discrepancies.

Redirection algorithms can also be altered to involve passive haptic feedback objects (Steinicke et al., 2008, 2009a). A proxy object in the real environment representing virtual objects with similar size, shape and surface structure can support passive haptic feedback to the users. Although more difficult to utilize, such passive haptic feedback improve the VR experience significantly (Insko et al., 2001). Other RDW techniques use a visuo-haptic interaction to modify the human spatial perception, such as Suma et al. (2011) and Matsumoto et al. (2016), to provide a sensation of walking in unlimited VR space in spite of walking in a limited real space. In these systems, since the users actually move their bodies in space, both motor commands and proprioceptive as well as vestibular information from the body movements can be utilized. Another technique for exploring architectural 3D models scales the virtual room to fit into the real room, so that users can feel the real walls when they reach to the virtual walls (Bruder et al., 2009). In this study, an intense redirection was used to force users go through a virtual door in a virtual wall, so that they did not collide with the real walls.

Recently, novel RDW techniques consider perceptual masking effects like saccades, blinks, and other perceptual suppressions. In this context, Sun et al. (2018) enhance redirected interaction by detecting saccades and amplifying redirection during the events without introducing virtual scene warping. Another work by Langbehn et al. (2018) conducts perceptual experiments to measure translation and rotation thresholds during eye blinks to facilitate RDW.

3.3. Locomotion Devices

Treadmills are allowing navigation of large-scale VEs via walking movements made within a limited space. While it is supposed to biomechanically identical to normal walking, it alters users' perception of motion due to missing vestibular feedback and alters the user's gait cycle (Durgin et al., 2007). Seminal work in this field was reported by the *Walkthrough* project (Brooks, 1987), which supported unidirectional movement, and the user

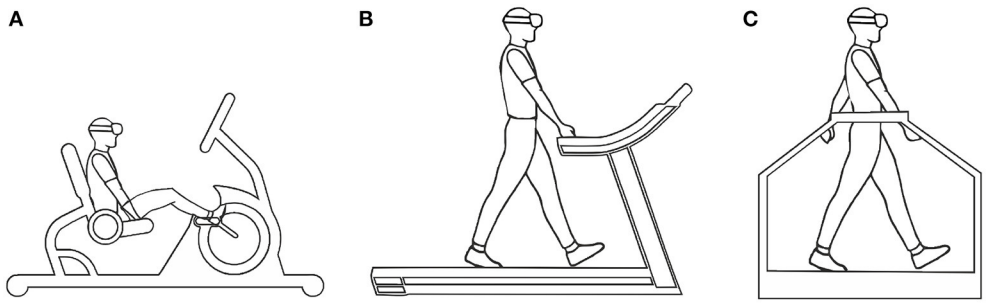

FIGURE 6 | Images for treadmill locomotion interfaces: **(A)** seated, **(B)** unidirectional, and **(C)** omnidirectional treadmills.

could rotate by using a steering bar similar to a bicycle. It allows for walking in one direction, but severely restricting the possibilities for navigation through VEs (Souman et al., 2010). Three generations of locomotion devices were developed for the U.S. Army's Dismounted Infantry Training Program (Darken et al., 1997). The Uniport was the first seated treadmill (**Figure 6A**) built for lower body locomotion and exertion, which did not feel natural and did not allow for making sidesteps. The second, Treadport is based on a standard unidirectional treadmill (**Figure 6B**) with the user being monitored and constrained from behind via a mechanical attachment to the user's waist. It was better compared to the first generation in which allowed for more natural locomotion, but was still limited to one direction of movement. The third generation system was the omnidirectional treadmill (**Figure 6C**) that enables locomotion in any direction of travel. The system consisted of 2D rotary motors that moved the treadmill belts to keep the user in the same place. The study showed that accurate user tracking and precise control over the speed of the belts were critical for usability of the system. Otherwise users experienced uncomfortable sudden movements. A similar system was developed in later studies and compared a 3DOF motion platform with controller-based locomotion (Darken et al., 1997; Iwata, 1999). In more recent studies, an improved omnidirectional treadmill so-called *CyberWalk* was compared with real walking (Schwaiger et al., 2007; Souman et al., 2011), which allows for natural walking in any direction through arbitrarily large-scale VEs. The CyberWalk needed to ideally be large enough to accommodate a gradual accelerations on the motion platform to keep the user at its center. Although the system was found to be effective in locomotion in VEs, it is extremely expensive to maintain and difficult to adjust in the real space (Frissen et al., 2013).

Furthermore, there are some atypical approaches to locomotion in this category. One of these studies was so-called *Cybersphere* (Fernandes et al., 2003). The authors used a large sphere in which the user could walk, run, jump or crawl freely in any direction to explore an infinite VE. Another similar product, which was commercialized, is called *VirtuSphere* (Medina et al., 2008). The VirtuSphere was designed to work with HMDs that enables users to walk in all directions by placing them inside a large, rotatable, hollow sphere. Due to the sphere having its own large mass, it will not stop, start, or change directions with a high degree of responsiveness, and users must essentially re-calibrate their movements to adjust for the movement of the surface under their feet. Another interesting approach to locomotion in VEs called *String Walker* (Iwata et al., 2007). In this approach, each foot was attached to four motor pulleys with strings. Once a forward motion was detected, the strings pulled the user to the center. This information was gathered with a touch sensor placed on each foot. It detected stance phase and swing phase of walking. The tension was only applied when the foot was on the ground. The motor-pulley mechanisms are mounted on a turntable driven by a motor when the walker changes direction of walking, the turntable is activated to follow the direction of the walker.

3.4. Controller-Based Virtual Walking

Manual devices such as joysticks, keyboards and VR controllers are widely available, which allow to perform walking inside the VE by involve user's hands and arms (Darken and Sibert, 1996; Marchal et al., 2011). Such joystick-based walking was compared with real walking using different display types (CAVE vs. HMD) (Grechkin et al., 2014). In this study, users performed perceptual-motor coordination tasks with different locomotion techniques. The results show that different velocity controls of each locomotion technique affect the timing and success rate of actions. In real walking, the speed can be controlled easily whereas with a joystick an almost constant speed is provided. Another study by Peck et al. (2011b) and Peck et al. (2011a) compared joysticks with other locomotion techniques in a virtual maze environment. They found that participants, who used joystick-based walking performed significantly worse than participants who used RDW or WIP. Furthermore, joystick- and keyboard-like devices were inferior for controlling spatial orientation compared to RDW techniques (Ruddle and Lessels, 2006). Riecke et al. (2010) compared real walking and joystick locomotion with an additional alternative of real rotation with joystick-based walking. They found that combining real rotation with joystick-based walking produce similar task performance scores as real walking. The results show that large tracked areas are not required for reasonable navigation performance in VR. On the other hand, Nabiyouni et al. (2015) compared joystick to a real walking and VirtuSphere; joystick received better results than VirtuSphere in terms of fatigue, ease of learning, ease of walking

and precision. The authors concluded that well designed low fidelity locomotion techniques such as joysticks often give better results compared to designs with moderate interaction fidelity like VirtuSphere.

Alternative locomotion techniques have been developed using VR controllers such as teleportation (Bozgeyikli et al., 2016). With teleportation the user's virtual viewpoint is moved while the user itself stays at the same position and orientation in the physical space. Bolte et al. (2011) developed the so-called *jumper metaphor* that uses the head direction to select the destination and a physical jump of the user to trigger the teleportation. Another work by Bozgeyikli et al. (2016), utilizes gesture-based interaction to point to where the user wants to go, and the main motion takes place through teleportation. In their work, teleportation was compared to WIP and joystick regarding usability. Results show that teleportation is subjectively preferred as a user friendly locomotion technique. However, an extended version of this teleportation technique for which it was possible to set a certain target direction into which the user should face after the teleportation, showed a decrease of the user experience. Bolte et al. (2011) compared teleportation to real walking and to the jumper metaphor. The result shows that teleportation and jumper metaphor are more effective techniques than real walking. Furthermore, in a CAVE setup, Freitag et al. (2014) compared teleportation to joystick and real walking with portals that were used to reorient the user in the tracking space. Teleportation was faster than real walking, but led to an increased loss of orientation compared to joystick. They could not find any differences between teleportation and real walking concerning motion sickness.

Overall virtual walking techniques may be a practical and useful tool to target sensory and cognitive deficits that contribute to gait impairments, and thus provide new opportunities to improve gait, mobility, and ultimately quality of life in those living with neurological and neurodegenerative diseases. In the following section we will discuss research utilizing virtual reality as a method for therapeutic intervention for gait impairments in different cohorts of neurological patients.

4. VIRTUAL WALKING TECHNIQUES FOR GAIT REHABILITATION

More recent reviews by Canning et al. (2020), Huygelier et al. (2021), and Keshner and Lamontagne (2021) highlighted the concrete contributions of VR to rehabilitation of balance and gait; suggesting that the most promising effects of VR are the ability to multitask in a VE that can replicate the demands of a physical space. There is indeed already a promising body of evidence for effective virtual walking techniques in populations such as stroke (Mirelman et al., 2010; Cai et al., 2021), multiple sclerosis (Samaraweera et al., 2013; Winter et al., 2021), Parkinson's disease (Janeh et al., 2019a; Quek et al., 2021), and Alzheimer's disease (White and Moussavi, 2016). In this section, we summarize the different VR-based gait rehabilitation approaches:

4.1. Treadmills

A commonly used virtual walking technique for gait rehabilitation is unidirectional treadmills (Yang et al., 2008; Mirelman et al., 2011; Peruzzi et al., 2017; Richards et al., 2018). Such non-immersive VR-based training hold promise for fully immersive VR, such as using an HMD in combination with treadmill walking (Luque-Moreno et al., 2015; Roeles et al., 2018), which provided motor cognitive challenges in a simulated, real life but safe environment, compared with the same dose of treadmill training alone (Canning et al., 2020). To date, a small number of studies have investigated gait training using an HMD (Parijat et al., 2015; Peterson et al., 2018; Chan et al., 2019), and a recent study showed that both young and older adults were able to use HMD during walking without adverse effects (Kim et al., 2017). More recently, research groups have also investigated the use of omnidirectional treadmills to walk through virtual environments (Lamontagne et al., 2019; Soni and Lamontagne, 2020), which allow changes in direction while accommodating gait speed changes that observed during overground locomotion.

In parallel to those clinical investigations, other studies have demonstrated VR foot pedals combined with neuroimaging techniques (functional MRI) or DBS surgery to investigate the pathophysiology underlying gait deficits in Parkinson's disease with freezing of gait; which in turn allowed the patients to navigate forward or turning through the virtual environment (Shine et al., 2013; van der Hoorn et al., 2014; Gilat et al., 2015; Georgiades et al., 2016; Ehgoetz Martens et al., 2018; Matar et al., 2019). Forward progression was only achieved when patients alternately depressed the pedals (i.e., left-right-left). Along the same lines, several studies already adopted a VR cycling training for the motor rehabilitation of old adults or stroke patients (Deutsch et al., 2013; Yin et al., 2016; Pedroli et al., 2018). Although, it seems that treadmills walking may lead to similar kinematic data to ground walking, but further studies will be necessary to ensure that the acquired skills from VE practice can be transferred to the real world (Lohse et al., 2014; de Rooij et al., 2016; Palma et al., 2017; Porras et al., 2018; Levac et al., 2019).

4.2. Virtual Stepping

Among the most promising one that requires bilateral limb coordination, Killane et al. (2015) investigated the effects of the addition of a non-immersive VR component to stepping in place on a balance board with cognitive loading aimed at reducing the number of FoG episodes in PD. These technologies, which allow stepping-in-place on a balance board, have been utilized previously in literature to mimic gait (Nantel et al., 2011). Accordingly, a virtual teacher has effectively instructed while healthy adults were stepping in place (Koritnik et al., 2008, 2010), and others have successfully been applied in rehabilitation (Duschau-Wicke et al., 2009). More recently, there has been an emphasis on using stepping over virtual obstacles placed on the path of walking, either projected onto the floor (Geerse et al., 2018, 2020b) or treadmill (Heeren et al., 2013; van Ooijen et al., 2016) or 3D holographic cues

seen through Microsoft HoloLens (Coolen et al., 2020; Geerse et al., 2020a; Miyake et al., 2021), or displayed on the floor of a virtual environment (Gómez-Jordana et al., 2018; Janeh et al., 2019a), which can be used for advance planning and real-time modification of the obstacle avoidance behavior (Edd et al., 2020). As such, the possible applications for this gait retraining paradigm are widespread, especially when combined with measures of gait biomechanics alterations (Sveistrup, 2004; Martens et al., 2014; Cano Porras et al., 2019). It has been previously shown that individuals are able to follow floor-projected foot placement visual cues aimed to modify gait parameters with an accuracy that is sufficient for the most common therapeutic applications (Bennour et al., 2018). Therefore, VR has the potential to present novel classes of stimuli, such as virtual humans and avatars that provide continuous information (Kiefer et al., 2013). It is therefore possible to imagine a number of ways that continuous information about the desired gait pattern could be presented to a patient. Liu et al. (2020) leverage embodiment in a virtual environment to help with rehabilitation from gait asymmetry, allowing the patient to see their own gait. Moreover, studies have shown that WIP is feasible on gait rehabilitation of stroke patients in which intensity, frequency, motion amplitude, and feedback can be manipulated to provide tailored motor training (Cai et al., 2021). Future studies might focus on identifying which control strategies can best facilitate stepping performance in patients at varying degrees of recovery following neurological injury.

4.3. Virtual Manipulations

One of the unique capabilities of VR is that visual information can be enhanced or manipulated during ongoing walking in a manner that is not possible in the real world, e.g., VEs can be used to manipulate visual cues to modulate the gait characteristics of patients with PD that provoke FoG and other impairments contributing to fall risk (Schubert et al., 2005). For instance, Janeh et al. (2019a) found that PD patients overcame the spatial asymmetry and exhibited a comparable step length by enlarging the step length of the short side, an adapted step time, and a swing time variability of both sides during the manipulation of visual-proprioceptive cues. Another example is by Barton et al. (2014) that has investigated the possibility of using the manipulation of visual cues with a time delay in a VE to alter gait using a Virtual Mirror Box. In their study, movements kinematics of the unimpaired leg were combined with the movement timing of the impaired leg to model a realistic avatar with a symmetric gait pattern. In addition, an extensive body of literature has examined the role of visual self-motion in the control of locomotion by selectively manipulating the direction or speed of the visual flow provided through the VE (Lamontagne et al., 2007, 2010). VR can also be used to manipulate the locomotor trajectory of patients during overground walking that varied the path's radius of curvature, to assess the impact of an emulated knee disability on the locomotor trajectory. Gérin-Lajoie et al. (2010). In many studies (Chou et al., 2009; Janeh et al., 2017a,b, 2018), where they manipulated the translation gain of walking in healthy younger and older adults, so that one step forward in the physical world corresponds to several steps forward in the VE. In contrast, Matsumoto et al. (2018) examined the effect of curvature and bending gains (**Figure 5D**) on walking biomechanics, which occurs when the curvature of the walking path in the VE was manipulated, while the actual walking path remains constant. Therefore, using VR to manipulate visual flow thus has the potential to alter the interaction space and provide notable information about locomotion speed and heading to the patient (Warren et al., 2001; Turano et al., 2005). Walking trajectory was shown to be affected when healthy young subjects were exposed to rotational, translational or a combination of both, demonstrating the importance of visual flow on steering behavior during locomotion (Sarre et al., 2008). Additionally, if the same rotational optic flow is generated via a simulated camera rotation in VE against an actual head rotation, a different locomotor behavior also emerges, whereby the simulated but not the actual head rotation results in a trajectory deviation (Hanna et al., 2017). Such findings support the potential contribution of the motor command in heading estimation (Banks et al., 1996; Crowell et al., 1998). These findings also corroborate the presence of multisensory integration of both visual and non-visual information (i.e., vestibular, proprioceptive, and somatosensory) to generate a single representation of self-motion and orientation in space (Karthik et al., 2014; Acerbi et al., 2018).

4.4. Controllers

Another technique was also employed using controller-based virtual walking, where participants were asked to walk around a VE and remembering objects and rooms that they had viewed in order to estimate cognition (Albani et al., 2002; Klinger et al., 2006; Cipresso et al., 2014). The authors have focused on motor control aspects related to action and navigation as well as performing activities of daily living (i.e., even though they were not actually walking). However, this basic research has implications for practice; suggesting that VEs can be used for the examination of cognitive deficits that may interfere with mobility. Moreover, the use of VR hand-held controllers allows users to interact with virtual elements using their hands as they do real-life, allowing exercise repetition, intensity variation, and task-oriented training (Cortés-Pérez et al., 2020). Although these studies have great potential in improving the assessment of cognition in a more ecological manner, more research studies are needed to know whether this will be useful, reliable, and clinically meaningful. Once this is established it would be useful to use these cognitive tasks to assess and quantify changes in gait in order to understand gait disorders.

5. CONCLUSION

As such, this review emphasized the importance of employing virtual walking techniques in rehabilitation, and thereby it is a promising approach and possibly effective for improving the gait of people with neurological diseases, suggesting that the severity of the disease can influence the effect of the use of VR during rehabilitation. Moreover, to determine the role of VR-based gait rehabilitation, further research is needed to

investigate the characteristics of each patient and his disorder to develop personalized techniques. Thus, potential changes in gait characteristics should be taken into consideration when designing virtual walking techniques.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Circuits for State-Dependent Modulation of Locomotion

*Alejandro J. Pernía-Andrade[1], Nikolaus Wenger[2], Maria S. Esposito[3] and Philip Tovote[1,4]**

[1] Institute of Clinical Neurobiology, University Hospital Würzburg, Würzburg, Germany, [2] Department of Neurology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany, [3] Medical Physics Department, Centro Atomico Bariloche, Comision Nacional de Energia Atomica, Consejo Nacional de Investigaciones Cientificas y Tecnicas, San Carlos de Bariloche, Argentina, [4] Center for Mental Health, University of Würzburg, Würzburg, Germany

Brain-wide neural circuits enable bi- and quadrupeds to express adaptive locomotor behaviors in a context- and state-dependent manner, e.g., in response to threats or rewards. These behaviors include dynamic transitions between initiation, maintenance and termination of locomotion. Advances within the last decade have revealed an intricate coordination of these individual locomotion phases by complex interaction of multiple brain circuits. This review provides an overview of the neural basis of state-dependent modulation of locomotion initiation, maintenance and termination, with a focus on insights from circuit-centered studies in rodents. The reviewed evidence indicates that a brain-wide network involving excitatory circuit elements connecting cortex, midbrain and medullary areas appears to be the common substrate for the initiation of locomotion across different higher-order states. Specific network elements within motor cortex and the mesencephalic locomotor region drive the initial postural adjustment and the initiation of locomotion. Microcircuits of the basal ganglia, by implementing action-selection computations, trigger goal-directed locomotion. The initiation of locomotion is regulated by neuromodulatory circuits residing in the basal forebrain, the hypothalamus, and medullary regions such as locus coeruleus. The maintenance of locomotion requires the interaction of an even larger neuronal network involving motor, sensory and associative cortical elements, as well as defined circuits within the superior colliculus, the cerebellum, the periaqueductal gray, the mesencephalic locomotor region and the medullary reticular formation. Finally, locomotor arrest as an important component of defensive emotional states, such as acute anxiety, is mediated via a network of survival circuits involving hypothalamus, amygdala, periaqueductal gray and medullary premotor centers. By moving beyond the organizational principle of functional brain regions, this review promotes a circuit-centered perspective of locomotor regulation by higher-order states, and emphasizes the importance of individual network elements such as cell types and projection pathways. The realization that dysfunction within smaller, identifiable circuit elements can affect the larger network function supports more mechanistic and targeted therapeutic intervention in the treatment of motor network disorders.

Keywords: circuits and circuit components, motor control, neural networks, gait, emotional states, locomotion

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****Correspondence:***
Philip Tovote
tovote_p@ukw.de

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INTRODUCTION

As animals evolved to adapt to highly dynamic environments, they developed nervous systems that supported a large arsenal of scaled behavioral responses to varying stimuli and contexts. Adequate action selection thus became dependent on complex internal states, capable of dynamically controlling specific motor patterns. Consequently, higher organisms may initiate movements relying on cognitive or emotional reference (Takakusaki, 2017). However, regardless of whether the driver of the movement is volitional or emotional, goal-oriented locomotion requires body postural control which includes balance adjustment and muscle tone regulation (Grillner, 1975). Pioneering studies implementing selective spinal cord and brain-region lesions in cats identified the spinal cord as the locus for the control of the step cycle (i.e., stance and swing, left and right alternation), usually referred to as central pattern generator (Grillner, 2003). Seminal studies identified three brain regions underlying the supraspinal control of locomotion, the DLR (originally referred to as the subthalamic locomotor region), the MLR, and the CLR (Shik and Orlovsky, 1976; Grillner, 2003). A reticulospinal excitatory network within the brainstem locomotor center was hypothesized as the ultimate supraspinal station producing locomotor patterns, in close interaction with sensory feedback (Grillner, 2003). Based on the organizational principle of functionally distinct brain areas, our knowledge on how the brain controls movements greatly improved throughout the following decades. While the region-specific function concept reflects important determinants of brain function, including motor control, the advent of combined genetic and optical methodologies in basic neuroscience has recently added the perspective of a brain-wide neuronal network (Ferreira-Pinto et al., 2018). This network consists of microcircuits interconnected by long-range projection pathways forming functional modules. In this system that is dependent on both, the hardwired microcircuits and their long-range interconnections, as well as the dynamic information flow within them, somatosensory information and emotions interact at different levels in high-order brain areas to orchestrate action selection from initiation to termination of locomotion. Therefore, gait dysfunction needs to be looked at from a network perspective. In this review, we aim to integrate both views by describing the large-scale interactions among brain areas for cognition, defense and movement as interactions of defined circuit elements that are required for the state-dependent modulation of gait.

Categorization of Locomotion

How do we address and operationalize complex state-dependent modulation of specific movement functions? It has been proposed that locomotion can be divided into three behavior-relevant categories, exploratory locomotion, primary appetitive locomotion and primary defensive locomotion. Such categories are regulated by the hypothalamus and the preoptic area of the BF of rats (Sinnamon, 1993), suggesting that emotions play a central role in the regulation of locomotor region functions and may guide moment-to-moment changes in exploratory or defensive states in an animal. Circuits-centric behavioral research has shown that exploratory and appetitive/consummatory locomotion rely mainly on the circuitry formed among the BF, the hypothalamus and BG (Sinnamon, 1993), whereas, defensive locomotion engages the orchestrated action of defensive circuits involving the amygdala, the hypothalamus and the periaqueductal gray (PAG) (LeDoux, 2012). On the other hand, early experiments in decerebrated cats indicate that the three locomotor regions have well defined roles for the initiation of movements, such that DLR-lesioned animals are unable to perform goal-driven locomotion but they are able to perform coordinated walking and running upon MLR stimulation (Shik and Orlovsky, 1976). Conversely, animals with cerebellar ablation can not walk by themselves but once the body position is assisted (e.g., head fixed and body suspended in a hammock) they can perform uncoordinated locomotion upon stimulation of DLR and MLR. This evidence suggests that volitional locomotion relies on DLR, the coordination of locomotion requires CRL, whereas executive locomotion relies on MLR. However, whether the emergence of a specific behavioral state (e.g., exploration, hunting or defensive behavior) requires the activation of one or several locomotor regions and whether the locomotor regions cooperate or compete to favor a specific behavioral outcome are still open questions.

While the categorization of locomotion based on the behavioral context directly points to the regulatory role of higher-order states, locomotion can also be differentiated more descriptively into initiation, maintenance and termination phases, temporal dynamics that are tightly linked to gait function (Sinnamon, 1993; Ferreira-Pinto et al., 2018). This approach supports the view that these motor phases and resulting locomotor patterns are not *per se* defined by a certain state, but represent basic motor programs accessible and modulated by higher-order states. Consequently, we will review experimental evidence dissecting the neural basis of state-dependent modulation of initiation, maintenance and

Abbreviations: AC, auditory cortex; AHN, anterior hypothalamic nucleus; BF, basal forebrain; BG, basal ganglia; BLA, basolateral amygdala; CCK, cholecystokinin; CeA, central amygdala; Chx10, CEH10 homeodomain-containing homolog; CLR, cerebellar locomotor region; CNF, cuneiform nucleus; CTX, cortex; DBS, deep brain stimulation; DCN, deep cerebellar nuclei; DLR, diencephalic locomotor region; DN, dentate nucleus; FN, fastigial nucleus; FoG, freezing of gait; GABA, gamma-aminobutyric acid; GAD2, glutamate decarboxylase 2; Gi (A, V), gigantocellular nucleus (alpha part, ventral part); GP (e, i), globus pallidus (external, internal); IN, interpositus nuclei; KARs, kainate glutamate receptors; LA, lateral amygdala; LC, locus coeruleus; LH, lateral hypothalamus; LPGi, lateral paragigantocellular nucleus; LPTN, lateral-posterior thalamic nucleus; MC, motor cortex; MLR, mesencephalic locomotor region; MN, mammillary nucleus; mRt, mesencephalic reticular region; NAcSh, nucleus accumbens shell; PAG (d, dl, l, vl, v), periaqueductal gray matter (dorsal, dorsolateral, lateral, ventrolateral, ventral); PBGN, parabigeminal nucleus; PCRt, parvicellular reticular formation; PD, Parkinson's disease; PFC (m, dm), prefrontal cortex (medial, dorsomedial); PMD, premammillary nucleus of the hypothalamus; PPN, pedunculopontine tegmental nucleus; PV, parvalbumin; REM, rapid eye movement; SN (c, r), substantia nigra (compacta, reticulata); SPN, striatal projection neuron (MSN); STN, subthalamic nucleus; SuC, superior colliculus; TH, tyrosine hydroxylase; vHIPPO, ventral hippocampus; VMH (c, vl, dm), ventromedial hypothalamus (central, ventrolateral, dorsomedial); ZI, zona incerta.

termination of locomotion as well as discuss their relevance in gait function.

INITIATION OF LOCOMOTION

Cellular Identity of Locomotor Initiation Drivers

Although classic electrical microstimulation studies have identified three regions in the brain capable of eliciting locomotion, MLR has been investigated the most using new genetic tools for the dissection of cell-type specificity. Light-induced stimulation of individual MLR neuronal subtypes demonstrated that glutamatergic activation is sufficient to induce locomotion from rest (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018), whereas stimulation of cholinergic neurons positively modulates the speed of ongoing locomotion (Roseberry et al., 2016). Conversely, among other studies, former research showed that electrical stimulation of the PPN, where cholinergic neurons reside, evokes atonia and induces rapid-eye movements in decerebrate cats (Takakusaki et al., 2004, 2005) suggesting that PPN hosts a strikingly complex neural network able to modulate motor responses supporting different brain states. Later on, Capelli et al. (2017) found that optogenetic activation of glutamatergic neurons in the LPGi of the medullary reticular formation was: (1) sufficient to initiate forward-directed full-body locomotion of mice in an open-field arena, and was (2) necessary for high-speed locomotion evoked by MLR stimulation (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018; Carvalho et al., 2020). This initiation of locomotion was restricted to LPGi glutamatergic neurons as similar stimulation of subnuclei adjacent to the reticular formation failed to initiate locomotion. These results provide direct evidence of an excitatory brainstem neuronal network underlying the initiation of locomotion (**Figure 1A**). However, it has recently been demonstrated that glutamatergic MLR neuronal subpopulations fulfill functional roles that extend far beyond the control of locomotion (Garcia-Rill et al., 1986; Sherman et al., 2015; Roseberry et al., 2016; Chang et al., 2020; Ferreira-Pinto et al., 2021). Strikingly, glutamatergic MLR neurons with descending projections to the spinal cord (**Figure 1A**) are tuned to full body behaviors such as rearing and locomotion, whereas glutamatergic MLR neurons with ascending axonal terminals impinging to BG output regions are tuned to forelimb behaviors such as handling and grooming. Both neuronal subpopulations are intermingled within the PPN and the adjacent mesencephalic reticular region (mRt) and can only be disentangled by their projection specificity. Moreover, gain- and loss-of-function experiments demonstrated the functional specificity of descending spinally projecting glutamatergic MLR neurons for body extension during rearing and the initiation of locomotion. In contrast, optogenetic manipulation of ascending glutamatergic MLR neurons resulted in a more generalized modulation of body movements (Ferreira-Pinto et al., 2021). The observation that opposing functions coexist within such small brain areas may explain controversial results on PPN function by previous studies showing a role of glutamatergic PPN neurons in low-speed exploratory locomotion, locomotion arrest or both (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018; Carvalho et al., 2020).

The initiation of fine and skillful locomotion is one of the functions of the MC (Grillner, 2003; Kawai et al., 2015; Dhawale et al., 2021), however, MLR may also complement MC through the modulation of brainstem premotor circuits (Esposito et al., 2014). Other studies have also shown that the activation of noradrenergic (alpha2), dopamine (D1/D2), and serotonin (5-HT2 and 7) receptors in the spinal cord is sufficient to initiate and maintain locomotion in intact and strikingly, even spinalized laboratory animals (Smythe and Pappas, 1989; Giroux et al., 2001; Jordan et al., 2008; Cregg et al., 2020). The selective activation of these receptors has been shown to modulate the spinal somatosensory-motor network, the step kinematics and the left-right limb coordination. Anatomical evidence indicates that the spinal noradrenergic afferents originate at the LC (Li et al., 2016), the dopaminergic afferents originate at the hypothalamus (Qu et al., 2006), whereas serotonin afferents originate at the parapyramidal region of the medulla oblongata (Jordan et al., 2008). Overall, excitatory circuit elements within the MLR play a central role in the initiation of locomotion, which is complemented by modulatory biogenic amines (**Figures 1A,B**).

Basal Ganglia Circuits as a Functional Module for the Initiation of Goal-Directed and Exploratory Locomotion

The striatum and STN receive topographically organized synaptic projections from several cortical motor and limbic association areas including primary MC, dorsal and ventral premotor cortices, supplementary motor area, and the rostral, dorsal and ventral portions of cingulate motor areas (DeLong and Wichmann, 2007). Therefore, BG is a central hub for the integration and execution of cortical information. Strikingly, while MC is essential for the acquisition of timed instrumental motor skills, the expression of these motor program kinematics, once learned, no longer relies on the MC but on the directly connected subcortical circuits of the dorsolateral striatum (Kawai et al., 2015; Dhawale et al., 2021). Extensive research on BG circuitry has shown that the initiation of goal-oriented locomotion, instrumental learning and its reinforcement happen through the activation of two BG synaptic pathways between the striatum and the main output areas, GPi and the substantia nigra pars reticulata (SNr) (Yin et al., 2005; DeLong and Wichmann, 2007; Kravitz et al., 2012; Freeze et al., 2013). One BG pathway, referred to as direct pathway, is made by monosynaptic inhibitory afferents from the SPNs in the dorsal striatum to GPi and SNr. The second BG pathway, referred to as indirect pathway, is made by a disynaptic disinhibitory projection from the dorsal striatum to the STN, GPi, and SNr via GPe (**Figure 1C**). Thus, activation of inhibitory SPNs from the indirect pathway will suppress the inhibitory control of GPe on STN, GPi, and SNr. Since STN is interconnected to the hypothalamus, it is possible that GPe functions as a gate for the emotional trigger of locomotion in order to initiate exploration or consummatory actions. However, deeper research on GPe as an emotional motor gate is needed.

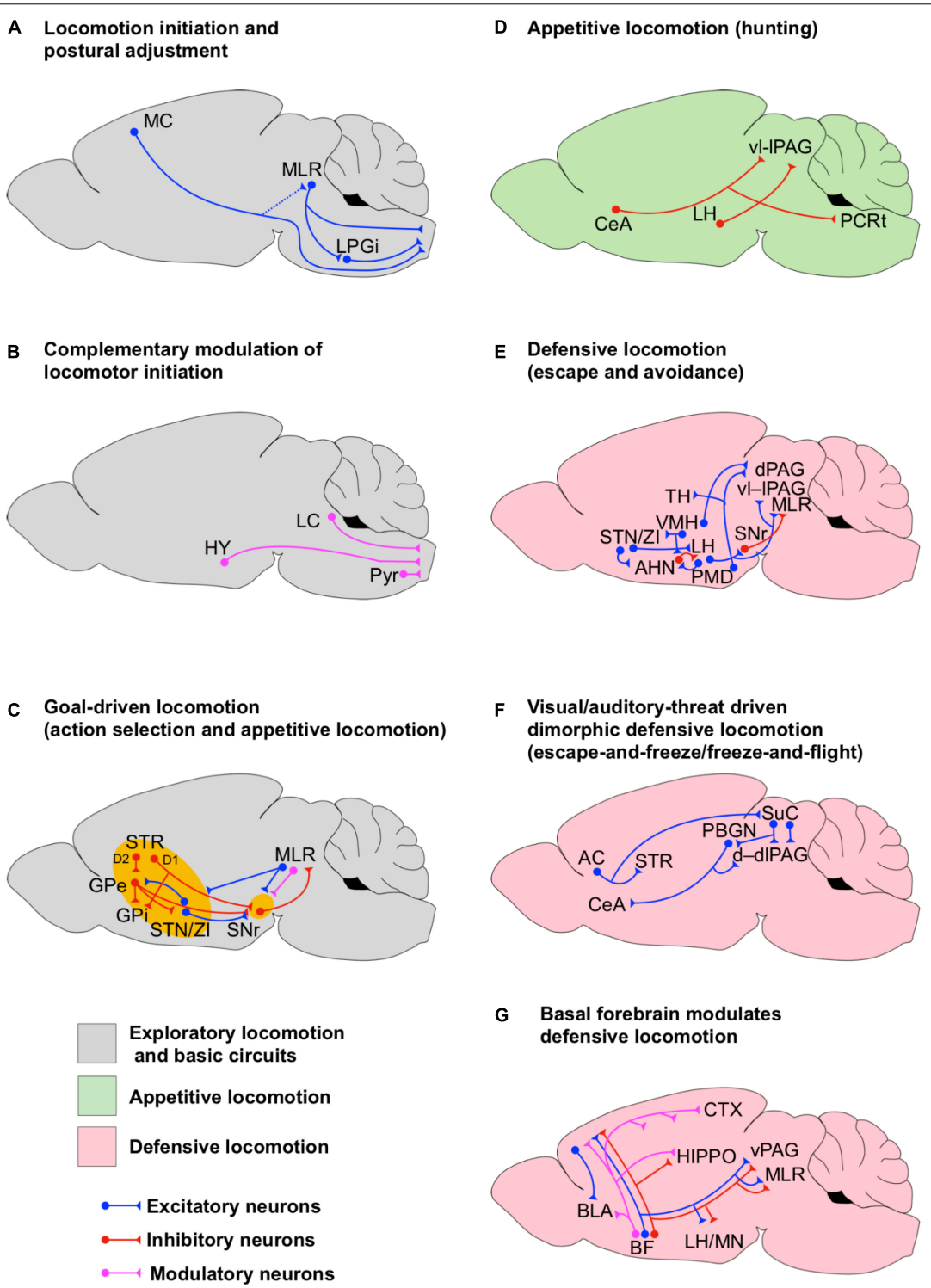

FIGURE 1 | Circuits for state-dependent initiation of locomotion. **(A)** Scheme of the basic neuronal circuits underlying the initiation of locomotion. The dotted line between the motor cortex (MC) and the MLR denotes minor monosynaptic contacts between both areas in rodents. **(B)** Scheme of the neuronal circuits underlying the complementary modulation of the initiation of locomotion. **(C)** Scheme of the neuronal circuits underlying the initiation of goal-driven locomotion. These circuits account for action selection and appetitive locomotion. Note the interconnections between BG and MLR. The BG circuits are highlighted in yellow to indicate that they are involved in the initiation of a particular state even if they are not fully shown for simplicity. **(D)** Scheme of the neuronal circuits underlying the initiation of appetitive locomotion. **(E)** Scheme of the neuronal circuits underlying the initiation of defensive locomotion. **(F)** Scheme of the neuronal circuits underlying the initiation of dimorphic defensive locomotion (escape-and-freeze and freeze-and flight). **(G)** Scheme of the basal forebrain neuronal circuits underlying the modulation of defensive locomotion.

Striatal projection neurons in the striatum involved in the BG indirect pathway express inhibitory dopamine receptors type 2 (D2) while SPNs involved in the BG direct pathway express excitatory dopamine receptors type 1 (D1) (Neve et al., 2004). Thus, dopamine release in the striatum by afferents from the substantia nigra pars compacta (SNc) exerts a differential modulation on both pathways, characterized by the suppression of the indirect path while facilitating the inhibitory influence of the direct path on GPi/SNr neurons (**Figure 1C**). Since STN sends excitatory projections to GPi and SNr, the temporal interplay and balance between the direct and indirect pathways as well as the functional organization of GPi/SNr neuronal engrams may determine the output of BG. SNr and GPi provide differential axonal projections to several components of the thalamocortical and brainstem motor systems turning BG into a central broadcaster for motor control (Kooy and Carter, 1981; McElvain et al., 2021). Interestingly, the GPi/SNr neurons have been shown to provide tonic inhibition to motor thalamocortical neurons and neural circuits in PPN (Grillner et al., 2005, 2008; DeLong and Wichmann, 2007). However, selective optogenetic stimulation of either the direct or indirect pathways *in vivo* generates both excitation and inhibition of subpopulations of neurons in SNr, although, the effectiveness of direct pathway stimulation in producing movement initiation is correlated with inhibited subpopulations of SNr neurons (Freeze et al., 2013). Conversely, effective indirect pathway-mediated motor suppression has been shown to be most strongly influenced by excited SNr neurons (Freeze et al., 2013). Former research has also shown a segregated effect of the activation or either pathway on gait functions during ambulation (Kravitz et al., 2010). Kravitz et al. (2010) found that the bilateral optogenetic excitation of the indirect pathway decreases locomotor initiation, increases immobility and promotes bradykinesia, whereas the activation of the direct pathway increases locomotion and reduces immobility. Moreover, these effects were mediated by MLR activity (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018; **Figure 1C**). Altogether, these data show that BG promotes movement by an overall disinhibition of downstream targets.

Further studies implementing selective optogenetic inhibition or excitation of either direct or indirect BG pathways *in vivo* (D1– or D2–type driven opsin expression respectively) has shown that there is a complementary interaction between both pathways for the initiation and maintenance of goal-driven consummatory actions (Tai et al., 2012; Tecuapetla et al., 2016; Yttri and Dudman, 2016). Optogenetic stimulation of the BG direct pathway in dorsomedial striatum (associative area) of mice biases the initiation of learned consummatory actions toward the contralateral site, whereas optogenetic stimulation of the BG indirect path does it for the ipsilateral site (Tai et al., 2012). However, the bias is effective only if the stimulation happens before the animal initiates motor actions. Furthermore, the stimulation of each pathway also increases the reaction time (latency) to a "Go" signal suggesting that both pathways cooperate in the decision-making process. Interestingly, outside the decision-making task, the stimulation of the direct path is able to facilitate contralateral motion while the stimulation of the indirect path is ineffective suggesting that the direct path, but not the indirect one, is also involved in body postural adjustment and locomotion direction control. Once the consummatory action has been initiated, the velocity of the forepaw to activate a reward system seems to reinforce the velocity of future motor consummatory actions in a positive or negative way depending on whether the direct path or the indirect path has been simultaneously stimulated in the dorsomedial striatum respectively (Yttri and Dudman, 2016). Surprisingly, the forepaw-velocity triggered optical stimulation does not affect the rate of motion initiation and reward consumption, suggesting a dissociation between the forepaw motor dynamics and a cognitive action-selection.

Other study indicates that the effect of optogenetic stimulation of the BG pathways on decision-making tasks is not restricted to the dorsomedial striatum as the stimulation of these pathways in the dorsolateral striatum (sensorimotor area) also produce comparable results on the latency and the reward consumption (Tecuapetla et al., 2016). However, the effect in the dorsolateral striatum is not reinforced as seen in the dorsomedial striatum (Kravitz et al., 2012). Tecuapetla et al. (2016) also showed that the decision-making process is not restricted to SPNs but also engages parvalbumin-positive (PV+) GABAergic interneurons in the striatum. Notably, stimulation of the indirect path, but not the direct path, interrupts the maintenance of consummatory behavior and favors ambulation (exploratory locomotion; **Figure 2B**), suggesting that the indirect path in the dorsolateral striatum is involved in the transition of behavioral states whereas the direct path seems to be engaged in action initiation.

All together, these results suggest that the BG pathways complement each other to form a functional module which supports goal-driven motor performance. In this BG module both pathways seem involved in the decision-making process (e.g., action selection), however, at the action execution level, the direct path seems to support the initiation of motor actions, postural adjustment and locomotion direction while the indirect path does it for the maintenance and the termination of goal-driven behaviors (state transition initiation, **Figure 1C**).

Interactions of Globus Pallidus and Hypothalamus With the Subthalamic Nucleus Mediate State-Dependent Behavioral Effects

Malfunction or damage of the striatal network may generate an imbalance in the locomotor control and maladaptive behavior. For instance, compulsive grooming in rodents appears to be a consequence of a reduced tonic inhibition on SPNs in the centromedial/dorsomedial striatum (Burguière et al., 2013, 2015). In normal conditions, such a tonic inhibition counterbalances the excitatory input from the neocortex to SPNs. Moreover, downstream from the striatum (**Figure 1C**), selective optogenetic activation of GPe GABAergic interneurons or GPe-projecting STN afferents produces hyperkinesia and abnormal involuntary movements in mice, such as abnormal forelimb posture, neck's torsion spasm, and compulsive grooming, chewing and licking

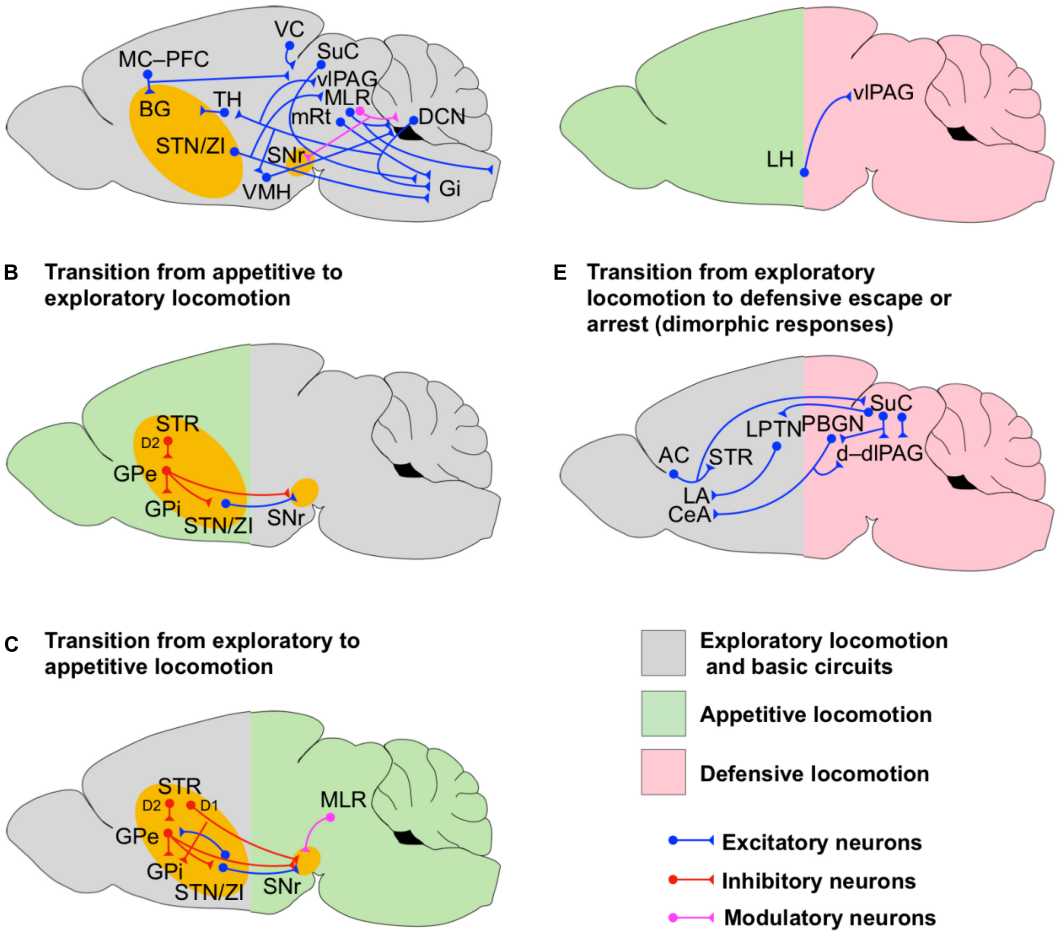

FIGURE 2 | Circuits for transition and maintenance of locomotion. **(A)** Scheme of the neuronal circuits underlying the maintenance and transition of locomotion. The intricate network among the cerebellum, BG, hypothalamus, PAG, MLR and their projections to Gi are shown. **(B,C)** Scheme of the BG neuronal circuits supporting the bidirectional transition from appetite to exploratory locomotion **(B)** and exploratory to appetite locomotion **(C)**. Notice that the transition from exploratory to appetitive locomotion is supported by feedback modulatory projections from MLR. The BG circuits are highlighted in yellow to indicate that they are involved in the initiation of a particular state even if they are not fully shown for simplicity. **(D)** Scheme of the neuronal circuits underlying the transition from appetitive to defensive locomotion. **(E)** Scheme of the neuronal circuits underlying the transition from exploratory locomotion to dimorphic defensive escape or arrest. Notice that the dimorphic defensive behaviors are driven by visual or auditory sensory inputs routed via the superior colliculus (SuC) and auditory cortex (AC) respectively.

(Tian et al., 2018). Noteworthy, the activity of STN neurons is also regulated by the hypothalamus, hence, compulsive behaviors may be triggered by altered emotional states as well.

Early experiments in anesthetized rats indicated that the hypothalamus modulates the firing rate of STN/ZI neurons (Narita et al., 2002). Narita et al. (2002) showed that activation of KARs in the VMH, which is part of the neural circuitry underlying the initiation of the defensive behavior (Sinnamon, 1993; LeDoux, 2012), increases the firing rate of STN/ZI neurons (**Figure 1E**). Interestingly, in another set of experiments these authors showed that activation of KARs in VMH increases the locomotion speed in rats walking on a running wheel, which could be due to the activation of defensive neural circuits. Importantly, the running speed was reduced by micro-injections of KARS antagonists or GABA (natural agonist of inhibitory GABA receptors) in STN/ZI, suggesting that they have a pivotal role in the initiation of defensive locomotion.

Anatomical evidence indicates that ZI projects to the AHN and to the LH (Mitrofanis, 2005), both of which are interconnected (**Figure 1E**) and work together in the initiation of defensive locomotion (Canteras, 2002; Wang et al., 2015; Li et al., 2018). Interestingly, a subset of excitatory LH projection neurons that co-releases glutamate and the neuropeptide orexin on their postsynaptic targets has been shown to facilitate the initiation, but not the maintenance, of locomotion in freely moving mice in a way that it is proportionally modulated by the hunger state of the animal (Karnani et al., 2020). Furthermore, studies in decerebrate cats have shown that microinjection of orexin in CNF, PPN and SNr has facilitatory effects on locomotion (Takakusaki et al., 2005). Orexin injected in CNF directly

increases MLR-electrically evoked locomotion by lowering the current threshold needed to evoke locomotion, whereas orexin injected in PPN and SNr reduces atonia associated with PPN-electrically induced rapid-eye movements. However, this last effect is reversed by subsequent injection of bicuculline (a $GABA_A$ receptor antagonist) in PPN, indicating that elevation of inhibitory synaptic transmission in PPN is needed for the induction of atonia. Moreover, activation of PPN inhibitory synapses counterbalances the pro-locomotion effect of orexin on PPN and SNr. Former research in anesthetized and acutely decerebrated cats indicates that SNr provides an important inhibitory synaptic control on PPN neurons needed for the induction of atonia (Takakusaki et al., 2004). The evidence presented in this section indicates how specific circuit elements within GP, SNr, STN/ZI, and hypothalamus may interact to initiate locomotion and mediate state-dependent behavioral effects (**Figures 1D,E**). Malfunction of the neural circuits residing in these areas may favor the emergence of maladaptive behaviors.

The Basal Forebrain, a Modulatory Cholinergic Center Wiring High-Order Brain Functions to the Initiation of Locomotion

Early studies implementing selective microinjection of glutamate or picrotoxin ($GABA_A$-receptor blocker) in the BF in anesthetized rats indicate that the activation of postsynaptic excitatory glutamate receptors and reduction of GABAergic inhibition in different BF nuclei elicit stepping (Sinnamon, 1993). How does it happen? This is still an open question, however, one possible explanation is that the initiation of locomotion in these physiological preparations may be due to the activation of downstream areas associated with motor or defensive circuits. BF contains intermingled populations of GABAergic, glutamatergic and cholinergic neurons which regulate a number of different brain functions such as arousal, memory, learning and defensive responses. This happens through the modulation of neuronal excitability and synaptic function in thalamus, cortex, hippocampus, and amygdala (Steriade et al., 1993; Vogt and Regehr, 2001; Rogers and Kesner, 2003; Sarter et al., 2003; Hasselmo, 2006; Henny and Jones, 2008; Hasselmo and Stern, 2014; Lin et al., 2015; Unal et al., 2015; Jiang et al., 2016; Gielow and Zaborszky, 2017; Howe et al., 2017). Subpopulations of non-cholinergic BF neurons encode salience, reward and punishment information to regulate learning and decision making (Lin et al., 2015). However, the modulation of learning not only relies on BF glutamatergic and GABAergic projections to the neocortex but also relies on the BF cholinergic projections to a broader range of cortical areas and the hippocampus, which also receives BF GABAergic projections (Rogers and Kesner, 2003; Sarter et al., 2003; Hasselmo, 2006; Henny and Jones, 2008; Hasselmo and Stern, 2014; Agostinelli et al., 2019). Cholinergic subpopulations of BF neurons regulate defensive neuronal circuits and associated behavioral responses via projections to the amygdala (Mark et al., 1996; Picciotto et al., 2012; Unal et al., 2015; Jiang et al., 2016). Namely, optogenetic activation of modulatory cholinergic BF projections to the BLA increases the encoding signal-to-noise ratio in BLA principal neurons and enhances glutamatergic synaptic transmission within the BLA, which favors the induction of long-term-potentiation of cortical-amygdalar synapses (Unal et al., 2015; Jiang et al., 2016). Whether subpopulations of BF neurons encoding for salience, reward and punishment are directly engaged in the modulation of defensive behavioral responses is still unknown. However, Jiang et al. (2016) have shown that the acquisition of fear memory depends on the activation of BF cholinergic projections to the BLA. BF also sends glutamatergic and GABAergic projections to a number of subcortical areas, including defensive circuits in the hypothalamus and PAG as well as circuits in MLR (Swanson et al., 1984; Agostinelli et al., 2019). The evidence presented above indicates that BF may affect defensive learning and locomotion via the modulation of an intricate network between cognitive, defensive and mesencephalic locomotor circuits (**Figure 1G**).

Extensive evidence has also shown that BF cholinergic neurons degenerate in different cognitive and motor neurodegenerative diseases in humans, such as Alzheimer's disease, Lewy Bodies dementia, atypical Parkinsonian's diseases (PD), alcoholic dementia and Parkinson's disease (Pepeu et al., 2015), indicating the central role of the BF modulatory system in the regulation of cognitive and motor functions in the human brain. The evidence presented in this section indicates that BF has a central role in the regulation of cognitive and motor actions via the modulation of distinct brain areas involved in the processing of high-order cognitive functions and emotions. However, while deterioration of the BF neurons has been associated with slow gait and falls in PD patients (Bohnen et al., 2019) the precise neuronal path underlying the initiation of locomotion remains elusive.

The Hypothalamus, Amygdala and Periaqueductal Gray Contain Circuits for the Initiation of Appetitive and Defensive Locomotion

A major hub for modulation of appetitive/consummatory and defensive locomotion is the hypothalamus (Sinnamon, 1993; Canteras, 2002; LeDoux, 2012). The hypothalamus in turn provides major monosynaptic excitatory and inhibitory neuronal projections from different subregions to PAG (**Figures 1E**, **2D,E**, **3B**; Vianna and Brandão, 2003; Motta et al., 2009; Keay and Bandler, 2015; Li et al., 2018). Early anatomical studies using chemical retrograde and anterograde tracing revealed that such projections are differentially distributed along the dorsoventral anatomical subdivisions of PAG sharing input areas with excitatory afferents from the auditory and visual sensory cortices, the anterior cingulate cortex and the retrosplenial cortex at the dorsal, dorsolateral and lateral PAG columns (d, dl, and lPAG, respectively), with afferents from the rostral prelimbic cortex at the ventral and ventrolateral PAG (v, vlPAG, respectively), with afferents from the fore- and hindlimb motor cortices at the v, vl, and lPAG and with diffuse afferents from the dorsal raphe nucleus (Vianna and Brandão, 2003). Other evidence shows that dPAG also receives monosynaptic glutamatergic projections from the SuC

(**Figure 1F**; Evans et al., 2018). In addition, the vlPAG receives inhibitory monosynaptic projections from amygdala via CeA (Keay and Bandler, 2015; Tovote et al., 2015; **Figure 1D**). The integration of hypothalamic, amygdalar, cortical and collicular synaptic inputs by PAG neurons may provide high-order correlated emotional, cognitive and sensory information to be delivered to MLR and medullary premotor neurons. Notably, recent evidence indicates that PAG is also involved in the modulation of arousal (Porter-Stransky et al., 2019) complementing the actions of LC (Aston-Jones and Cohen, 2005). Namely, norepinephrine released from LC afferents increases glutamatergic synaptic transmission onto vPAG-DA neurons, as a consequence wakefulness is increased. Arousal modulates the activity of primary visual cortex neurons by enhancing visual encoding and reducing noise correlation (Vinck et al., 2015), which may improve the quality of visual information delivered to PAG and associative cortices, for instance. Interestingly, arousal seems to complement locomotion in the modulation of the activity of primary visual cortex neurons (Vinck et al., 2015), such a modulation may help to tune the visual information processed during exploratory and goal-driven behaviors.

Selective optogenetic activation of inhibitory (GABAergic) and excitatory (glutamatergic) projections from LH to the ventrolateral and lateral areas of PAG (vl–lPAG) in mice has been shown to drive predation and threat evasion respectively (**Figures 1D,E**, **2D**; Li et al., 2018). Li et al. (2018), using projection specific optogenetic manipulation and fiber photometry *in vivo*, demonstrated that LH GABAergic neurons become transiently active when a mouse starts attacking a prey but remain silent during prey consumption. Li et al. (2018) also showed that optogenetic inhibition of LH GABAergic cell bodies or their afferents on vl–lPAG suppresses predatory behavior. Conversely, optogenetic stimulation of LH GABAergic afferents in vl–lPAG is sufficient to increase the attack probability. These results suggest that these LH GABAergic–vl–lPAG circuits are engaged in the initiation of appetitive locomotion such as hunting (**Figure 1D**). Furthermore, a recent study suggests that hunting behavior driven by LH GABAergic neurons occurs through the inhibition of vl–lPAG neurons involved in the facilitation of defensive behaviors like flight and cornering (protective arrest) for instance (Rossier et al., 2021). Rossier et al. (2021) realized that during prey recognition, which requires several approaches, the mice are in a defensive state (showing defensive signs), then, once the actual prey is identified the mice turn into a predatory mode. These authors found that optogenetic stimulation of LH GABAergic afferents in the vl–lPAG (**Figure 1D**) during early prey recognition time (dominated by defensive behavior) reduced attack latency and increased attack persistence while reducing cornering and escape. Furthermore, stimulation of LH GABAergic fibers reduced the activity of vl–lPAG neurons associated with defensive and exploratory investigation behavior (sniffing environment). Interestingly, stimulation of LH GABAergic somas in settled predators not only increased the attack performance but also increased compulsive biting without changing food consumption. These results suggest that LH GABAergic neurons are sufficient to drive hunting behavior partially by suppressing the activity of pro-defensive and exploratory neurons in vl–lPAG, however, LH GABAergic neurons also favor aggressive and compulsive behavior.

Other evidence suggests that predatory behavior is also complemented by the inhibitory projections from CeA on to vl–lPAG (**Figure 1D**; Han et al., 2017). Han et al. (2017) suggested that CeA commands a modular system to drive predatory hunting. This modular system is made by subpopulations of CeA GABAergic neurons projecting to vl–lPAG and to the parvicellular reticular formation (PCRt). The activation of the vl–lPAG pathway increased the stalking time on the prey and hunting velocity while reducing latency to hunt and capture duration. On the other hand, the CeA-PCRt pathway increased mastication and tuned the postural muscles of the neck to facilitate feeding. The coexistence of the LH and CeA systems suggest that an optimal hunting performance requires the integration of emotional and sensory information (via amygdala and hypothalamus) at the vl–lPAG and postural control and feeding via PCRt.

Li et al. (2018), also showed that vl–lPAG projecting LH glutamatergic neurons are directly related to the initiation of evasive behaviors (**Figure 2D**). Activation of these neurons caused mice to immediately cease food retrieval and to start running and jumping in the opposite direction. On the other hand, inhibition of this pathway reduces, but not abolishes, the escape responses to actual physical threats, suggesting that this LH-vl–lPAG path is not the only one supporting the transition from appetitive to defensive escape. Another study has shown that a single hypothalamic nucleus is able to initiate opposing behaviors depending on its postsynaptic targets. Optogenetic activation of glutamatergic neurons in the dorsomedial and central areas of VMH (dm/cVMH) promotes avoidance to a safe environment with increased locomotion (**Figure 1E**) but at the same time facilitates immobility (Wang et al., 2015). Wang et al. (2015) showed that these opposing behavioral effects are due to the fact that, on one hand, dm/cVMH neurons form functional circuits with GABAergic neurons in AHN to promote avoidance and increase locomotion (**Figure 1E**), but on the other hand, it forms circuits with dlPAG to facilitate immobility (**Figure 3B**). Interestingly, dm/cVMH has subpopulations of neurons projecting exclusively to either area and another subpopulation projecting to both areas, however, the specific natural contextual trigger activating each pathway is unknown. The results of Wang et al. (2015) agree with the observation of an increased running speed in rats after the microinjection of kainate in VMH (Narita et al., 2002). However, Narita et al. (2002) also showed that such a VMH motor effect is sensitive to the pharmacological manipulation of STN/ZI. We discussed before that ZI projects to AHN and LH (**Figure 1E**; Mitrofanis, 2005). In LH, a subset of excitatory orexinergic neurons that co-releases glutamate and orexin on CNF, PPN and SNr facilitates the initiation of locomotion in behaving mice (**Figure 1E**; Karnani et al., 2020) and in decerebrate cats (Takakusaki et al., 2005). Hence, it is possible that the initiation of locomotion induced by dm/cVMH also engages the neuronal paths ZI–AHN/LH to modulate the activity of CNF, PPN, and/orSNr neurons (Mitrofanis, 2005; Takakusaki et al., 2005; Karnani et al., 2020).

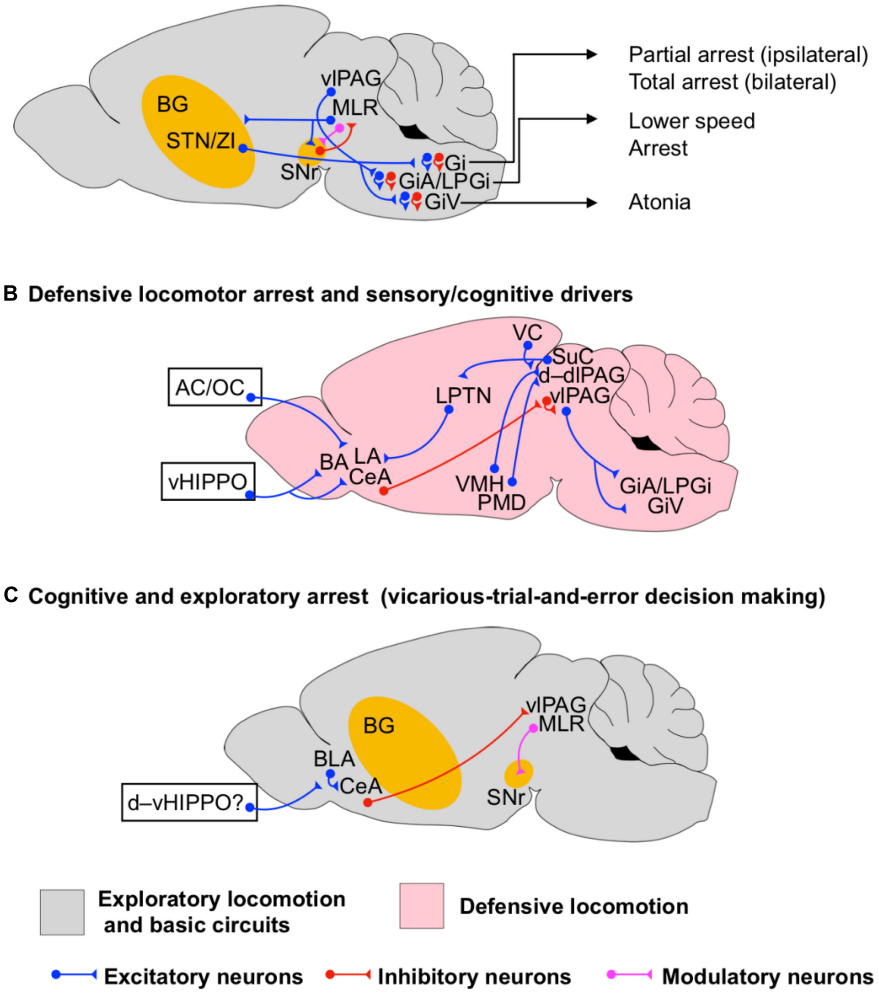

FIGURE 3 | Circuits for locomotor arrest during exploratory and defensive states. **(A)** Scheme of the premotor neuronal circuits underlying locomotor arrest and their putative synaptic drivers. Different types of locomotion arrest executed by premotor neuronal circuits in the medullary reticular formation are indicated (arrows). **(B)** Scheme of the neuronal circuits underlying the initiation of defensive locomotor arrest. Sensory and cognitive synaptic drivers are shown such as from auditory cortex (AC), olfactory cortex (OC), and the ventral hippocampus (vHIPPO). **(C)** Scheme of the neuronal circuits underlying cognitive arrest during spatial exploration, such as that seen during exploratory decision making. Potential synaptic drivers from the dorsoventral hippocampus (d–vHIPPO) involved in non-defensive spatial memory processing are shown. The question mark indicates that the actual synaptic path from d–vHIPPO to BLA/CeA underlying decision-making-driven arrest has not been identified. The BG circuits are highlighted in yellow to indicate that they are involved in the initiation of a particular state even if they are not fully shown for simplicity.

However, further research must be done to identify the specific neuronal subpopulations involved in the initiation of defensive locomotion. Recent evidence has also shown that ZI is directly connected to executive premotor excitatory neurons in Gi involved with the control of locomotion direction (Cregg et al., 2020) and to glutamatergic neurons in PPN and CNF (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018). Therefore, further research should explore the neural circuits within and among hypothalamus, MLR and other brainstem motor regions to see how they contribute to the initiation of locomotion in a broader range of behavioral states.

Recent evidence indicates that dPAG also receives excitatory projections from CCK-expressing glutamatergic neurons residing in the PMD (Wang et al., 2021). These CCK-expressing PMD neurons favor defensive escape (**Figure 1E**). Interestingly, a subpopulation of these neurons projecting to the thalamus are also activated during context-specific escape that requires spatial navigation (**Figure 1E**). The dPAG also receives visual information from SuC via monosynaptic glutamatergic projections (**Figure 1F**). This pathway provides salience threatening visual cues that defines a synaptic threshold for dPAG activation and the initiation of escape (Evans et al., 2018). Subpopulations of PV+ excitatory projection neurons in SuC have been shown to initiate dimorphic defensive behaviors such as escape and freezing when an animal is exposed to visual environmental threats such as looming visual stimuli

(Shang et al., 2015, 2018). Such neurons do not project directly to the PAG but they do to the parabigeminal nucleus (PBGN) and the LPTN (**Figures 1F**, **2E**, **3B**). LPTN projects to LA (Doron and LeDoux, 2000) while PBGN projects to CeA (Usunoff et al., 2006; Shang et al., 2015) and dlPAG (Meller and Dennis, 1986; Klop et al., 2006). Activity within the SuC-LTPN-LA pathway has been shown to trigger freezing (Shang et al., 2015, 2018; Wei et al., 2015) whereas, PBGN has been shown to initiate a behavioral pattern of escape-and-freeze responses (Shang et al., 2018). Strikingly, both pathways compete against each other to initiate a specific behavioral outcome (escape-and-freeze or freeze alone), as optical inactivation of PBGN favors freezing while optical inactivation of LPTN favors escape-and-freeze. However, the precise neural mechanism underlying the natural balance between PBGN and LTPB to control the expression of dimorphic defensive behaviors via amygdala and dlPAG is still an open question. Recently, looming auditory cues have also been shown to initiate complex behavioral defensive sequences, such as freeze-and-flight (Li et al., 2021). The underlying network comprises divergent projections from the AC onto striatal D2-SPNs and SuC neurons (**Figure 1F**). Finally, although it is not explicitly discussed in this review, we acknowledge that putative excitatory circuits between the ventrolateral area of VMH and d–dlPAG underlie aggressive defense (e.g., fight) (Hashikawa et al., 2016), which may also contribute to the initiation of defensive locomotion (**Figure 1E**). However, extensive research on this pathway is still needed.

In light of the evidence presented in this section, we hypothesize that the initiation of goal-driven, appetitive, and defensive locomotion relies on well-defined and distinct functional neuronal modules (**Figures 1**, **2D,E**), which may work together in a context-dependent manner. While MC supports fine motor control, the MLR is involved in postural adjustments as well as high and low speed locomotion (**Figure 1A**). Moreover, modulatory projections from LC, the hypothalamus and the parapyramidal region of the medulla oblongata to the spinal cord support the initiation and maintenance of locomotion (**Figure 1B**). Furthermore, BG supports general goal-driven locomotion, action selection and associative learning (e.g., Pavlovian and instrumental learning; **Figure 1C**) and it can also be influenced by appetitive and defensive information via the hypothalamic projection to STN (**Figure 1E**). The initiation of appetitive locomotion is supported by vlPAG which integrates synaptic information from the hypothalamus and the amygdala (**Figure 1D**). Interestingly, PAG seems to have a special role in the integration and sorting of synaptic information conveying either appetitive or defensive signals (**Figures 1E,F**), having its more dorsal domains (i.e., d–dlPAG) engaged mainly in active defensive locomotion, whereas the more ventral domains (i.e., l–vlPAG) are involved in appetitive as well as active and passive defensive responses. Information of active defense, such as escape and flight, is conveyed by the synaptic inputs from several specific hypothalamic nuclei (**Figure 1E**) and the SuC (**Figure 1F**). Interestingly, it has been shown that glutamatergic CNF neurons are necessary for escape responses triggered by an air-puff (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018). Whether and how defense circuits interact with glutamatergic CNF neurons to trigger active responses remains to be addressed. Finally, the BF is involved in a broad range of brain functions, but it may support defensive locomotion via the modulation of several defensive circuits and its direct projection to MLR (**Figure 1G**).

MAINTENANCE AND COORDINATION OF LOCOMOTION

Basic Network Control of Locomotion Rhythm and Direction

Coordination of rhythmic locomotion and gait rely to a large extent on the activity of spinal circuits in vertebrates (Sinnamon, 1993; Grillner, 2003). However, in order to contribute to goal-driven locomotion, these spinal circuits must be activated by supraspinal locomotor centers (Grillner et al., 2008; Cregg et al., 2020). Excitatory neurons in the MLR are directly responsible for setting locomotion speed and gait patterns (**Figures 1A**, **2A**; Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018). For instance, high-speed synchronous locomotion is mediated by CNF glutamatergic neurons while PPN glutamatergic and cholinergic neurons contribute to low-speed locomotion and arrest (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018). The three DCN (**Figure 2A**) in the CLR, such as the FN, the IN and the DN, interact to govern posture, locomotion, fine finger movements, gaze, the acquisition of Pavlovian oculomotor conditioning and refined complex computational prediction-error processes underlying the encoding and reinforcement of fear memories (Bostan et al., 2013; Vitale et al., 2016; Hintzen et al., 2018; Wang et al., 2018; Cregg et al., 2020; Frontera et al., 2020). Such a diverse set of functions of the cerebellum relies on the synaptic interactions with vlPAG, PPN, the pontine and medullary premotor neuronal nuclei, and the thalamic ventrolateral nucleus (**Figure 2A**). Interestingly, the activity of Purkinje cells at the cerebellar cortex and neurons in FN and IN are modulated by the stepping rhythm (Orlovsky, 1972a,b) suggesting that the cerebellum is directly involved in sensing rhythmic locomotion. FN is directly involved with the control of postural muscles and locomotion (Mori et al., 1998) and together with the DN projects to excitatory premotor neurons in Gi (**Figure 2A**; Cregg et al., 2020). Neurons of FN have also been shown to project to the vlPAG (**Figure 2A**) targeting excitatory (Chx10-positive), inhibitory (GAD2-positive), and modulatory (TH-positive) neurons (Vaaga et al., 2020). However, optical stimulation of FN afferents has controversial effects on Chx10-positive neurons. On one hand, FN optical stimulation produces an artificial postsynaptic depolarization of Chx10-positive neurons which brings these neurons to fire trains of action potentials. On the other hand, such an optical stimulation not only induces a postsynaptic reduction of the amplitude of evoked excitatory currents on Chx10-positive neurons but also induces a postsynaptic increase of the amplitude of evoked inhibitory synaptic currents on these neurons via the activation of dopamine receptor type 2 (D2) *in vitro*. Since activation of vlPAG

glutamatergic projection neurons to the magnocellular nucleus of the medulla promotes locomotion arrest (Tovote et al., 2016; **Figure 3B**), FN may favor locomotion by enhancing synaptic inhibition on these neurons, however, whether the selective stimulation of FN afferents *in vivo* favors or not locomotion arrest is still an open question. The evidence presented above indicates that the cerebellum is a neural hub involved in the processing of information in defensive and sensorimotor circuits (**Figure 2A**), hence, it may have a pivotal role in the general control of locomotion.

Cregg et al. (2020) found that optogenetic activation of Gi glutamatergic Chx10-positive neurons (**Figure 2A**) causes inhibition of ipsilateral rhythmic locomotion activity and excitation (contraction) of ipsilateral axial muscles in mice. Such a dual action bends the mouse body trunk on the ipsilateral site, reduces the ipsilateral flexor-locomotor activity and force generation, and promotes ipsilateral turning. Conversely, unilateral inhibition of Chx10-positive neurons facilitates contralateral turning. The unilateral motor effect of Chx10-positive neurons in Gi is due to the activation of spinal inhibitory circuits as it is sensitive to the pharmacological blocking of spinal inhibitory synaptic transmission. Further anatomical studies with transsynaptic tracers showed that Chx10 Gi neurons receive synaptic inputs from the contralateral SuC, ipsilateral ZI, ipsilateral mRt and from the deep cerebellar nuclei DN (bilateral) and IN (ipsilateral), suggesting that Chx10 Gi neurons integrate somatosensory and motor information from the DLR and the CLR to drive spinal motor circuits and evoke turning (**Figure 2A**). Surprisingly, Chx10 Gi neurons do not receive synaptic projections from MLR (**Figures 2A**, **3A**) suggesting a greater complexity of the neural network underlying locomotion initiation, maintenance and direction. While initiation mainly requires LPGi (collecting MLR information), maintenance also requires Gi (collecting DLR and CLR information). Interestingly, Cregg et al. (2020) also showed that mice do not have the ability to compensate for the dysfunction of the Gi-Chx10 turning system which suggests that deterioration of the Gi-Chx10 network or its supraspinal drivers may have direct consequences on gait function. The evidence presented before suggests that the premotor circuits in Gi are critical for the postural adjustment needed for the maintenance of locomotion (**Figure 2A**).

The Cerebellum and the Basal Ganglia as a Hub for the Multilevel Integration of Sensory-Motor, Defensive and Cognitive Information

Maintenance of locomotion and gait requires the coordination of circuits underlying sensorimotor integration and computation of higher-order brain functions. It is thought that the cerebellar and BG circuits manage the integration of sensorimotor and cognitive information supporting anticipatory postural adjustment and gait function. This integration happens through reciprocal connections with the frontal-parietal and motor cortices, brainstem, and spinal sensory-motor circuits (Koutsikou et al., 2015; Takakusaki, 2017; Frontera et al., 2020). Both BG and cerebellum are interconnected through the disynaptic loops DN–thalamus–dorsal striatum and STN–PPN–DN–cerebellar cortex (**Figure 2A**; Bostan et al., 2013; Vitale et al., 2016). However, the determination of the specific roles of these circuits in the maintenance and coordination of locomotion is still a challenge. One possible explanation of this difficulty is that the activation of PPN neurons produces different effects on their postsynaptic targets and induces opposing behavioral responses. For instance, electrical microstimulation of PPN enhances the cerebellar output by directly increasing the activity of DCN neurons in rats (Vitale et al., 2016). Such a neuronal effect is mediated by cholinergic and glutamatergic PPN projections, however, the actual behavioral consequence of the PPN-evoked excitation of DCN neurons remains elusive. Other evidence indicates that electrical microstimulation of PPN induces atonia in decerebrate cats which depends on the elevation of inhibitory synaptic transmission in PPN (Takakusaki et al., 2004, 2005). Further evidence indicates that the ascending PPN-cholinergic neuronal projections onto SNr provide direct inhibition to striatal direct pathway axonal terminals, which results in a reduction of the velocity of locomotion (Moehle et al., 2017). Conversely, other results showed that optogenetic activation of cholinergic PPN neurons positively modulates ongoing locomotion while the activation of glutamatergic neurons in PPN favors low-speed exploratory locomotion and locomotion arrest (Roseberry et al., 2016; Capelli et al., 2017; Caggiano et al., 2018; Josset et al., 2018; Carvalho et al., 2020). Since the same putative cell type can generate opposite behavioral responses, we hypothesize that the output of PPN depends on the dynamic interaction of competing glutamatergic, cholinergic and GABAergic neuronal engrams supporting the maintenance and coordination of locomotion in a context dependent manner.

As mentioned before, the cerebellum (**Figure 2A**) participate in a broad range of motor and cognitive brain functions (Bostan et al., 2013; Vitale et al., 2016; Hintzen et al., 2018; Wang et al., 2018; Cregg et al., 2020; Frontera et al., 2020). Furthermore, evidence shows that the ascending sensory and proprioceptive information traveling to the cerebellum via the spino-olivary pathways is under the modulatory control of PAG, which seems to provide a selective filter for balancing the nociceptive and proprioceptive information (Koutsikou et al., 2015). Likewise, Koutsikou et al. (2015) indicated that PAG also modulates the cerebellar output. The described modulation of sensory input and output of the cerebellum by PAG activity suggests that defensive circuits may play a very important role in the modulation of cerebellar functions. Anatomical and electrophysiological studies in rats have shown that the cerebellum is also interconnected with the hypothalamus (**Figure 2A**; Supple, 1993; Onat and Çavdar, 2003). The anterior cerebellar vermis receives projections from the ventrolateral hypothalamus (VMH/LH area). Supple and collaborators reported that stimulation of VMH/LH generates a transient increase-decrease sequence in the firing rate of putative Purkinje cells. On the other hand, back projections from the cerebellum via FN neurons have also been reported to arrive at the posterior and the dorsomedial hypothalamic nuclei (Newman and Reza, 1979; Onat and Çavdar, 2003). However, the functional role of these projections on cerebellar or autonomic functions is

unknown. As aforementioned, the hypothalamus plays a direct role in the initiation of defensive locomotion via interactions with the BG circuits (**Figure 1E**; Narita et al., 2002; Mitrofanis, 2005; Takakusaki et al., 2005; Karnani et al., 2020), therefore, the cerebellum might be also involved in the initiation of defensive locomotion. Together, the evidence presented in this section suggests that the cerebellum-BG network provides a neural system that supports different types of locomotion (**Figure 2A**). Moreover, this system has multiple points of interaction with the defensive circuits via PAG and hypothalamus, allowing its emotional or defensive modulation (**Figures 1E**, **2A**).

Cholinergic Counterbalance of the Dopaminergic Control of Basal Ganglia Output

The output of BG is modulated by the activation of cholinergic neurons in the striatum and PPN facilitating the reduction of locomotion upon the exposure to a contextual reward (**Figures 1C**, **2A**; Picciotto et al., 2012; Moehle et al., 2017). The striatal cholinergic neurons pause their firing (Goldberg and Reynolds, 2011) while the PPN cholinergic neurons increase their firing upon the exposition to salient reward-related cues (Picciotto et al., 2012). Tonically active striatal cholinergic interneurons increase neural excitability of SPNs and suppress feed-forward excitatory and feed-back inhibitory synapses onto SPNs (Oldenburg and Ding, 2011). This happens via activation of the muscarinic acetylcholine receptors type M1 and M2. The tonic cholinergic control of the striatal network may also support adaptive adjustment in the processing of sensory information as it undergoes different forms of synaptic plasticity (Oldenburg and Ding, 2011; Davis et al., 2018; Abudukeyoumu et al., 2019). On the other hand, PPN cholinergic neurons provide direct inhibition to the synaptic terminals of D1-expressing SPNs arriving at the SNr (**Figures 1C**, **2A**) via activation of the muscarinic receptor type M4 (Moehle et al., 2017). While the striatal cholinergic modulation may provide a mechanism for the direct computation of sensory information by SPNs, the PPN cholinergic modulation is more in charge of the direct regulation of the BG output. This evidence also suggests that the PPN-striatal cholinergic system may counterbalance the pro-locomotion effect of dopamine in a context–dependent manner, which may facilitate the transition from high-speed locomotion to slow locomotion and arrest.

Locomotor State Transitions Support Adaptive Behavior

Transitions between distinct locomotion states are required for switching between adaptive behaviors when an organism copes with environmental and situational challenges. The correct communication within a global network supports optimal evaluation and selection of action options such as exploratory, appetitive and defensive locomotion. Evidence presented in the former sections indicates that the activation of the indirect pathway of BG facilitates the transition from consummatory to exploratory behavior (**Figure 2B**; Tecuapetla et al., 2016). Upon presentation of salient reward-related cues, cholinergic PPN neurons increase their activity (Picciotto et al., 2012). These neurons project back to SNr where they inhibit the direct BG pathway input to slow down and arrest locomotion (Moehle et al., 2017). This system may facilitate the transition between exploration to consummatory behavior (**Figure 2C**). Upon a potential threat, LH-glutamatergic neurons projecting to vlPAG terminate food retrieval and promote defensive escape (**Figure 2D**; Li et al., 2018). Escape can be also complemented by the activation of the dm/cVMH-AHN pathway (**Figure 1E**; Wang et al., 2015). Furthermore, VMH may also increase the activity of STN/ZI neurons (Narita et al., 2002) augmenting the weight of information in the BG indirect pathway which may lead to reduction of speed or may bias goal-driven behavior (Tai et al., 2012; Tecuapetla et al., 2016). However, how the VMH-STN/ZI pathway modulates goal-driven locomotion is still unknown. Higher-order state regulation involves neurons in the basal amygdala, which predict the transition between exploratory, non-exploratory, and defensive behavioral states (Gründemann et al., 2019). Finally, dimorphic defensive behaviors such as escape-and-freeze orchestrated by the SuC-PBGN/LPTN networks (**Figure 2E**; Shang et al., 2018) and freeze-and-flight managed by the cortico-striatal and cortico-collicular networks (Li et al., 2021) are examples of the capacity of the sensory system to drive transitions between behavioral states. Overall, transitions from one to another locomotion state, although ultimately resulting in stereotyped behavioral and gait patterns, require activity within specific circuit elements depending on the context, stimulus and internal state of the organism.

Based on the evidence presented in the previous subsections, we hypothesize that the maintenance and coordination of locomotion rely on the precise temporal interaction among neuronal modules in the cerebellum, BG, hypothalamus, amygdala, PAG and MLR (**Figure 2**). Remarkably, BG seems to be self-sufficient to drive the bidirectional transition between appetitive and exploratory locomotion, although the regulation of locomotion speed is supported by MLR (**Figures 2B,C**). Sensory information arriving to the brain via sensory cortices and the cerebellum, may be then routed to BG, TH, and PAG (**Figures 2A,E**). Motor information processed by MC and BG is then transmitted to PAG and MLR (**Figures 2A–C,E**). In PAG, the sensory/motor information may be integrated with appetitive and defensive information arriving from hypothalamus and amygdala (**Figures 1E**, **2D**). In MLR/mRt, the information may be sent back to BG via ascending feedback projections (**Figures 1C**, **2A,C**) for further processing and to medullary LPGi and Gi neurons via descending projections (**Figures 1A**, **2A**) to initiate locomotor transitions. In turn, Gi may integrate and compute motor commands from mRt, cerebellum, BG and PAG to send postural-adjustment commands to the spinal motor circuits, while LPGi may provide to the spinal cord the trigger command for the initiation of locomotion (**Figure 1A**).

TERMINATION OF LOCOMOTION

While termination of locomotion, strictly speaking, only describes the moment in which gait is stopped, it is tightly linked

to immobility, which in many instances follows termination of locomotion. In the threatening contexts, this immobility is commonly termed freezing, originally defined as the absence of all movements despite respiration. To capture termination of locomotion in various contexts and across different states, we will use the more descriptive term arrest, which conceptually includes termination of locomotion and subsequent immobility (**Figure 3**).

Basic Network Underlying the Termination of Locomotion

Different to the initiation and maintenance of rhythmic locomotion, the basic neural circuitry underlying the termination of locomotion is more diversified. Bouvier et al. (2015) found that bilateral optogenetic activation of Chx10 Gi glutamatergic neurons results in locomotor arrest by inhibiting the rhythmic motor activity in the spinal cord (**Figure 3A**). Later on, Cregg et al. (2020) found that the unilateral activation of the same neurons halts the ipsilateral rhythmogenesis, facilitating directional turning during exploratory locomotion. In addition, Capelli et al. (2017) found that optogenetic activation of glycinergic neurons in the medullary reticular formation elicits different forms of locomotion arrest (**Figure 3A**). Whereas stimulation of LPGi and GiA glycinergic neurons is sufficient to reduce speed and halt locomotion without affecting posture, GiV neurons provoked body collapse resembling behavioral atonia, and Gi neurons also produced body collapse and spasms. These results suggest that distinct functional forms of locomotor arrest are mediated by the activation of different subpopulations of neurons located in the hindbrain. Other evidence shows that the direct inhibitory control of MLR glutamatergic neurons encoding locomotor state and speed by BG circuits and/or activation of local GABAergic MLR neurons is necessary and sufficient to terminate locomotion (Roseberry et al., 2016). Furthermore, optogenetic activation of a glutamatergic MLR neuronal subpopulation identified by its ascending projection to BG output regions evoked halting of locomotion as well as other behaviors (Garcia-Rill et al., 1986; Sherman et al., 2015; Roseberry et al., 2016; Chang et al., 2020; Ferreira-Pinto et al., 2021). All together, this evidence suggests that the termination of locomotion relies on the dynamics of the MLR–BG network, and hindbrain circuits including GiA, GiV, LPGi and Gi (**Figure 3A**). However, whether specific circuits are recruited to drive context- or state-dependent locomotor arrest remains to be determined.

Higher Order Network Elements for the Termination of Locomotion

Next to a role in locomotion initiation, the hypothalamus also plays a central role for its termination. As mentioned before, the postsynaptic activation of the VMH network increases the firing rate of STN/ZI neurons (Narita et al., 2002), as a consequence, the BG indirect pathway may suppress exploratory locomotion (Kravitz et al., 2010; Freeze et al., 2013). Moreover, Wang et al. (2015) found that selective optogenetic activation of steroidogenic-factor 1 (SF1)-expressing neurons in dm/cVMH projecting to dlPAG produces arrest (**Figure 3B**). Stimulation of dm/cVMH also produces autonomic responses resembling the development of behavioral stress such as pupil dilation, increase in breathing rhythm and in heart rate. However, Wang et al. (2015) also reported that the changes of autonomic responses are dissociated from active locomotion as they happen during freezing behavior, suggesting that defensive arrest is functionally associated with an elevation of stress.

Motta et al. (2009) have shown that neurons in the PMD (**Figure 3B**) become differentially activated by distinct contextual threats (i.e., conspecific and predatory threats) and the downstream PAG responds differentially to these threats as well. Analysis of the activation of the early gene c-fos at PAG revealed that dominant conspecific threats activate neurons in PAG in a way that follows the axonal projections from the ventrolateral region of PMD (vlPMD, where c-fos is upregulated by the intruder), whereas a predatory threat generates a c-fos pattern that follows the projections from the dorsomedial region of PMD (dmPMD, where c-fos is upregulated by the predator). Exposure to a predator increases c-fos activity mainly in d–dlPAG, whereas exposure to a dominant conspecific not only increases c-fos at d–dlPAG but also at lPAG. However, the increase of c-fos at lPAG may also be due to the correlated activation of sensory cortical and collicular inputs for instance (Shang et al., 2018; Li et al., 2021). Furthermore, whether the correlated conspecific-predator responses between PMD and d–lPAG rely on the activation of PMD-CCK-expressing glutamatergic neurons (Wang et al., 2021) is still an open question. Analysis of defensive reactions in PMD-lesioned mice showed that defensive arresting behaviors (i.e., freezing and playing dead) were reduced while active defensive behaviors (i.e., standing upright position, boxing and fleeing) were unaffected in reference to control animals. These results suggest that the dmPMD/vlPMD–d,dl,lPAG circuits are specially involved in the facilitation of defensive behavioral arrest.

The defensive neural circuits involved in the processing of auditory, visual, and olfactory sensory stimuli can elicit defensive arrest (**Figure 3B**), presented as a single behavioral sign or in complex behavioral sequences such as freeze-and-flight (Euston et al., 2012; Lisman et al., 2017; Rozeske et al., 2018). Using optogenetic manipulations of specific cell types, single-unit recordings and rabies-mediated neuroanatomical tracings, Tovote et al. (2016) dissected a pathway from CeA to the vlPAG that mediates freezing by disinhibition of the vlPAG glutamatergic output to descending premotor neurons in the magnocellular nucleus of the medulla (i.e., LPGi, GiA and GiV) (**Figure 3B**). Inhibition of glutamatergic PAG neurons greatly attenuated freezing behavior both to learned and innate threats. However, whether the excitation of these premotor neurons also engages the activation of GiA-, and/or LPGi-glycinergic neurons to promote defensive arrest remains elusive. Later on, Xu et al. (2016), by using trans-synaptic viral tracing and optogenetic manipulations, found that the vHIPPO (a central component of circuits processing emotions and contextual memory) and the amygdala interact via multiple parallel pathways (**Figure 3B**). Projections from subsets of vHIPPO to the basal amygdala mediates the retrieval of context-dependent freezing (after fear extinction), whereas a parallel projection from a distinct subset of vHIPPO neurons onto CeA neurons projecting to

the vlPAG is necessary for context-dependent renewal of cued fear memories. These results suggest that the activation of parallel circuits between vHIPPO and the amygdala underlies the behavioral expression of high-order cognitive functions such as the retrieval and renewal of contextual memory leading to defensive locomotor arrest. Other evidence suggests that the neural circuits between vHIPPO and the amygdala also support the behavioral expression of non-defensive spatial memory, which is a natural function of the dorsal hippocampus in rodents (Lisman et al., 2017; **Figure 3C**). Using behavioral analyses, circuit mapping, single-cell calcium imaging and closed-loop optogenetic approaches, Botta et al. (2020) identified cell ensembles in BLA whose activation was correlated with momentary pauses (∼1 s) in exploratory locomotion. Usually the arrests were followed by changes in the angular speed of the head resembling the movements made by rodents while performing vicarious-trial-and-error decision making (**Figure 3C**; Redish, 2016). This suggests that during such an arrest the animal may be going through a cognitive processing to evaluate the spatial options. Interestingly, optogenetic activation of CeA-projecting BLA neurons decreases locomotion and promotes arrest while inhibition of glutamatergic BLA neurons facilitates movements. Furthermore, the BLA neuronal ensembles are spatially modulated as they become reactivated when the animals revisit familiar locations (i.e., habituation-home area and the boundaries of an open field maze). However, whether the described non-defensive behavioral arrest engages CeA-vlPAG projections or not still needs to be demonstrated.

Hippocampus and the medial PFC (mPFC) work together in the processing of associative memory and learning. While HIPPO is involved in encoding and early consolidation, mPFC is involved in late consolidation and the development of schematic representations of cognitive tasks and emotional contexts (Dejean et al., 2016; Karalis et al., 2016). More specifically, the dorsomedial PFC (dmPFC) is directly involved in contextual fear discrimination by the dynamic neural representation of threatening and non-threatening contexts (Rozeske et al., 2018; Bagur et al., 2021). Rozeske et al. (2018), demonstrated that subpopulations of l–vlPAG-projecting neurons in dmPFC (**Figure 2A**) have the property to dynamically represent both threatening and non-threatening multisensory contexts. This occurs by increasing their firing rate in non-threatening contexts. Thus, the activity of this subpopulation of dmPFC neurons is inversely correlated with freezing. Furthermore, optogenetic activation of dmPFC afferents at l–vlPAG reduces freezing while inhibition favors it. However, whether the effect of dmPFC relies on the dopaminergic modulation of the Chx10-positive neurons at l–vlPAG (Vaaga et al., 2020) remains to be determined. Interestingly, other studies indicate that the frequency-modulated synchronization between dmPFC and the amygdala is essential for the initiation of contextual freezing (Li et al., 2021). Moreover, synaptic dynamics and neuronal firing of fear-related dmPFC neurons and the maintenance of contextual freezing appears to be modulated by breathing-related neuronal activity of the olfactory bulb (Bagur et al., 2021).

Locomotor arrest can also be triggered upon the identification of visual threats (e.g., looming visual stimuli in mice). Such arrest occurs through the activation of competing neuronal paths driven by SuC (Shang et al., 2015, 2018). Activation of the path SuC(PV+ excitatory neurons)-LPTN–LA favors freezing, whereas, activation of the paths SuC(PV+ excitatory neurons)-PBGN-CeA and SuC(PV+ excitatory neurons)-PBGN-dlPAG favors a complex escape-and-freeze behavioral sequence (**Figures 2E**, **3B**). However, the precise neural mechanism underlying the natural balance between PBGN and LTPB is unknown. Furthermore, whether the activation of escape-and-freeze behavior relies on the sequential activation of PBGN-dlPAG and PBGN-CeA-vlPAG for instance also remains elusive.

Moreover, the cerebellum via the FN may oppose the termination of locomotion. As mentioned before, optical activation of afferents from FN at vlPAG (**Figure 2A**) augments inhibitory control onto Chx10-positive neurons via the activation of D2 dopamine receptors (Vaaga et al., 2020). Vaaga et al. (2020) also showed that optogenetic activation of the Chx10-positive neurons in vlPAG is sufficient to induce freezing. Since activation of vlPAG glutamatergic neurons induces defensive freezing (Tovote et al., 2016), it is probable that the Chx10-positive neurons belong to the same subpopulation of freezing-triggering glutamatergic vlPAG neurons. Hence, increased inhibition of these neurons is expected to reduce freezing while disinhibition does otherwise. Since the FN favors an increase of inhibitory dopaminergic control of vlPAG Chx10 glutamatergic neurons, the cerebellum might also complement the action of the BG direct pathway. However, further studies must be performed to know whether dopamine is released by local TH+ neurons (Vaaga et al., 2020) or by SNc afferents arriving onto vlPAG (Lima et al., 2018).

In summary, the evidence presented in this section indicates that termination of locomotion due to threats (defensive arrest) is supported by the neural circuits residing within hypothalamus (dm/cVMH, PMD), ventral HIPPO, Amygdala (CeA, BLA), and PAG (dl/l/vlPAG) (**Figure 3B**). The fact that specific pathways between these interconnected subregions have been functionally identified to either directly trigger or more sluggishly promote defensive arrest, indicates that under unperturbed conditions, dynamic contributions of the individual network elements are orchestrated to elicit an adaptive, state-dependent response. Moreover, exploratory arrest is supported by CeA-projecting BLA neurons (**Figure 3C**). On the other hand, visual-threat driven arrest is mediated by the competing pathways SuC(PV+ excitatory neurons)-LPTN–LA and SuC(PV+ excitatory neurons)-PBGN-dlPAG and PBGN-CeA (**Figures 2E**, **3B**). It remains to be determined how each of these pathways is integrated with downstream motor circuits to generate a coordinated behavioral outcome.

DISCUSSION

In this review, we described neuronal circuits identified as neural substrates for the state-dependent modulation of locomotion (**Figures 1**–**3**). While future studies will likely reveal additional and refine known network elements, in the present review we identified a number of non-exclusive neuronal circuits

supporting the different phases of initiation of locomotion, maintenance and arrest/termination.

A brain-wide network involving excitatory circuit elements connecting cortex, midbrain and medullary areas appears to be the common substrate for the initiation of locomotion across different states. In this brain-wide network, the MC and the MLR drive the initial postural adjustment and initiation of locomotion *per se* (**Figure 1A**). On the other hand, the BG circuits, by implementing action-selection computations, trigger the initiation of goal-directed locomotion (**Figure 1C**). In addition, the initiation of locomotion is regulated by neuromodulatory circuits residing in the LC, the BF, the hypothalamus and the medulla oblongata (**Figures 1B,G**). Strikingly, the maintenance of locomotion also requires the interaction of an even larger neuronal network encompassing motor, sensory and associative cortices, as well as the SuC, the cerebellum and Gi (**Figure 2**). It is conceivable that this is likely due to the need for integration of several information streams, such as sensory and proprioceptive feedback as postural command signals during ongoing locomotion. Nonetheless, the BG seems self-sufficient to drive the bidirectional transition between appetitive and exploratory locomotion, while the regulation of locomotion speed is supported by MLR.

The reviewed evidence indicates that BG and MLR are modulated by both, excitatory as well as inhibitory circuits residing in the hypothalamus, amygdala and PAG to guide the initiation of state-dependent locomotion, i.e., appetitive and defensive locomotion. Complementing these direct influences, GABAergic projections from the LH and the CeA to vl–lPAG are instrumental for the initiation and performance of appetitive locomotion (**Figure 1D**). Glutamatergic projections from the LH to the vl–lPAG are engaged in the initiation of escape/avoidance behaviors (**Figure 2D**). Glutamatergic projections from the VMH to the GABAergic neurons in the AHN support the initiation of escape/avoidance behaviors (**Figure 1E**). Glutamatergic projections from the ventromedial and premammillary hypothalamic nuclei and SuC to d–dlPAG mediate the initiation of aggressive defensive behaviors (**Figures 1E,F**). Importantly, not only the behavioral context, but also distinct sensory cues establish transient states of emotional valence, which then drive different network elements to elicit adaptive locomotor responses. For example, rapid identification of a visual threat evokes complex dimorphic defensive responses via excitatory neurons in the SuC, which activate the downstream circuits in the parabigeminal nucleus projecting to dlPAG and the CeA (**Figure 1F**). On the other hand, dimorphic defensive responses are also supported by sensory circuits in the AC projecting to the striatum (D2-SPNs) and to SuC upon the detection of an auditory threat.

Although circuits within the BG seem sufficient to mediate non-defensive yet goal-oriented state transitions, state-dependent initiation, maintenance and termination of locomotion are tightly related to the action of defensive circuits. The transition between non-defensive and defensive behavioral states is strongly reflected by BLA neuronal activity (Gründemann et al., 2019; Fustiñana et al., 2021) and may be functionally complemented by the intra-hypothalamic circuits (Mitrofanis, 2005; Wang et al., 2015), LH-glutamatergic projections to vlPAG, and the SuC-PBGN path to the amygdala (Shang et al., 2018). In addition, the interplay among BG, MLR, and DCN may be the core system for the transition of behavioral states, which require the adaptation of postural muscles. For instance, postural adjustment might be made by activation of ipsilateral synaptic projections from the ZI onto Chx10 Gi glutamatergic neurons, and by the direct communication of glutamatergic MLR neurons to the spinal cord (Bouvier et al., 2015; Ferreira-Pinto et al., 2021).

Locomotor arrest is an important component of defensive emotional states, such as acute anxiety, which are mediated via a network of survival circuits involving hypothalamus, amygdala and PAG, connecting to medullary premotor centers (**Figure 3A**). Activation of hindbrain GiA/LPGi/GiV/Gi glycinergic neurons and the bilateral activation of Chx10 Gi glutamatergic neurons can all also directly trigger gait disruption resulting in locomotor arrest. On the other hand, behavioral arrest driven by decision-making processes relies more on a complex interaction between the BLA (Botta et al., 2020), the BG-MLR circuits (Kravitz et al., 2012; Picciotto et al., 2012; Roseberry et al., 2016; Moehle et al., 2017; Ferreira-Pinto et al., 2018) and PAG. While these findings suggest that PAG circuits constitute major regulatory units for state-dependent locomotion, the precise mechanisms on how this is translated into specific motor programs are poorly understood. Conceptually, the PAG plays multiple roles in the control of state-dependent locomotion by integrating coherent information from the SuC, the amygdala, the hypothalamus, and the cortex, as well as, calculating threat probability (Wright and McDannald, 2019) and delivering an adaptive executive command to downstream premotor circuits. In line, neuroanatomical data support a possible routing of integrated state-dependent information from the PAG to MLR to drive locomotion (Caggiano et al., 2018).

Integration of Supraspinal and Spinal Cord Circuits

While during the last decade, research has greatly promoted our understanding of supraspinal circuits involved in locomotion, how specific supraspinal circuits communicate with the spinal cord, where these pathways converge, and which circuit elements are shared remains poorly understood. Nonetheless, recent evidence points toward several integration centers throughout the neural axis. For example, one described locomotion initiation pathway resides in the MLR–LPGi glutamatergic circuit, while MLR-spinal cord glutamatergic pathway controls postural adjustments which are required for proper locomotion initiation. Moreover, maintenance of rhythmic locomotion and locomotion termination rely on glutamatergic and glycinergic circuits located in Gi, LPGi, and GiA, which receive differential synaptic input from DLR, CLR, and MLR. Since activation of GiV glycinergic neurons produces atonia, these neurons help to keep a relaxed state of skeletal muscles during sleep (Garcia et al., 2018). Furthermore, the control of gait function requires the orchestrated interaction of neural circuits residing in sensory brain areas, associative-limbic areas, and attentional/reward areas with defensive circuits providing direct control of motor responses and autonomic functions. In the neural concert of gait function, it is conceivable that the hypothalamus, the

amygdala and PAG play a central role by funneling emotional information into the MLR. In this concert, the BG together with the cerebellum will drive cognitive goal-oriented locomotion with adaptive postural adjustment which may support the transition among several locomotion states.

Translation of Circuit Mechanisms From Animal to Human Brains

Unsurprisingly, there is a large overlap of circuits for state-dependent control of locomotion. However, while it is clear that gait coordination on the mechanical level needs temporally precise circuit interactions, such as those proposed for central pattern generators, the multi-level interaction of higher-order centers for state-dependent modulation of locomotion is striking. In the modern era of circuit neuroscience, with its cell-type and projection-specific tools as well as complex behavioral and kinematic analyses, we have just begun to understand the complexity of the control of locomotion. As a consequence, much of the detailed findings obtained in animal models remain to be translated into research approaches in humans. Emotional states such as appetite, anger and fear are important drivers of volitional movements in humans, and there is abundant evidence that these basic emotional states involve similar brain regions across mammalian species. But do the neuronal pathways and circuits, based on findings from animal studies, account for the modulation of initiation, maintenance, and termination of locomotion, as well as postural control also in humans? Unfortunately, lower resolution so far limits the investigation of cell-type specific circuits in the living human brain, a barrier that will be hard to overcome in the near future. Nonetheless, findings from animal models on the level of brain (sub-)regions support the design of testable hypotheses to be pursued via functional neuroimaging approaches in humans. To push the translational relevance of research in animal models, efforts to integrate small-scale circuit findings on the level of cell types with the larger networks across brain regions (Mace et al., 2013; Cardin et al., 2020; Markicevic et al., 2021) should be undertaken. Furthermore, the development of similar behavioral paradigms and use of common readouts as well as analyses present promising avenues for successful cross-species translation. Clearly, basic insights into circuit function can inform and help refine established interventional strategies such as deep-brain electrical stimulation (DBS) or new approaches using ultrasound or electromagnetic energy to manipulate local brain activity.

The Handling of Pathological Gait Dysfunctions

Clinical evidence shows that gait dysfunction occurs upon the damage of different brain areas such as the cerebellum, the BG circuits including putamen, internal globus pallidus and external globus pallidus, the primary MC, the brainstem, the midbrain/tegmentum, the corpus callosum and the parasagittal white matter (Nutt et al., 2011; Fasano et al., 2017). Moreover, imaging alterations in networks for executive attention, including frontal lobe, and networks for emotional processing, including amygdala, have been linked to locomotor dysfunction, such as FoG in PD (Fasano et al., 2015; Gilat et al., 2018). Since FoG in PD patients is understood as the inability to produce effective forward stepping, any emotional or cognitive restraint preventing or delaying the activation of neural circuits underlying the initiation of locomotion may favor the emergence of FoG. Although clear links between anxiety and motor symptoms in PD such as FoG have been established (Martens et al., 2016), their interplay is mechanistically not understood. Our review introduces a more holistic perspective, thereby identifying points of interaction within the larger neuronal network, where (pre-) motor circuits mediating termination of locomotion and the "limbic" circuits mediating emotional states such as fear and anxiety converge. Further research using selective optogenetics, transsynaptic tracing, calcium imaging and electrophysiology *in vivo* and *ex vivo* needs to be done in animal models of PD and ataxia to better understand the functional alterations of the neural network dynamics and synapses in different locomotor regions.

The clinical standard treatment of PD symptoms, dopamine replacement, has been proven relatively ineffective to ameliorate gait dysfunction. Non-pharmacological alternative procedures to mitigate gait dysfunction in advanced PD patients have been implemented. Many of these procedures rely on DBS targeting STN, GPi and PPN (PPT) or less invasive spinal cord electrical stimulation (Peppe et al., 2010; Welter et al., 2015; Samotus et al., 2018; Hartmann et al., 2019; He et al., 2020). However, the mechanisms of action remain largely unclear as the outcomes are highly variable depending on the assessed gait parameter, body parts (e.g., legs, arms or trunk postural muscles), stimulation frequency, targeted brain area or whether the stimulation is combined or not with pharmacological treatment. A major caveat of DBS, besides its invasiveness, is that electrical stimulation does not discriminate among neuronal cell types, which may generate major alterations in the natural performance of unspecific neighbor networks. For example, direct stimulation of PPN may dampen volitional locomotion either via activation of a counterbalancing feed-back cholinergic control on the BG direct pathway or via increased PPN glutamatergic drive to BG output regions. Moreover, DBS in PPN may alter glutamatergic descending pathways conveying postural and locomotor commands to the spinal cord and may activate DCN with distinct cognitive and motor functional roles. However, combinations of pharmacological receptor blockade and DBS could in principle increase the pathway selectivity of electrical stimulation (Creed et al., 2015). As it becomes increasingly clear that the network functions underlying control of locomotion and gait are highly state-dependent, more dynamically adjusted DBS, such as closed-loop approaches involving concomitant recordings and stimulation, could present more precise and potentially more effective network "retuning" action.

Overall, part of the tremendous complexity of the state-dependent circuitry regulating locomotor functions can be explained by the demand to react to various environmental changes and challenges. This requires dynamic integration of fast behavioral responses to specific cues with evaluation of varying contexts, constituting a selection pressure that drove step-wise evolution of interactive neuronal circuit modules serving ever-increasing flexibility of adaptive behavioral repertoires. However, the highly interconnected, and inter-dependent function of these

networks thereby became vulnerable for dysregulation within individual modules. Consequently, from a modern systems neuroscience perspective, motor dysfunctions reflect network diseases, so called circuitopathies, which take into account the regulation of locomotor functions by higher-order states.

AUTHOR CONTRIBUTIONS

AP-A, NW, ME, and PT wrote the review article. All authors contributed to the article and approved the submitted version.

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Mobile Electroencephalography for Studying Neural Control of Human Locomotion

Seongmi Song[1] *and Andrew D. Nordin*[1,2,3]*

[1]*Department of Health and Kinesiology, Texas A&M University, College Station, TX, United States,* [2]*Department of Biomedical Engineering, Texas A&M University, College Station, TX, United States,* [3]*Texas A&M Institute for Neuroscience, College Station, TX, United States*

Walking or running in real-world environments requires dynamic multisensory processing within the brain. Studying supraspinal neural pathways during human locomotion provides opportunities to better understand complex neural circuity that may become compromised due to aging, neurological disorder, or disease. Knowledge gained from studies examining human electrical brain dynamics during gait can also lay foundations for developing locomotor neurotechnologies for rehabilitation or human performance. Technical barriers have largely prohibited neuroimaging during gait, but the portability and precise temporal resolution of non-invasive electroencephalography (EEG) have expanded human neuromotor research into increasingly dynamic tasks. In this narrative mini-review, we provide a (1) brief introduction and overview of modern neuroimaging technologies and then identify considerations for (2) mobile EEG hardware, (3) and data processing, (4) including technical challenges and possible solutions. Finally, we summarize (5) knowledge gained from human locomotor control studies that have used mobile EEG, and (6) discuss future directions for real-world neuroimaging research.

Keywords: EEG signal processing, motor neuroscience, neuroimaging, locomotion, mobile EEG, electroencephalography (EEG), EEG hardware

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***Correspondence:**
Andrew D. Nordin
nordina@tamu.edu

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INTRODUCTION

Understanding human brain processes during real-world behaviors is a major neuroscience challenge. Moving cognitive and motor neuroscience studies beyond stationary, seated experiments and into complex, realistic environments is a necessary step forward to decipher real-world human brain dynamics. Because walking is a fundamental motor task that can have profound effects on quality of life and requires complex interactions throughout the nervous system, there is a need to better understand healthy human neuromotor control and to identify pathways affected by a loss of neurological function due to disease, disorder, injury, or aging (Snijders et al., 2007). Although basic locomotor control can be primarily attributed to subcortical structures and spinal central pattern generators, a growing body of evidence has shown that cortical structures directly

modulate locomotion, including motor planning, execution, and error correction. Understanding cortical involvement during locomotion is, therefore, necessary to improve clinical detection and rehabilitation results.

Contemporary brain imaging technologies can measure neural dynamics by capturing a number of contrasting physiological signals. Neural electromagnetic signals can be measured using electroencephalography (EEG) and magnetoencephalography (MEG), changes in blood oxygenation can be measured using hemodynamic measurement methods such as magnetic resonance imaging (MRI) and functional near-infrared spectroscopy (fNIRS), and molecular imaging methods such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) enable scientists and clinicians to non-invasively study human brain functions. Technological limitations, however, have largely limited neuroimaging studies to motionless conditions from participants who are seated or lying supine due to the physical size of the recording equipment or because of noise introduced by participant or equipment motions that compromise signal recording quality. In recent years, a growing need for continuous brain monitoring during movement has promoted the development of mobile brain/body imaging (MOBI) approaches. The advantages and limitations of each technology must be considered in the context of the temporal and spatial resolution of each system and the associated cost and portability. Although fNIRS can portably measure human brain hemodynamics, and advancements in MEG technologies that rely on novel optically pumped magnetometers (OPM) (Boto et al., 2018; Hill et al., 2020; Tierney et al., 2020) provide promising paths forward for studying real-world human brain dynamics, the low-cost portability and precise temporal resolution of EEG has enabled the expansion of human neuromotor research into more complex and dynamic tasks (Allali et al., 2018).

A primary limitation of mobile EEG for studying real-world human brain dynamics has been the need to eliminate noise contamination from scalp EEG recordings. During unconstrained movements such as walking, electrode motions on the scalp and cable sway increase along with electrophysiological signals from the heart, eye movements, and facial and neck muscle activities. Low signal-to-noise ratio and comparatively poor spatial resolution in relation to fMRI and molecular imaging methods have been progressively addressed through advanced signal processing to isolate and localize electrocortical source activity using independent component analysis and forward head modeling techniques (Delorme and Makeig, 2004; Acar and Makeig, 2010; Vorwerk et al., 2018). Leveraging these advancements, recent locomotion studies have extended our understanding of human brain activity during treadmill (Castermans et al., 2014; Nathan and Contreras-Vidal, 2016; Bradford et al., 2016; Nordin et al., 2019a) and overground locomotion (Luu et al., 2017a) in complex virtual (Luu et al., 2016, 2017b) and real-world environments (Bruijn et al., 2015; An et al., 2019; Peterson and Ferris, 2019), and during robotically assisted gait (Wagner et al., 2012; Li et al., 2018).

Improved capabilities for measuring real-world human brain dynamics using state-of-the-art mobile EEG technologies will continue to advance the field of human cognitive and motor neuroscience. Here, we identify current mobile EEG technologies and analysis methods that have enabled groundbreaking discoveries into human neuromotor control during locomotion, and we briefly summarize some of the remaining challenges and paths forward for human mobile brain and body imaging studies.

MOBILE EEG HARDWARE

Table 1 provides a summary of representative commercially available mobile high-density EEG system specifications. The range of electrode array density (number of channels), recording electrode type, system size, portability, and mass provide advantages and disadvantages for studying neural control of human locomotion. Here, we discuss considerations for measuring human electrical brain dynamics using contrasting mobile EEG system configurations.

EEG Recording Electrodes

Non-invasive EEG signal acquisition occurs using electrodes placed on the scalp. The recorded signal represents the summation of post-synaptic electrical potentials from the underlying and surrounding brain structures (Teplan, 2002; Sanei and Chambers, 2013), together with electrical noise from the surrounding environment, recording equipment, and ongoing electrophysiological activity from the eyes (Dement and Kleitman, 1957; Overton and Shagass, 1969; Schlögl et al., 2007), heart (Stephenson and Gibbs, 1951; Park et al., 2002), muscles (Goncharova et al., 2003; Whitham et al., 2007; Muthukumaraswamy, 2013). Electroencephalographic signals measured from the scalp show microvolt-scale fluctuations (peak-peak range: 0.5 μV–100 μV; Teplan, 2002), while noise contamination can occur at the millivolt scale (1,000× greater amplitude). The electrode characteristics and scalp-electrode interface can have large implications on EEG signal quality. Typical EEG electrodes commonly use silver/silver chloride (Ag/AgCl) that interfaces indirectly with the scalp through a conductive gel in a so-called wet electrode configuration. The Ag/AgCl wet electrodes have favorable reliability and signal integrity, with a low electrical impedance that diminishes low-frequency noise compared to high impedance electrodes recording in a warm, humid environment (Kappenman and Luck, 2010; Laszlo et al., 2014; Mathewson et al., 2017; Hinrichs et al., 2020). Any EEG setup can cause discomfort for the participant during prolonged use, but the main drawback of wet EEG electrodes is that the conductive gel dries over time, which reduces signal recording quality.

Dry contact electrodes were proposed to resolve some of the disadvantages of wet electrodes (Taheri et al., 1994; Gargiulo et al., 2008; Lopez-Gordo et al., 2014) by enabling electrical brain recordings over longer durations without a need for conductive gel (Xu et al., 2017). Additional advantages of dry contact electrodes include reduced setup time and limited inconvenience to the participant. However, dry contact electrodes show a higher impedance range and are more vulnerable to motion artifacts

TABLE 1 | Mobile high-density EEG systems for studying neural control of human locomotion.

System	Channel density	Electrode type				Size (mm)	Portability	Mass
		Active		Passive				
		Wet	Dry	Wet	Dry			
BIOSEMI:ActiveTwo	Up to 271-channels (256 scalp+ 8ECG or EMG + 7 external channels)	√				120 × 150 × 190	Body worn recording hardware	1.1 kg
Cognionics:CGX MOBILE-128	Up to 128-channels (EEG)	√				90 × 60 × 20	Body worn recording hardware	1 kg (98 g:Recording system only)
ANT Neuro:eego sports	Up to 128-channels (EEG or EMG)			√	√	160 × 205 × 22	Body worn recording hardware	<500 g (Recording system only)
G.Tec:g. NAUTILUS RESEARCH HEADSET	Up to 64-channels (EEG)	√	√			78 × 60 × 26	Head worn entire system	<140 g (Recording system only)
Brain Products:LiveAmp 64	Up to 64-channels (EEG, EMG, ECG, EOG)	√	√	√		140 × 83 × 18	Body worn recording hardware	<130 g (Recording system only)
EMOTIV:EPOC flex	Up to 32-channels (EEG)			√		220 × 155 × 50	Head worn entire system	1 kg

than wet electrodes due to the sensitive direct skin-electrode interface that is critical to mobile EEG signal recording quality (Xu et al., 2017). To overcome this, pressure is often applied to the electrodes and scalp through mechanical tension in the setup, which can lead to discomfort.

Quasi-dry electrodes, which combine advantages from both wet and dry contact electrodes, have been introduced as an intermediate solution for robust EEG signal recording (Mota et al., 2013). The quasi-dry electrode has a hydrated local skin interface with a moisturizing solution drawn from a reservoir inside the electrode. The significant advantages of quasi-dry electrodes include maintenance of lower electrode impedance similar to wet electrodes, with reduced discomfort compared to dry electrodes (Xu and Zhong, 2018). Quasi-dry electrodes also allow long-term EEG measurements due to the small amount of moisturizing solution that spreads and dries on the scalp less than typical wet electrode conductive gel (Mota et al., 2013). Quasi-dry electrodes do, however, often require additional pressure placed on the electrode to dispense the gel, which can result in non-uniform scalp pressure and discomfort.

Novel electrode configurations have also been introduced, including concentric ring electrode designs (He et al., 2001; Besio et al., 2006, 2014). By simultaneously recording from multiple closely-spaced recording sites on each electrode, signal-to-noise ratio and EEG spatial resolution can improve compared to conventional recording electrodes. Tripolar concentric ring electrodes have even outperformed bipolar and quasi-bipolar electrode designs by calculating the surface Laplacian or spatial second derivative using a multi-point differential among concentric rings on each electrode (He et al., 2001; Besio et al., 2006, 2014). Flexible electrodes provide another promising opportunity for configuring mobile EEG systems by relying on compliant, lightweight materials that can improve user comfort and enable longer duration recordings (Wang et al., 2012; Debener et al., 2015; Someya and Amagai, 2019; Acar et al., 2019; Shustak et al., 2019). Non-invasive flexible EEG electrodes, such as tattoos (Kim et al., 2011; Shustak et al., 2019; Ferrari et al., 2020) and conductive textiles (Löfhede et al., 2010, 2012), are capable of measuring electrocortical signals from the scalp, but are compromised by hair underlying the recording surface (Löfhede et al., 2012; Casson, 2019) and have therefore typically been placed on the forehead or around the ears (Kim et al., 2011; Debener et al., 2015; Acar et al., 2019; Shustak et al., 2019). These approaches have remained limited in locomotion studies or restricted to motor-related brain regions (Bunge, 2004), but fully portable and wireless EEG recording hardware with soft scalp electrodes that minimally penetrate the epidermis can provide a viable alternative (Mahmood et al., 2021). Widespread adoption of these innovative technologies remains dependent on signal recording quality, the ability to record electrical brain activity across the entire scalp surface, and user comfort. Mobile EEG recording innovations will continue to emerge and improve our abilities for measuring robust electrocortical activity during human locomotion.

EEG Signal Amplification

In addition to the skin-electrode interface, electrode configurations and system designs have been proposed to enhance EEG signal recording quality. One representative idea is to integrate miniature amplifiers on each electrode, in a so-called active electrode configuration. Because active electrodes amplify the EEG signal at the recording site, EEG signal quality can improve by minimizing noise induced by cable sway (Mathewson et al., 2017). The influence of signal pre-amplification on EEG data quality using active electrodes, however, likely depends on the overall system configuration and

relative placement of the system components (Scanlon et al., 2020). Active electrode designs can also enable skin-electrode impedance monitoring periodically throughout a data recording session to ensure low scalp-electrode impedance and high signal quality are preserved over time (Patki et al., 2012). Compared to standard passive EEG electrode configurations, each active electrode amplifier is electrically powered, often requiring additional wiring (Xu and Zhong, 2018).

MOBILE EEG DATA PROCESSING

Source Separation Methods for Artifact Removal

Measured at the scalp, EEG electrodes record electrical potentials from the brain that are a mixture of multiple source components (Hyvärinen and Oja, 2000). Blind source separation methods, specifically independent component analysis (ICA; Bell and Sejnowski, 1995; Makeig et al., 1997), can effectively decompose the channel-based electrode recordings into independent source components. Widely available through MATLAB-based open-source scripts in EEGLab (Delorme and Makeig, 2004), ICA is central to many mobile EEG studies for isolating electrocortical signals from the complex mixture of signal and noise measured from EEG channel recordings. Independent components that are isolated from the electrode channel recordings can then be categorized into brain components and other components such as noise or other physiological signals. Although numerous ICA-based algorithms exist for deriving source components from high-density EEG channel data, an adaptive mixture independent component analysis algorithm (AMICA; Palmer et al., 2012) that relies on an unsupervised learning approach has been reported to be most effective at reducing mutual information among ICA-derived source components (Delorme et al., 2012). This approach is also able to detect time-varying brain states through multiple modeling (Hsu et al., 2018), though sufficient data are needed from long-duration EEG recordings to effectively separate source signal components, which comes at a higher computational cost.

Distinguishing independent components that originate from the brain and non-brain sources is a critical step when studying human electrical brain dynamics during locomotion. In practice, identification criteria have included, but are not limited to, scalp topography, source dipole location, time series, and power spectrum. Subjective methods based on visual inspection and objective statistical criteria have each been used for selecting electrocortical source activity derived from ICA, but the effectiveness of these approaches is dependent on ICA decomposition quality and between-subject variability (Ullsperger and Debener, 2010). To increase consistency and efficiency for classifying brain and non-brain independent components, automatic classification data processing toolboxes available in EEGLab have been made available. Some of these toolboxes include ICLabel (Pion-Tonachini et al., 2019), MARA (Multiple Artifact Rejection Algorithm; Haresign et al., 2021), FASTER (Fully Automated Statistical Thresholding for EEG Artifact Rejection; Nolan et al., 2010), SASICA (Semi-Automated Selection of Independent Components of the electroencephalogram for Artifact correction; Chaumon et al., 2015), ADJUST (Automatic EEG artifact Detection based on the Joint Use of Spatial and Temporal features; Mognon et al., 2011), and IC_MARC (Frølich et al., 2015). Although these approaches can help to distinguish the brain and non-brain source components from ICA decomposition, visual inspection is still typically advisable.

Multivariate source separation techniques used in Brain-Computer Interface (BCI) applications, may also provide viable alternatives to ICA signal decomposition. Because BCI studies have fewer trials for real-time control, preprocessing is essential (Wolpaw and McFarland, 2004; Kübler et al., 2005; Blankertz et al., 2007), with data-driven supervised decomposition algorithms typically used as a spatial filter (Blankertz et al., 2007; Nikulin et al., 2011; Dähne et al., 2014; Haufe et al., 2014). Common Spatial Patterns (CSP; Müller-Gerking et al., 1999; Ramoser et al., 2000; Blankertz et al., 2007) generate spatial filters to improve BCI classification and can improve EEG signal quality by optimizing spatial filters based on predominant event-related desynchronization or synchronization (ERD: spectral power decrease and ERS: spectral power increase, respectively) within a certain frequency band compared between conditions (Blankertz et al., 2007). Source Power Comodulation (SPoC; Dähne et al., 2014) is designed to find spatial filters for extracting oscillatory signals from continuous variables, and when applied to scalp patterns from simulation data, improved ground truth source power estimation compared to ICA (Dähne et al., 2014). Spatio-spectral decomposition (SSD; Nikulin et al., 2011) has also been used to improve signal quality within specific frequency bands by estimating noise around the frequency range of interest. Because SSD assumes that noise spans a broad frequency range from a few Hz to tens of Hz, rather than white or 1/f noise (Nikulin et al., 2011), researchers should also consider noise traits specific to each dataset.

Electrocortical Source Localization

Estimating the source locations of electrical brain activity using independent components derived from scalp EEG recordings requires the solution of a so-called inverse problem. That is, determine the source signal locations required to produce the mixture of signals recorded at the scalp electrodes. It is essential for clinical and functional brain research applications to identify the brain structures involved in a task or behavior (Cuffin, 1998; Keil et al., 2014), but finding accurate spatial source locations is difficult due to the effects of volume conduction (Jung et al., 2001) as the electrical source activity propagates through cortical tissues, cerebrospinal fluid, resistive scalp layers, and the skull (Burle et al., 2015). To solve the EEG inverse problem, various techniques, such as non-parametric and parametric methods, were proposed (Grech et al., 2008). Modeled as an electrical dipole, non-parametric approaches assume that source components distributed in the whole brain maintain fixed orientations. Such methods include LORETA (Low resolution electrical tomography; Baillet, 1998), VARETA

(Variable resolution electromagnetic tomography; Valdes-Sosa et al., 2000; Bosch-Bayard et al., 2001), S-MAP (Spatial regularization; Baillet, 1998; Grech et al., 2008), ST-MAP (Spatio-temporal regularization; Baillet and Garnero, 1997; Grech et al., 2008), LAURA (Local autoregressive average; de Peralta Menendez et al., 2004), SSLOFO (Standardized shrinking LORETA-FOCUSS; Liu et al., 2005), and ALF (Adaptive standardized LORETA/FOCUSS; Schimpf et al., 2005). In contrast, parametric approaches consider dipole changes in time and try to search for the best dipole positions and orientations. These methods include FINES (First Principle Vectors; Xu et al., 2004), simulated annealing (Miga et al., 2002), and computational intelligence algorithms [e.g., Neural network (Robert et al., 2002) and Artificial neural network (Van Hoey et al., 2000)]. Source localization technologies exist to improve source location estimation by co-registering the precise location of EEG electrodes on the scalp with the subject-specific head anatomy. Imaging technologies, such as 3D scanning, ultrasound, optoelectronic, or camera-based computer vision methods, therefore, provide opportunities to improve electrical source localization accuracy (Koessler et al., 2010; Baysal and Sengül, 2010; Shirazi and Huang, 2019) when combined with forward head models that incorporate subject-specific MRI scans and conductivity estimates for anatomical head structures.

Temporal and Spectral Dynamics

The millisecond temporal resolution of EEG enables the study of precise electrocortical dynamics during rapid movements or in reactive real-world scenarios. Many EEG analysis methods have been used to record electrocortical responses elicited by external stimuli. By studying changes in electrical potentials from the brain that are tied to an event of interest, such as auditory, visual, somatosensory, or vestibular cues, event-related potential (ERP) studies have uncovered changes in electrical brain activity during cognitive and motor behaviors (Kappenman and Luck, 2010). Event-related potentials represent phase-locked neural responses that can be measured during experimental manipulations (Gutberlet et al., 2009; Nidal and Malik, 2014) by repeating an event of interest (Galambos, 1992) to study the latency, morphology, and scalp topography of positive and negative voltage peaks and deflections. These analyses can be extended to study electrocortical changes in both time and frequency. During EEG analyses, the spectral power is used to study the distribution of signal power among frequencies (Sanei and Chambers, 2013) that are grouped into frequency bands based on functional roles and characteristics in the brain, including delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (15–30 Hz), and gamma bands (>30 Hz). Lower frequency bands indicate a subconscious state, while higher frequency reflects a more active and aroused state (Jensen et al., 2016). In order to track the temporal changes of the frequency spectrum, time-frequency EEG analyses were proposed. Event-related spectral perturbation (ERSP) analyses can show stimulus-induced, non-phase-locked brain activity over time (Tallon-Baudry et al., 1996; Rossi et al., 2014) and can provide insight into specific frequency bands that relate to functional brain processes (Rossi et al., 2014).

Functional Connectivity Metrics

Beyond quantifying spatial, temporal, and spectral dynamics of electrical brain activity, the use of mobile EEG for studying the neural control of human locomotion can improve our understanding of functional interactions between brain structures and between brain and muscle during locomotor control. When significant temporal or spatial correlations are observed between neurophysiological processes, this phenomenon is often referred to as functional connectivity (Fingelkurts et al., 2005; Sakkalis, 2011). Coherence or correlation strength is considered directly proportional to the degree of functional connectivity between neuroanatomical structures when comparing electrophysiological signals (Thatcher et al., 1986; Im, 2018). To quantify signal interdependence without consideration for directional causation (Bullock et al., 1995; Kaplan et al., 1997), non-directed functional connectivity metrics such as correlation, coherence, mutual information, phase locking value, and pairwise phase consistency have been used (Bastos and Schoffelen, 2016). To quantify directed functional connectivity with consideration for causation, metrics such as cross-correlation, phase slope index, Granger causality, and transfer entropy, have been applied (Granger, 1969; Bastos and Schoffelen, 2016). These metrics can also be categorized based on considerations for signal amplitude or phase. Signal amplitude comparisons are conducted using correlation, mutual information, cross-correlation, Granger's causality, partial directed coherence, transfer entropy, and dynamic causal modeling metrics (Im, 2018). Phase domain analyses include coherence, phase locking, pairwise phase consistency, and phase slope index (Im, 2018). Phase comparisons can also be assessed using Granger causality methods that include both parametric and non-parametric approaches (Geweke, 1982). Non-parametric Granger causality is calculated using autoregression and does not require model order to be determined (Bastos and Schoffelen, 2016). Parametric Granger causality is based on Fourier or wavelet-based methods, which require less data than non-parametric equivalents (Bastos and Schoffelen, 2016). For single-trial data and when model order is known, parametric Granger causality methods have shown greater sensitivity for quantifying neural functional connectivity compared to non-parametric Granger causality methods (Richter et al., 2015; Bastos and Schoffelen, 2016).

MOBILE EEG DATA PROCESSING CHALLENGES AND SOLUTIONS

Physiological Artifacts and Solutions

Electrophysiological signals not limited to electrical brain activity are detectable from scalp EEG measurements. The heart rhythm, eye movements, and electrical muscle activity can influence each obscure electrocortical source activity and may also present contrasting signal characteristics that require specific noise removal strategies beyond independent component analysis. Cardiac activity is detectable from EEG measurements when the electrode is placed on or

near a blood vessel (Goncharova et al., 2003). The repetitive low-frequency (∼1.2 Hz) signal characteristics of the heart rhythm are distinguishable from cerebral activity, and removal can be assisted by relying on a reference waveform or an electrocardiogram (ECG; Jiang et al., 2019).

Ocular artifacts caused by eye blinks and saccades present large amplitude and low-frequency voltage fluctuations compared to EEG signals. Because of the different signal characteristics between brain activity and eye movements, electrooculographic (EOG) recordings from electrodes placed on the skin around the eye can help to parse EOG from EEG signals using ICA or regression methods (Jung et al., 1998; Li et al., 2006; Schlögl et al., 2007; Winkler et al., 2015). Alternative statistical decomposition methods that can be implemented in a sliding window to remove transient large amplitude artifacts have proven to be particularly effective. Artifact subspace reconstruction (ASR; Kothe and Jung, 2016) is a component-based artifact removal method that can be used to clean large-variance signal components based on thresholds compared to clean baseline data and subsequent reconstruction of EEG channel data. By pre-conditioning EEG channel data and removing eye movement and muscle artifacts ahead of ICA, it is possible to improve ICA decomposition quality (Chang et al., 2019).

Myoelectric artifacts can appear in EEG signals due to muscular contractions from the scalp, face, and neck. Electromyographic (EMG) recordings can present broad spectral distributions, including low and high frequencies (>200 Hz; Shackman et al., 2009; Urigüen and Garcia-Zapirain, 2015) but are usually more localized in higher frequency bands above 14 Hz (Narasimhan and Dutt, 1996). Conventional low pass filtering approaches can remove high-frequency signal content but may also eliminate electrocortical signals in beta (13–30 Hz) or gamma bands (>30 Hz) depending on the selected filter cutoff. To minimize the risk of undesirable signal loss, canonical correlation analysis (CCA) has been used to remove muscle artifacts from EEG data (De Clercq et al., 2006; Raghavendra and Dutt, 2011; Jiang et al., 2019). CCA measures the linear relationship between two datasets to derive signal components based on correlation or autocorrelation when derived from a single dataset, such as EEG channel recordings. Due to the high-frequency spectral characteristics of electrical muscle activity, canonical components with low autocorrelation tend to show high-frequency spectral content indicative of electrical muscle activity. Component removal or filtering can therefore help to eliminate myoelectric EEG signal contamination.

Electromechanical Artifacts and Solutions

In addition to the mixture of electrophysiological signals captured by EEG recording electrodes, external noise sources can contaminate mobile EEG data. External artifacts can include alternating current power line noise, electromagnetic interference from electronic devices in the surrounding environment, and movement-related artifacts introduced by the movement of mobile EEG system components, such as cables and electrodes. Alternating current power line noise predominantly occurs at either 50 Hz or 60 Hz, depending on the country, and can largely be eliminated using a notch filter at the respective frequency band (Leske and Dalal, 2019). However, notch filtering can eliminate electrocortical target signals in gamma band (>30 Hz) depending on notch filter width. Alternative methods for power line noise removal have been implemented, such as Discrete Fourier Transform (DFT) filter (Oostenveld et al., 2011), frequency-domain regression (Bigdely-Shamlo et al., 2015), and spectrum interpolation (Leske and Dalal, 2019).

Inherent to the study of neural control of locomotion using mobile EEG, gait-related movement artifacts have posed non-trivial challenges to researchers. Small electrode motions on the scalp, cable sway (Symeonidou et al., 2018), and system component vibrations introduce signal contamination during each step of the gait cycle, causing voltage fluctuations in the EEG signal that exceed electrical brain activity. Signal fluctuations occur at the step frequency but can also extend into higher frequency bands at harmonics of the step cycle, with a non-uniform influence of noise among recording electrodes across the scalp (Kline et al., 2015; Snyder et al., 2015). Cable bundling and more effectively securing electrodes and system components to the participant can minimize motion artifact causes (Nathan and Contreras-Vidal, 2016), but it remains difficult to completely eliminate motion-induced noise through ICA decomposition methods alone. High pass filtering mobile EEG data provides a partial solution (Winkler et al., 2015), with a 1–2 Hz high pass filter improving subsequent ICA decomposition results, but a number of alternative signal processing solutions have been implemented in mobile EEG studies. Adaptive filtering (Kilicarslan et al., 2016), template regression (Gwin et al., 2010), and component-based statistical decomposition methods, including artifact subspace reconstruction (Chang et al., 2018, 2019), have been used to eliminate motion artifacts from mobile EEG data at relatively slow gait speeds ($<$1.0 m/s; Gwin et al., 2010; Wagner et al., 2012, 2016; Bradford et al., 2016, 2019; Oliveira et al., 2017a,b; Bradford et al., 2019), but gait speeds closer to, and in excess of, preferred human walking speed (1.4 m/s; Bohannon, 1997) have remained challenging and have required novel solutions.

Automatic Preprocessing Toolboxes

Many EEG preprocessing procedures have been developed and incorporated into EEGLab toolboxes to provide standardized data analysis pipelines for improving rigor and reproducibility among mobile EEG studies (Bigdely-Shamlo et al., 2015; Gabard-Durnam et al., 2018; Pedroni et al., 2019). The PREP pipeline (Bigdely-Shamlo et al., 2015), AUTOMAGIC (Pedroni et al., 2019), and HAPPE (Harvard Automated Processing Pipeline for EEG) have each introduced functions for analyzing EEG data. These toolboxes include methods for identifying and removing unusually noisy channel data (findNoisyChannels; Bigdely-Shamlo et al., 2015; Pedroni et al., 2019), a multi-stage robust referencing scheme that eliminates noise from recorded EEG signals prior to computing a common average reference (Bigdely-Shamlo et al., 2015), alternating current powerline noise removal (cleanLineNoise and ZapLine; de Cheveigné, 2020), and artifact corrections for eye movements (Pedroni et al.,

2019). Automatic open-source data processing toolboxes can improve consistency among mobile EEG analyses, but it remains important to ensure that mobile EEG hardware is configured to eliminate as many possible signal contaminating noise sources ahead of EEG data recording.

Hardware-Assisted Solutions for Mobile EEG Motion Artifact Reduction

A common approach for mobile EEG artifact removal is to rely on simultaneously recorded reference signals from sources known to exist in the complex mixture of signals captured in EEG recordings (e.g., EOG, EMG, or ECG). Similar approaches using isolated motion and/or electrical noise recordings have been developed and applied. Using information about the participant's head motions during gait is one possible solution for quantifying the causes of motion artifacts in mobile EEG. Optoelectronic motion capture, accelerometry, or inertial measurement units can be used for this purpose (Casson, 2019). Adopted from solutions to overcome significant signal contamination introduced by gradient artifacts during simultaneous MRI and EEG (Chowdhury et al., 2014), isolated noise recordings have recently been used to eliminate motion artifacts from mobile EEG during human locomotion using dual-layer EEG (Nordin et al., 2018). In this configuration, one layer of EEG electrodes measured a mixture of physiological signals and motion artifacts from the scalp, but the second layer of electrodes measured only electrical noise and motion artifacts from mechanically coupled but electrically isolated secondary electrodes. Noise-only electrodes were referenced to an overlaid conductive fabric cap that served as an artificial skin circuit but also more effectively secured the recording electrodes to the participant's head. By conducting benchmark tests using a robotically controlled motion platform that reproduced human head motions during walking and an electronic head phantom device that generated ground truth artificial brain signals (Nordin et al., 2018; Richer et al., 2020), the ability of dual-layer mobile EEG for motion artifact removal was validated. These methods were subsequently applied during human treadmill locomotion at a range of gait speeds (Nordin et al., 2019a,b), including while navigating over unexpected obstacles on a treadmill belt (Nordin et al., 2019c).

MOBILE EEG FOR STUDYING THE NEURAL CONTROL OF LOCOMOTION

Recent mobile EEG studies have expanded our understanding of human supraspinal locomotor control, revealing electrocortical spectral power fluctuations tied to each step in the gait cycle (Wagner et al., 2012, 2016; Bradford et al., 2016, 2019; Luu et al., 2017a; Nordin et al., 2019a,c). Broadly distributed electrocortical network dynamics further show activations from the frontal cortex (Sipp et al., 2013; Bulea et al., 2015; Wagner et al., 2016), anterior cingulate cortex (Bulea et al., 2015; Bradford et al., 2016; Wagner et al., 2016; Luu et al., 2017a; Yokoyama et al., 2020), sensorimotor cortex (Wagner et al., 2012; Sipp et al., 2013; Bradford et al., 2016; Luu et al., 2017a; Nordin et al., 2019a; Yokoyama et al., 2020), auditory cortex (Wagner et al., 2016; Nordin et al., 2019a,b), supplementary motor area (Nordin et al., 2019c), premotor cortex (Nordin et al., 2019c), motor cortex (Wagner et al., 2012; Bulea et al., 2015), somatosensory cortex (Yokoyama et al., 2020), and the parietal cortex (Bulea et al., 2015; Bradford et al., 2016; Wagner et al., 2016; Luu et al., 2017a) during locomotor tasks ranging from steady treadmill gait to navigating over complex terrain or walking with robotic assistance. Knowledge gained from these studies provides the basis for understanding human electrocortical dynamics during balance and gait control that can be used for the development of assistive devices and neuroprostheses for rehabilitation, and to restore locomotor function for individuals with neurological disorders and disease.

Locomotor Control

A growing body of evidence shows dynamic cortical activations during the initiation, maintenance, and modification of human gait (Choi and Bastian, 2007; Grillner et al., 2008; Wagner et al., 2012; Castermans et al., 2014; Bradford et al., 2016; Nordin et al., 2019c). During each step of the gait cycle, sensorimotor electrocortical spectral power modulations occur in alpha (8–12 Hz) and beta bands (13–30 Hz). Multiple studies have shown alpha and beta band spectral power increases during double support and decreases during limb swing of continuous gait (Gwin et al., 2010; Wagner et al., 2012; Bulea et al., 2015; Bradford et al., 2016, 2019; Oliveira et al., 2017b; Nordin et al., 2018, 2019a,b). Detectable changes in electrocortical spectral power have also been identified between uphill, downhill, and level treadmill gait (Bradford et al., 2016), walking with eyes closed compared to eyes open (Oliveira et al., 2017b), during transitions in gait speed (Wagner et al., 2016), and when navigating over complex terrain (Luu et al., 2017a). Compared to level and downhill walking (Bradford et al., 2016), during incline walking spectral power from the anterior cingulate cortex, sensorimotor cortex, and the posterior parietal cortex increased in theta band (4–7 Hz) and decreased in gamma band (>30 Hz). Walking with restricted vision induced desynchronization from theta to beta bands during the transition to single support for the somatosensory cortex (Oliveira et al., 2017b), suggesting that restricted vision increases sensory processing and integration compared to visually guided walking. Although changes in gait speed can be largely controlled subcortically, alpha and beta band sensorimotor electrocortical spectral power were shown to decrease at faster gait speeds (2.0 m/s) compared to slower walking (0.5 m/s; Luu et al., 2017a). While navigating complex overground terrain that included level ground, ramps, and stairs, participants showed reduced alpha and beta band spectral power from sensorimotor cortex during ramp and stair ascent compared to level-ground walking (Luu et al., 2017a). Beta and gamma-band spectral power also increased from the sensorimotor cortex during initial limb swing while ascending stairs. Collectively, these findings uncover a distributed network of cortical activity involved in movement control and sensory processing during gait, leaving considerable work to uncover dynamic interactions among brain structures and how these locomotor network dynamics differ among populations.

Balance Control and Perturbation Responses

During bipedal gait, dynamic balance maintains upright posture by supporting body weight. The ability to maintain and recover from the loss of balance is critical to healthy gait function. The unexpected loss of balance due to external perturbations has been associated with electrocortical activations from primary sensory and motor cortices, supplementary motor area, premotor cortex, anterior cingulate cortex, prefrontal cortex, temporal cortex, parietal cortex, and visual cortex (Massion et al., 1999; Slobounov et al., 2009; Sipp et al., 2013; Marlin et al., 2014; Varghese et al., 2019). Loss of balance while walking on a balance beam has also shown greater theta band power and reduced beta power from the sensorimotor cortex compared to steady treadmill walking (Sipp et al., 2013). Divergent electrical brain dynamics also emerge during a loss of balance due to physical or visual perturbations (Peterson and Ferris, 2018). While walking on a balance beam, participants who experienced a physical pull at the waist, compared to a visual rotation of the environment using a virtual reality headset, showed increased spectral power from the sensorimotor cortex in the theta band and decreased beta power after perturbation onset (Peterson and Ferris, 2018). Compared to the loss of balance due to a physical pull at the waist, however, visual perturbations elicited more prominent responses from the parieto-occipital areas. During recovery from loss of balance during unexpected slips, compared to steady walking, spectral power from sensorimotor cortex similarly increased in the theta band and decreased in the alpha band, while alpha and beta band spectral power decreased from the parietal cortex (An et al., 2019). In response to unexpected obstacles that appeared on a treadmill belt during walking and running, event-related spectral power fluctuations from time-frequency analysis further identified spectral power increases from the premotor cortex, supplementary motor area, and the parietal cortex in the delta, theta, and alpha bands. The timing of electrocortical activation onset varied with locomotion speed, initiating two steps before stepping over the obstacle to enable foot placement planning around the obstacle (Nordin et al., 2019c). The ability to detect perturbation onset in advance of motor responses could provide bio signals for developing brain-machine interface technologies to properly assist in counteracting the loss of balance due to perturbations or changes in the environment during standing balance and gait.

Mobile EEG for the Development of Neurotechnologies

Robotic-assistive devices are widely used for rehabilitation purposes to provide bodyweight support or to guide locomotor limb movements. To better understand the influence of robotic assistance on human locomotor control, researchers have studied changes in electrocortical spectral dynamics using mobile EEG. By comparing electrical brain activity during active treadmill gait to walking with assistive forces applied to the limbs or passive limb motions with bodyweight support, changes in sensorimotor processing have been uncovered. During robotically-assisted gait that provides bodyweight support and limb guidance, spectral power from premotor cortex and sensorimotor areas increased in alpha, beta, and gamma bands, compared to active treadmill walking (Wagner et al., 2012; Knaepen et al., 2014; Seeber et al., 2014). Recent mobile EEG studies that used a unilateral lower-limb exoskeleton to generate assistive joint torque outside the laboratory also showed hemispherical effects on parietooccipital regions in beta band compared to walking without robotic assistance (Li et al., 2018). As assistive robotic technologies for rehabilitation continue to develop, it becomes more important to better understand healthy human brain dynamics during locomotion. This knowledge not only informs how changes in electrocortical activity influence movement control, but also provides possible biomarkers for measuring adaptation to assistive devices or tracking rehabilitative progress and provides the mechanism for identifying electrocortical control signals that can be used for brain-machine interface technologies.

Brain-machine interfaces have shown increasingly promising applications for controlling output devices using direct communication with the human brain (Millán et al., 2004; Lebedev and Nicolelis, 2017; Tariq et al., 2018). Non-invasive EEG-based brain-machine interface systems can provide effective closed-loop strategies for deciphering user intentions while controlling physical or virtual machines, including multi-directional brain-actuated wheelchairs (Vanacker et al., 2007; Galán et al., 2008) or lower-limb exoskeletons (Noda et al., 2012; Contreras-Vidal and Grossman, 2013; Sczesny-Kaiser et al., 2015). Recent brain-computer interface demonstrations have allowed users to control a walking avatar in virtual reality using scalp EEG signals. In this application, alpha band spectral power from the posterior parietal cortex and inferior parietal lobe decreased along with increased gamma band spectral power from the anterior cingulate cortex, which has been attributed to error monitoring during walking (Luu et al., 2016, 2017b). Continued innovations using non-invasive EEG-based brain-machine interfaces can therefore advance current capabilities and lead to more intuitive assistive devices for rehabilitation, injury prevention, or human performance enhancement using the user's own neurophysiological control signals.

DISCUSSION

In this review, we discussed mobile EEG technologies, including advancements in hardware and signal processing technologies for mobile applications. We identified different hardware strategies for improving signal recording quality and contemporary analytical methods for effectively extracting electrocortical source signals that can be localized to specific cortical structures with progressively better spatial resolution. We also identified the benefits of these fast timescale recordings for studying changes in voltages and spectral power that can be used to better understand how electrical brain activity changes during dynamic behaviors. Current state-of-the-art mobile EEG methods have led to considerable discoveries in the neural control of human locomotion, and through continued mobile hardware and signal processing innovations, new discoveries will

continue to emerge that will enable studies in more realistic tasks and environments. Recent locomotion studies have revealed complex electrocortical dynamics that can be measured in time, space, and frequency. Effectively extracting and decoding these electrical brain signals will enable the development of robust, non-invasive brain-computer interface technologies for use in restoring, maintaining, and improving human gait.

Future improvements in mobile EEG technologies that enhance system usability will lead to more widespread adoption of these methods, including the use of compact, lightweight, and wireless system designs that can be entirely worn on the head and require reduced preparation time, but are also comfortable for the user to wear and remove to enable robust long-term recordings (Hairston et al., 2014; Izdebski et al., 2016; Oliveira et al., 2016; Bateson et al., 2017; Athavale and Krishnan, 2017). Analytical methods that cssan be realistically implemented in real-time for closed-loop applications will also enable the development of next-generation neurotechnologies. In addition to advancements in mobile EEG recording and analysis methods, unified approaches for simultaneously recording biosignals, such as eye gaze, electromyography, and biomechanical measures for quantifying whole-body human movement outside of conventional laboratory environments, will continue to expand the study of neural control of human locomotion into real-world scenarios.

AUTHOR CONTRIBUTIONS

SS and AN drafted and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Can Motor Arrests in Other Effectors Be Used as Valid Markers of Freezing of Gait?

*Nicholas D'Cruz and Alice Nieuwboer**

KU Leuven, Department of Rehabilitation Sciences, Neurorehabilitation Research Group, Leuven, Belgium

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BACKGROUND

People with Parkinson's disease (PD) have an increased risk of falling, which is often associated with the manifestation of freezing of gait (FOG) (Pelicioni et al., 2019). Not surprisingly, turning and gait initiation are frequent triggers of FOG as these complex maneuvers require precise control of the center of mass as well as adaptation of the locomotion pattern (Bekkers et al., 2018). Key to the motor deficits of PD is the loss of motor automaticity, defined as the ability to perform movements without attention directed toward the details of movement (Wu et al., 2015). As such, fine-tuning of gait control becomes especially compromised in daily life when locomotion is less regulated by conscious processing in PD. FOG is more imminent when people with PD are multi-tasking and coping with doorways and obstacles (Beck et al., 2015; Mancini et al., 2018). Equally, FOG is more likely when under stress of FOG-anticipation at "freezing hotspots" or when experiencing fear of falling (Economou et al., 2021). While recognizing that there may be common-end mechanisms between FOG, dynamic balance disturbances, attention and anxiety, in this view point we want to focus on the relevance of studying freezing of repetitive movements of the extremities as a handle on understanding FOG.

The main bottleneck to better understand when and why FOG emerges and how to manage it is the lack of valid markers of FOG, justifying the search for models of freezing in other effectors than in gait. Several instrumented methods for measuring FOG episodes in daily life as well as during standardized lab tests are currently in the validation pipeline (Mancini et al., 2021; Pardoel et al., 2021). However, as yet, they have not demonstrated robust construct and predictive validity, particularly for short and more subtle episodes that are likely to occur in early disease and when ON-medication (Mancini et al., 2019). Digitized outcome measures of FOG vary from fairly simple detection algorithms, as derived from wearable sensor signals, to artificial intelligence-based methodologies (Pardoel et al., 2021). Most of these algorithms are apt in capturing the high frequency movement phenomena associated with FOG, including leg trembling or small shuffling steps (Mancini et al., 2021; Pardoel et al., 2021). Yet, "akinetic FOG," displaying no discernable movement during the episode is more difficult to distinguish from voluntary stops (Cockx et al., 2021). Also, the variable and often interrupted gait bouts observed in daily life provide a noisy background from which to pick up FOG-signals, creating high rates of false positives (Mazilu et al., 2015). The heterogeneous clinical manifestation of FOG by itself also complicates validation work as it affects the robustness of the gold standard measure of FOG. At present, the percentage time frozen (%timeFR) determined during expert video annotation of standardized gait tests constitutes

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Monika Pötter-Nerger, University of Hamburg, Germany

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Daniel Boari Coelho, Federal University of ABC, Brazil

***Correspondence:**
Alice Nieuwboer
alice.nieuwboer@kuleuven.be

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the best reference test, most notably when performing turning tasks (Morris et al., 2012). However, turning is also a hazardous test when no supervision is available to prevent falling, especially in a home setting. As such, markers of freezing which are safe, reliable, responsive and predictive of FOG along the disease progression axis are much needed.

STATE OF THE ART ON FREEZING IN OTHER EFFECTORS

Our group was one of the first to acknowledge the remarkable similarity between features of FOG and motor arrests when performing sequential finger and writing movements uni- and bimanually (Nieuwboer et al., 2009; Vercruysse et al., 2012). While freezing was worse in bimanual sequences, it also occurred in uni-manual ones, suggesting that bilateral co-ordination was a contributing but not a deciding factor for triggering a freezing response (Vercruysse et al., 2012). Both types of freezing were typically preceded by the so-called "sequence effect," defined as the rapid diminishment of amplitude and/or speed with each repetition (Tinaz et al., 2016). Interestingly, we found that motor arrests arising from the sequence effect were triggered by bringing the motor system in overdrive at two dimensions, i.e., by reducing the scale as well as by increasing the rhythm of movement cycles (Nieuwboer et al., 2009; Vercruysse et al., 2012). The pathophysiology of the sequence effect can be understood as a failure of central motor energy, which is partly responsive to levodopa (Tinaz et al., 2016). Indeed, magnetic resonance imaging (MRI) showed that levodopa restored the function of the motor circuit associated with better writing sizes, as performed in the scanner, but did not alter "progressive micrographia" (Wu et al., 2016). Interestingly, we also found "sequence effect-like" abnormalities during accelerated weight-shifting sequences without stepping in a standing-in-place task (Dijkstra et al., 2021). Here, the axial amplitudes of weight-shifts were reduced and showed earlier breakdown in freezers compared to non-freezers and this more so in OFF compared to ON medication (Dijkstra et al., 2021). Returning to non-gait freezing, not only impaired regulation of motor vigor, but also increased energy in the high frequency bands appeared to be involved in sequence breakdown, resembling the oscillatory features of FOG (Vercruysse et al., 2012). These dysrhythmic abnormalities were interpreted to indicate faulty initiation-termination responses (Stegemöller et al., 2017), or arising from a pathological frequency content of the antagonistic muscles, albeit distinct from resting or action tremor frequencies (Scholten et al., 2016).

As upper limb freezing was brought on when people with PD were subjected to similar motor challenges as in FOG, we recently investigated whether producing up-and-down strokes on a writing tablet within a funnel figure, with wide, narrow and transitioning pieces, elicited motor arrests similar to presenting a doorway to trigger FOG in a gait lab or in the home (Heremans et al., 2019). We found that motor arrests were most prominent in the narrow and decreasing parts of the funnel, despite the fact that this motor adaptation task provided target lines, expected to energize and provide feedback on the scale movement. Similar to earlier findings, the frequency and duration of the motor arrests more than doubled when motor load was increased by imposing fast speed conditions and this while subjects were "ON" medication.

CONSTRUCT VALIDITY OF FREEZING IN OTHER EFFECTORS

As for construct validity of non-gait freezing, a review on freezing episodes in a variety of tasks, i.e., handwriting, hand and foot tapping and speech revealed that the clinical manifestation of these events appeared to be overlapping (Vercruysse et al., 2014a). However, a profound definition of what exactly constitutes a non-gait freezing event is still lacking, especially with regards to including hastening epochs and the transition phase between normal movement and freezing. So far, pragmatic definitions were employed largely based on visual criteria for rating FOG (Vercruysse et al., 2012; Heremans et al., 2019). Also, in 20 out of the 23 studies of the above-mentioned review in which the relationship between freezing in other effectors and FOG was explored, non-gait freezing was more prevalent in patients with FOG or correlated with higher FOG-severity. However, none of these studies applied formal classification statistics to discern whether non-gait freezing can accurately distinguish between groups with and without FOG.

As for "fast funnel freezing," freezing events occurred in 23 out of 49 patients and its frequency was correlated to self-reported FOG severity, though this correlation was not found for %timeFR during the funnel task (Heremans et al., 2019). As well, a substantial number of people without FOG had motor arrests in the funnels. The opposite pattern was also reported, namely that out of 16 people with FOG only 9 displayed upper limb freezing (Scholten et al., 2016). All this could suggest three things. First, upper limb freezing is less indicative of FOG than suggested previously, questioning its value as a proxy marker. Second, the most optimal method to elicit freezing in other effectors (high speed conditions) was not always employed, which may have precluded the events from occurring. Third, it could be that people without FOG but with freezing in other body parts have a higher likelihood to convert to FOG showing the potential for repetitive movement paradigms to serve as predictive markers for FOG.

PREDICTIVE VALIDITY OF FREEZING IN OTHER EFFECTORS

Prospective study conducted by Delval et al. demonstrated, that episodic events during foot-tapping, hand-tapping, and syllable repetition in early-stage PD patients without FOG were predictive of FOG emerging in the next two years, albeit in a small cohort of 30 subjects (Delval et al., 2016). Notably, the speed of the alternating tapping and speech, tasks that were objectively measured, were imposed by a metronome with increasing rhythms eliciting freezing as well as hastening events.

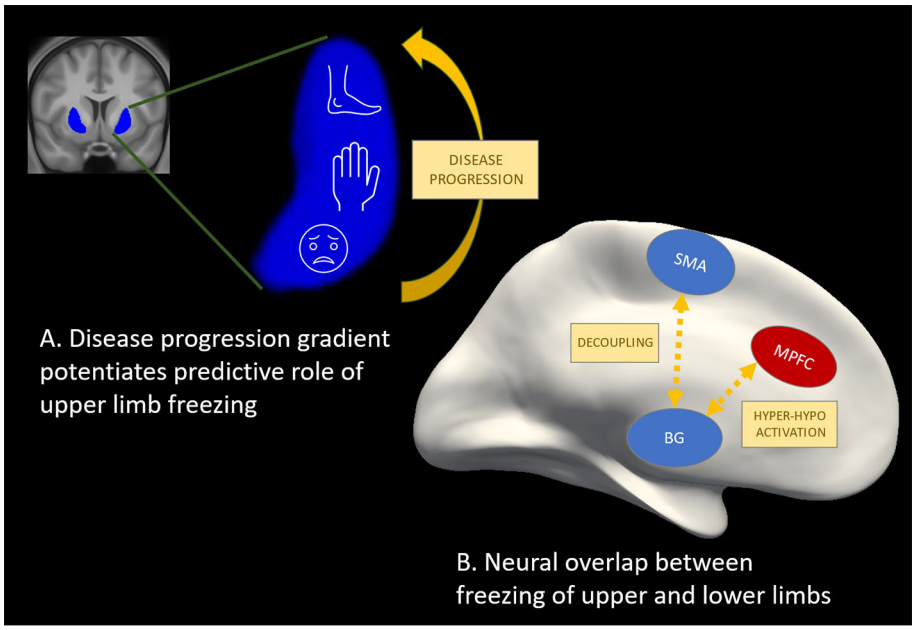

FIGURE 1 | Potential for other effectors as valid markers of freezing of gait. **(A)** The motor representation in the putamen (Nambu, 2011) (in blue) aligns with the gradient of dopaminergic loss in the putamen (Kish et al., 1988) (from caudal to rostral) such that the face and upper limbs are affecter earlier, potentiating predictive utility of upper limb freezing. **(B)** Hyper-activation (in red) and hypo-activation (in blue) in cortical and sub-cortical regions as well as desynchronization or decoupling between these regions has been shown during freezing episodes in finger tapping (Vercruysse et al., 2014b; Brugger et al., 2020), foot pedaling (Shine et al., 2013a,b; Matar et al., 2019), and during real gait (Pozzi et al., 2019) studies. These findings point to a common neural mechanism underlying freezing in gait and non-gait effectors, which is promising for future work aiming to further explore freezing mechanisms as well as therapeutic effects on the freezing circuitry.

Recently, we also conducted a prospective study on 60 patients without FOG to assess the predictive value of several motor and non-motor outcomes as markers of FOG conversion (D'Cruz et al., 2020). Over a follow-up of two years, 20% of patients converted. Next, we investigated the contributions of amplitude, rhythm, coordination and the freezing ratio exhibited during repetitive motor tests in the extremities as well as during gait and turning. Unlike in Delval et al., movement tests were largely self-generated and mostly delivered at a comfortable pace. After applying robust techniques to reduce the number of variables, two main components in a multivariable model were found to predict FOG conversion within the next year with an area under the curve of 0.79. The two main components were: (1) worse disease severity (on a number of specific items including upper limb tasks) and (2) worse finger tapping movements (smaller amplitude, inconsistent timing and poor coordination). While these results suggested that altered movement generation during repetitive movements is central to FOG, it is possible that disease progression was also inadvertently captured by the deterioration of the quality of repetitive movements. Recently, it was shown that a digitized alternating finger tapping task was the most sensitive and specific motor test for detecting conversion to PD prospectively in a prodromal cohort with idiopathic REM sleep disorder (Fereshtehnejad et al., 2019). Furthermore, **Figure 1A** illustrates that the motor representation in the putamen aligns with the gradient of dopaminergic loss in the putamen (from caudal to rostral) such that the face and upper limbs are affecter earlier (Kish et al., 1988; Nambu, 2011), potentiating the role of the degradation of upper limb motion for predicting the onset of FOG.

NEURAL CORRELATES OF FOG AND FREEZING IN DIFFERENT EFFECTORS

Mobile neuroimaging techniques as well as local field potential recordings are increasingly applied to better understand the brain circuit dysfunctions underlying actual FOG episodes obtained during over-ground walking (Tard et al., 2015; Pozzi et al., 2019). While such methods are developed further, a number of studies have used motor arrests provoked during repetitive foot or finger motion to study the neural mechanisms related to freezing events with non-mobile electroencephalography set-ups (EEG) or in a MRI scanner. Functional MRI and EEG mainly highlight cortical activations and their outcomes are highly task-specific, limiting the interpretation of these findings to a heterogeneous phenomenon such as freezing. Taking these drawbacks in consideration, the most influential model of FOG (Lewis and Shine, 2016) stems from a "foot pedaling" fMRI-paradigm executed while lying in a scanner and while "moving forward" through a virtual reality (VR) corridor. When confronted with conditions of high cognitive load in the VR, episodes of increased pedaling latency were found to be associated with decreased activation in sensorimotor cortical and several basal ganglia

regions (Shine et al., 2013a). In contrast, frontoparietal activation was higher compared to successful pedaling, suggesting that cortico-subcortical decoupling underlies freezing events. A strikingly similar cortical-basal ganglia mismatch of hyper and hypo-activity, respectively, during motor blocks of repetitive finger movements was also found (Vercruysse et al., 2014b), suggesting some overlap between the foot and finger studies (Vercruysse et al., 2014a) as displayed schematically in **Figure 1B**. However, differences were apparent too with respect to the involvement of the superior structures of the brainstem known to control gait and posture, which only came out of the pedaling study. When showing narrow and not wide doorways during the foot pedaling task, freezing events were accompanied with hypo-activity in pre-Supplementary Motor Area (pSMA) and reduced connectivity between the pSMA and the Subthalamic Nucleus, suggesting involvement of the hyperdirect pathway (Matar et al., 2019). As well, the cortico-subcortical decoupling was already noticeable in the run-up to freezing episodes of the feet (Matar et al., 2019), similar to FOG (Pozzi et al., 2019). All this work has substantially influenced current thinking on FOG as a phenomenon which can be brought on by various failures in different task-related networks, converging toward a common neural pathway dysfunction (Lewis and Shine, 2016).

As for seated EEG, one recent study demonstrated that movement initiation of a finger sequencing task displayed reduced beta-desynchronization in the SMA and this more so in freezers compared to non-freezers (Brugger et al., 2020). Interestingly, the SMA was found to be a central hub in the locomotor fine-tuning network in young healthy people while experiencing gait perturbations as highlighted by PET-imaging of the brain's glucose metabolism (Hinton et al., 2019). In line, the SMA proved to be less involved when people with FOG were undergoing a FOG-provoking gait-protocol compared to those without FOG, assessed with PET (Tard et al., 2015). A second EEG study showed that an increase of left prefrontal beta band synchronization was predictive of upper limb freezing, pointing to the relevance of prefrontal executive dysfunction in analogy to FOG (Scholten et al., 2020). Taken together, it seems that non-gait freezing paradigms are able to capture components of the supraspinal locomotor networks and how it is disrupted during freezing.

CONCLUSION AND FUTURE DIRECTION

We have highlighted that studying freezing in other effectors has great potential as a model for investigating component-mechanisms of FOG. However, we also showed that further validation of non-gait freezing as a behavioral biomarker of FOG is indicated. Therefore, prospective cohort studies are needed including recently diagnosed patients with PD, as well as positive control groups with FOG to be able to track progression of both gait and non-gait freezing-severity. As for measuring repetitive finger movements, keyboards as well as tablets and smartphones technology could be used to quantify motor blocks (Trager et al., 2020) and foot tapping assessments can be quantified by wearable sensors at the feet and ankles (Rovini et al., 2017). These research paradigms are relatively easy to apply in a home setting in a sitting position with remotely controlled reminders or as part of telemedicine platforms. In a lab environment, these tests can safely be combined with sensitive tests of FOG, such as performing 360° turns. As highlighted in this view point, stringent conditions to bring subjects to the limits of their performance need to be employed so that longitudinal change in symptom progression can be captured and more importantly so that freezing events actually come to the fore. To move the field forward, we further recommend to clarify and refine the clinical definition of non-gait freezing events, in analogy to FOG, to serve as the gold standard criterion for future automatic detection.

AUTHOR CONTRIBUTIONS

ND drafting manuscript. AN conceptualizing and revising manuscript. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Comparison of Shod and Unshod Gait in Patients With Parkinson's Disease With Subthalamic and Nigral Stimulation

*Martin A. Horn[1], Alessandro Gulberti[1,2], Ute Hidding[1], Christian Gerloff[1], Wolfgang Hamel[3], Christian K. E. Moll[2] and Monika Pötter-Nerger[1]**

[1] Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2] Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3] Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

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***Correspondence:**
Monika Pötter-Nerger
m.poetter-nerger@uke.de

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Background: The Parkinsonian [i.e., Parkinson's disease (PD)] gait disorder represents a therapeutical challenge with residual symptoms despite the use of deep brain stimulation of the subthalamic nucleus (STN DBS) and medical and rehabilitative strategies. The aim of this study was to assess the effect of different DBS modes as combined stimulation of the STN and substantia nigra (STN+SN DBS) and environmental rehabilitative factors as footwear on gait kinematics.

Methods: This single-center, randomized, double-blind, crossover clinical trial assessed shod and unshod gait in patients with PD with medication in different DBS conditions (i.e., STIM OFF, STN DBS, and STN+SN DBS) during different gait tasks (i.e., normal gait, fast gait, and gait during dual task) and compared gait characteristics to healthy controls. Notably, 15 patients participated in the study, and 11 patients were analyzed after a dropout of four patients due to DBS-induced side effects.

Results: Gait was modulated by both factors, namely, footwear and DBS mode, in patients with PD. Footwear impacted gait characteristics in patients with PD similarly to controls with longer step length, lower cadence, and shorter single-support time. Interestingly, DBS exerted specific effects depending on gait tasks with increased cognitive load. STN+SN DBS was the most efficient DBS mode compared to STIM OFF and STN DBS with intense effects as step length increment during dual task.

Conclusion: The PD gait disorder is a multifactorial symptom, impacted by environmental factors as footwear and modulated by DBS. DBS effects on gait were specific depending on the gait task, with the most obvious effects with STN+SN DBS during gait with increased cognitive load.

Keywords: barefoot, shoes, gait, deep brain stimulation, subthalamic nucleus, substantia nigra, Parkinson's disease

INTRODUCTION

Gait disorders with freezing of gait (FOG) remain some of the treatment-resistant symptoms in Parkinson's disease (PD) (Ebersbach et al., 2013; Armstrong and Okun, 2020), which became a focus of interest in terms of precise characterization, clinical phenomenology, treatment effects, and environmental conditions in recent years (Nutt et al., 2011). In the clinical assessment and rehabilitative setting of the Parkinsonian gait disorder, there remains one simple question regarding environmental conditions: shod or unshod gait, i.e., do they differ, and if so, which one is better in the analysis and training setting in patients with PD?

On the one hand, walking with shoes represents the most commonly used gait condition of the daily routine in patients with PD. Besides, the study used shoes as a vehicle and developed specifically designed shoes with foot-worn wearable sensors to monitor gait and posture (Martinez et al., 2018; Lee et al., 2021; Liu et al., 2021) with the option to capture gait abnormalities in everyday-life situations in PD. In addition, there were newly designed shoes with potential therapeutic use as visual cueing using laser shoes to alleviate FOG (Barthel et al., 2018a,b) or the "PDShoe" with step-synchronized vibration applied to the feet of patients with PD (Winfree et al., 2013), although some of the textured and stimulating insoles for balance and gait improvement in patients with PD seemed to have no effect (Alfuth, 2017). On the other hand, there are general discussions about the advantages of walking barefoot in younger (Cranage et al., 2020) or older people (Lord and Bashford, 1996), so that walking barefoot might be useful in the rehabilitative setting. One advantage of walking barefoot is assumed to enhance proprioceptive integration. In PD, sensorimotor deficits as tactile or proprioceptive impairments and impaired foot sole sensitivity are described (Pratorius et al., 2003; Conte et al., 2013), so that walking barefoot might be a useful rehabilitative strategy.

Beneath the rehabilitative therapeutic approaches for the PD gait disorder, there are medical and interventional therapeutic strategies as deep brain stimulation (DBS) (Nonnekes et al., 2015). DBS in the subthalamic nucleus (STN) or globus pallidus internus (GPi) improve general motor symptoms (Deuschl et al., 2006; Follett et al., 2010) and certain aspects of the hypokinetic, dopa-responsive gait disorder PD (Potter-Nerger and Volkmann, 2013); however, the long-term observations reveal residual and progressive gait symptoms (Krack et al., 2003; Potter-Nerger and Volkmann, 2013; Schlenstedt et al., 2017). As a new DBS mode to alleviate the Parkinsonian gait disorder and FOG, the combined stimulation of STN and substantia nigra (STN+SN DBS) was proposed (Weiss et al., 2011a). In a monocentric, randomized trial, STN+SN DBS was demonstrated to improve clinically FOG (Weiss et al., 2013) with a particular impact of SN-stimulation on the temporal regularization of gait integration (Scholten et al., 2017). STN+SN DBS was based on the neurophysiological consideration of dense reciprocal interconnections of substantia nigra pars reticulata (SNr) and the mesencephalic locomotor region (MLR) in the brain stem, which are involved in the control of locomotion and posture (Collomb-Clerc and Welter, 2015). It is assumed that the pathologically enhanced excitatory activity of the STN drives the SNr to excessively inhibit the MLR resulting in the decreased activation of spinal centers and consecutively impaired gait. Along this hypothesis, STN+SN DBS would functionally suppress the STN and SNr resulting in the release of the pathologically MLR inhibition and improved gait performance.

The aim of this study was 2-fold. We intended to assess, on the one hand, the effects of the rehabilitative, environmental factor "footwear" on gait and, on the other hand, the effect and possible interaction between different DBS modes, i.e., DBS of the STN (STN DBS) and STN+SN DBS, on temporal and spatial gait characteristics in patients with PD.

METHODS

Participants

Fifteen patients (two female, age: 62.5 ± 6.7 years) suffering from moderate idiopathic PD [disease duration: 12.0 ± 5.0 years; Hoehn & Yahr stage: 2.2 ± 0.4 in the regular dopaminergic medication (MED ON) and STN DBS ON condition; Hoehn & Yahr stage: 2.6 ± 0.8 in the MED OFF condition preoperatively] participated in the study. Detailed information is shown in **Table 1**. No other medical or orthopedic conditions that might impact gait quality were reported in the medical history of patients with PD. Further clinical characteristics were described previously (Hidding et al., 2019).

Patients with PD were included if (1) bilateral electrode implantation in the STN for DBS was performed at least 5 months before, (2) the deepest contacts of the implanted electrodes were positioned within the dorsal aspect of the SN along image-based electrode reconstruction (location of the electrode tip at least 4.5–6 mm inferior to AC-PC line), and (3) dopaminergic medication and stimulation parameters were unchanged in the preceding 4 weeks before baseline measurements. Notably, 10 patients with PD were implanted with Medtronic DBS systems (model 3389; Medtronic, Minneapolis, MN, USA), and five patients with 8-poled electrodes from Boston Scientific (Valencia, CA, USA). Preoperatively, all patients with PD were screened and selected for DBS surgery in accordance with the common guidelines of DBS surgery [Core Assessment Program for Surgical Interventional Therapies (CAPSIT) protocol (Defer et al., 1999)]. Patients showed significant improvement in the motor subscore (part III) of the Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) after the intake of immediate-release soluble levodopa (MED OFF: 38.0 ± 17.7, MED ON: 12.0 ± 8.4, improvement of 67%). The daily levodopa-equivalent dose decreased from 990.3 ± 205.8 mg preoperatively to 654.7 ± 245.7 mg postoperatively. Four patients withdrew from the study during STN+SN DBS mode due to side effects such as general uncomfortable feeling, increased confusion, hallucinations, aggressiveness, and a lack of beneficial effects of levodopa intake. We also evaluated 11 healthy individuals who were matched by gender (two females), age (64 ± 6.8 years for controls vs. 62.5 ± 6.7 years for PD patients), and the Montreal Cognitive Assessment (MoCA)

TABLE 1 | Clinical and demographic characteristics of patients with Parkinson's disease (PD).

Case Gender Age	Age at onset	Disease duration (years)	Time with DBS (months)	LEDD (mg)	MoCA	BDI	PDQ 39 OFF/STN/ STN+SN	FOG OFF/STN/ STN+SN	Berg-balance OFF/STN/ STN+SN	UPDRS-III OFF/STN/ STN+SN	H&Y OFF/ STN/STN+SN	System	STN-DBS parameters	Combined STN+SN DBS parameters	X, Y, Z, coordinates
													Left electrode Right electrode	Left electrode Right electrode	Left electrode Right electrode
1 M 61	38	23	54	1,150	27	13	36.6/28.5/29.6	2/0/0	49/54/56	32/18/30	2/2.5/2	ME	2- C+, 3.5 V, 60 μs, 125 Hz 9- 10- C+, 2.7 V, 60 μs, 125 Hz	2- C+, 3.5 V, 60 μs, 125 Hz; 0- C+, 2.0 V, 60 μs, 125 Hz 9- 10- C+, 2.7 V, 60 μs, 125 Hz; 8- C+, 2.0 V, 60 μs,125 Hz	10.9, 2.2, 4.7 10.5, 3.8, 4.7
2 M 63	40	23	105	860	26	9	46.5/25.2/25.5	2/4/0	43/52/47	41/28/29	2.5/2.5/2.5	ME	C+, 1.9 V 60 μs, 125 Hz; 2- C+, 2.9 V, 60 μs, 125 Hz 9- C+, 1.9 V, 60 μs, 125 Hz; 10- C+, 3.3 V, 60 μs, 125 Hz	2- C+, 2.9 V, 60 μs, 125 Hz; 1- 0- C+, 1.9 V (1.5 V), 60 μs, 125 Hz 10- C+, 3.3 V, 60 μs, 125 Hz; 8- 9- C+, 1.9 V (1.5 V), 60 μs, 125 Hz	11.2, 1.9, 5.6 8.3, 5.5, 4
3 M 56	47	9	36	880	26	15	21.0/26.0/28.2	14/4/1	56/54/55	39/25/30	3/2.5/2	ME	1+ 2- C+ 2.2 V, 60 μs, 125 Hz 10- C+, 4.3 V, 60 μs, 125 Hz	2-C+, 2.2 V, 60 μs, 125 Hz; 0- C+, 1.0 V, 60 μs, 125 Hz 10- C+, 4.3 V, 60 μs, 125 Hz, 8- C+, 1.0 V, 60 μs, 125 Hz	9.5, 2.8, 6.4 11.2, 1.4, 7.2
4 M 67	51	16	60	600	23	2	9.5/4.4/5.3	6/6/3	45/49/51	34/10/15	2/2/2.5	ME	C+, 1.5 V, 60 μ, 125 Hz 9- 10- C+, 3.9 V, 60 μs, 125 Hz	C+, 1.5 V, 60 μ, 125 Hz; 0- C+, 2.0 V, 60 μs, 125 Hz 9–10- C+, 3.9 V, 60 μs, 125 Hz; 8- C+, 2.0 V, 60 μs, 125 Hz	9.6, 4.7, 6.6 11.7, 3.1, 3.2
5 M 65	56	9	9	300	28	1	4.3/1.9/2.7	0/0/1	49/54/56	40/16/14	2.5/2/2	ME	C+, 2.8 V, 60 μs, 125 Hz 9- C+, 3.0 V, 60 μs, 125 Hz	C+, 2.8 V, 60 μs, 125 Hz; 0- C+, 1.5 V, 60 μs, 125 Hz 9-C+, 3.0 V, 60 μs, 125 Hz; 8- C+, 1.5 V, 60 μs, 125 Hz	10.9, 1.4, 7.7 11.1, 2.7, 6.7
6 M 74	65	9	9	360	22	1	1.6/1.0/3.8	6/0/0	55/55/56	34/23/18	2/2/2	ME	C+, 2.7 V, 130 Hz 9- C+, 2.6 V, 60 μs, 130 Hz	C+, 2.7 V, 60 μs, 125 Hz; 0- C+, 1.5 V, 60 μs, 125 Hz 9- C+, 2.9 V, 60 μs, 125 Hz; 8- C+, 1.5 V, 60 μs, 125 Hz	10.7, 2.6, 4.9 10.2, 2.5, 4.5
7 M 51	42	9	15	900	27	5	29.9/33.1/34.2	11/2/11	49/56/54	34/31/50	3/2.5/3	BS	2- 30%, 3- 70%, 3.4 mA, 60 μs, 125 Hz 10- 20%, 11- 80%, 4.0 mA, 60 μs, 125 Hz	23%, 2- 23%, 3- 54%, 4.4 mA, 60 μs, 125 Hz 9- 20%, 10- 16%, 11- 64%, 5.0 mA, 60 μs, 125 Hz	8.8, 3.4, 7.4 7.1, 4.3, 6.4
8 M 57	50	7	18	580	27	6	23.5/20.2/24.1	0/0/0	54/56/56	16/12/8	2/2/2	BS	3- 70%, 4- 30%, 4.5 mA, 60 μs, 130 Hz 12- 100%, 3.8 mA, 60 μs, 130 Hz	3- 61%, 4- 26%, 1- 13%, 5.2 mA, 60 μs, 130 Hz 12- 85%, 9- 15%, 4.5 mA, 60 μs, 130 Hz	11.9, 3.4, 6.1 11.6, 2.7, 5.9

(Continued)

TABLE 1 | Continued

Case Gender Age	Age at onset	Disease duration (years)	Time with DBS (months)	LEDD (mg)	MoCA	BDI	PDQ 39 OFF/STN/ STN+SN	FOG OFF/STN/ STN+SN	Berg-balance OFF/STN/ STN+SN	UPDRS-III OFF/STN/ STN+SN	H&Y OFF/ STN/STN+SN	System	STN-DBS parameters	Combined STN+SN DBS parameters	X, Y, Z, coordinates
													Left electrode Right electrode	Left electrode Right electrode	Left electrode Right electrode
9 M 71	61	11	13	600	27	11	37.0/50.6/41.8	4/3/1	53/53/54	34/27/16	2.5/2/2	ME	C+, 3.5 V, 60 μs, 125 Hz 9- C+, 2.7 V, 60 μs, 125 Hz	C+, 3.5 V, 60 μs, 125 Hz; 0- C+, 1.0 V, 60 μs, 125 Hz 9- C+, 2.7 V, 60 μs, 125 Hz; 8- C+, 1.0 V, 60 μs, 125 Hz	1.3, 2.2, 6.2 12.2, 0.2, 5.2
10 M 66	54	13	6	300	22	10	25.2/38.9/33.2	0/0/0	56/54/54	51/16/14	2.5/2.5/2	ME	C+, 3.8 V, 60 μsec, 130 Hz 9- C+, 3.6 V, 60 μz 130 Hz	3.8 V 60 μsec 125 Hz 0- 1.0 V 60 μsec, 125 Hz 9- C+ 3.6 V, 60 μsec, 125 Hz 8- C+ 1,0 V 60 μsec, 125 Hz	11.2, 6.5, 6.6 10.5, 4.2, 5.1
11 F 66	56	10	5	440	25	2	6.8/5.0/4.2	4/0/0	54/56/55	27/7/10	2/2.5/2.5	BS	5-6-7- (Ring) C+, 2.2 mA, 60 μsec, 130 Hz 13-14-15- (Ring) C+, 2.4 mA 60 μsec, 130 Hz	5- (23%) 6- (23%) 7- (23%) 1- (31%) C+, 2.9 mA, 60 μsec, 130 Hz 13-(24%) 14- (23%) 15-(23%) 9-(30%) C+, 3.1 mA, 60 μsec, 130 Hz	10.9, 2.5, 5.7 10.4, 0.44, 5.2
12 F 66	57	9	5	700	25	13	30.4	18	55	42	2	ME	Withdrawal in phase I, experimental phase II not performed	2- C+, 2.4 V, 60 μs, 125 Hz; 0- C+, 0.7 V, 60 μs, 125 Hz 11- C+, 2.5 V, 60 μs, 125 Hz; 8- C+, 0.7 V, 60 μs, 125 Hz	10.2, 0.9, 5.2 9.0, 0.6, 7.8
13 M 55	42	13	23	700	28	5	13.3	5	56	28	2	ME	Withdrawal in phase I, experimental phase II not performed	3- C+, 2.9 V, 60 μs, 125 Hz; 0- C+, 0.7 V, 60 μs, 125 Hz 10- C+, 2.9 V, 60 μs, 125 Hz 8- C+, 0.7 V, 60 μs, 125 Hz	9.2, 2.8, 7.7 10.2, 2.4, 6
14 M 53	43	10	16	860	24	8	14.7	0	55	20	2.5	BS	Withdrawal in phase I, experimental phase II not performed	3-C+ 2,7 mA, 60 μs, 119 Hz; 1- C+, 0.7 mA, 60 μs, 119 Hz 12-/13- C+, 4,7 mA, 60 μs, 119 Hz; 9- C+, 0.7 mA, 60 μs, 119 Hz	10.7, 5.3, 6.9 7.7, 3.1, 6.8
15 M 66	57	9	5	590	28	5	6.8	9	56	34	2	BS	Withdrawal in phase I, experimental phase II not performed	13- (16%) 14- (45%) 15- (16%) 9- (23%) 4.5 mA, 60 μsec, 130 Hz 5- (29%) 6-(15%), 7- (29%), 1- (27%), 3.7 mA, 60 μsec, 130 Hz	11.6,4.1, 7.4 10.9, 2.2,6.2

"Disease duration (years)" is calculated from the date of the first diagnosis to the date of baseline measurement of the experiment. Electrode coordinates are given in relation to the anterior and posterior commissure (AC-PC) line (mm) lateral to the midline (X), posterior to the midcommissural point (Y), and inferior to the intercommissural plane (Z). Notably, the deepest contacts were contact 0 and 8 (Medtronic) or contact 1 and 9 (Boston Scientific). LEDD, levodopa equivalent daily dose; ME, Medtronic; BS, Boston Scientific; MoCA, Montreal Cognitive Assessment score; BDI-I, Becks Depression Inventory; Berg Balance scale sum score; short form of the Berg Balance scale comprehending only items 1, 6, 8, 9, 10, 13, 14; FOG, Freezing of Gait Assessment Course score; UPDRS-III, motor-subscore (part III) of Unified Parkinson's Disease Rating Scale of the Movement Disorder Society; H&Y, Hoehn & Yahr scale; NA, not applicable.

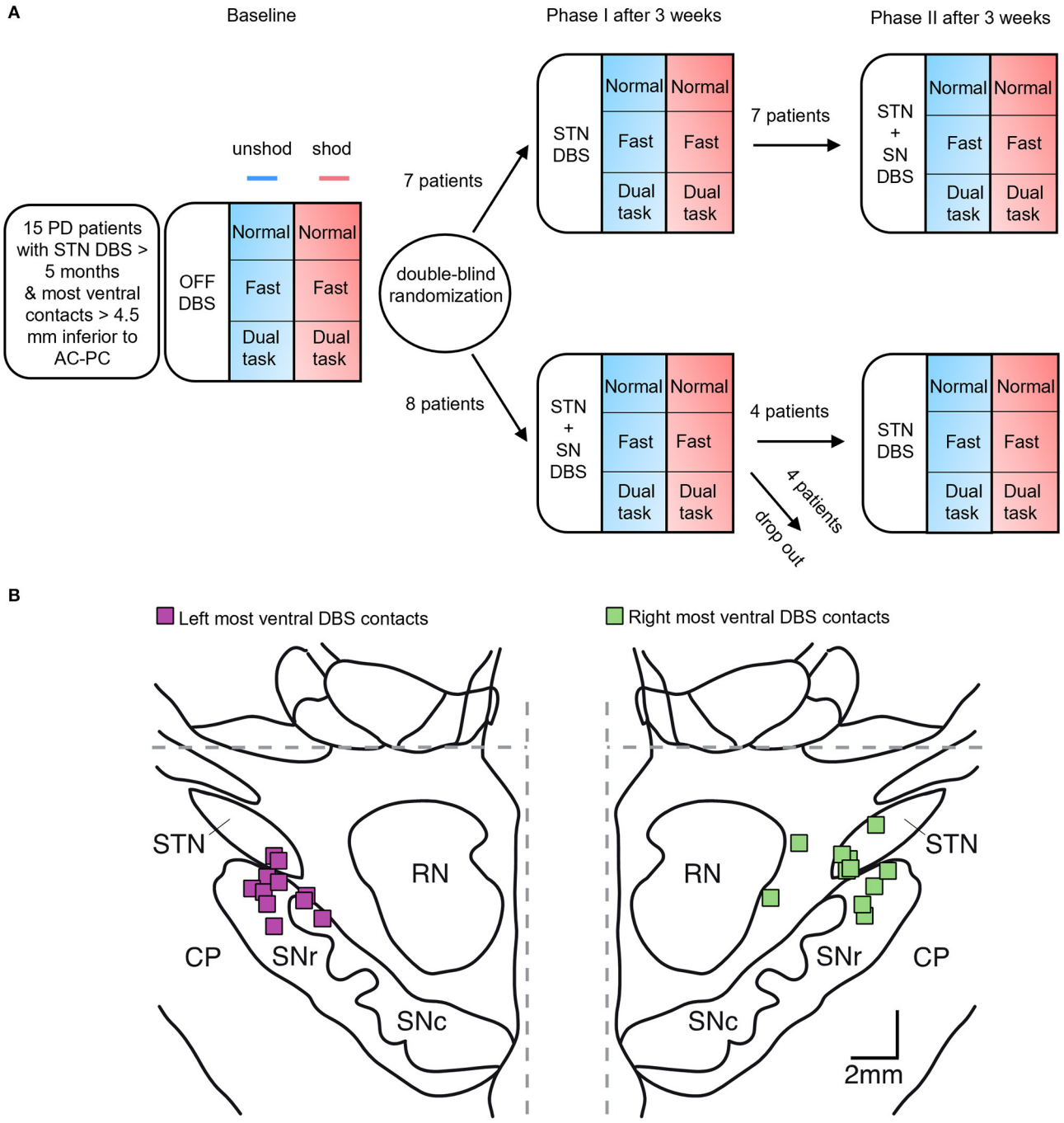

FIGURE 1 | Experimental setting. **(A)** Study design: randomized crossover trial over 6 weeks. At baseline, patients were evaluated in the STIM OFF mode. Spatiotemporal parameters of gait were measured under six paradigms in randomized order: the three gait tasks were performed at normal pace, at a fast pace, and in a dual-task setting either shod (red squares) or unshod (blue squares), followed by the other footwear condition. After baseline assessment, patients with Parkinson's disease (PD) were assigned in phase I to either conventional deep brain stimulation of the subthalamic nucleus (STN DBS) or combined STN and substantia nigra (STN+SN) stimulation in a double-blind randomized order. After 3 weeks, patients were switched to the other stimulation mode for the next 3 weeks. Of note, four patients with PD programmed in STN+SN DBS withdrew within the first week and terminated the study prematurely. **(B)** stereotactic reconstruction of 11 patients included in statistical analysis: squares indicate the localization of the most ventral DBS electrode contacts for the left and right hemisphere, on frontal sections of the stereotactic atlas of Morel (2007), at a level 5 mm behind midcommissural point. Interrupted gray lines denote midline and anterior and posterior commissure (AC-PC) level, respectively. CP, cerebral peduncle; RN, red nucleus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; STN, subthalamic nucleus.

(Gill et al., 2008) score (28.5 for controls vs. 25.5 for PD patients).

Design

The project was a single-center, randomized, double-blind, crossover clinical trial at the departments of neurology and neurosurgery at the University Medical Center Hamburg-Eppendorf (UKE) to compare the effect of STN stimulation vs. STN+SN DBS in patients with PD as described previously (Hidding et al., 2017) (**Figure 1**). In this study, we compared temporal and spatial characteristics of gait while walking barefoot or with shoes during STN+SN DBS, conventional STN DBS, or no stimulation (STIM OFF) in patients with PD.

At baseline, we did a monopolar review of the most ventral contacts located in the SN. Thresholds with side effects were 3.3 ± 0.9 mA (range: 2.0–5.0 mA) in left SN and 3.3 ± 1.1 mA (range: 1.5–5.0 mA) in right SN. The stimulation strength of at least 0.5 mA below the individual side effect threshold was chosen, which was in the range given in the literature (Weiss et al., 2013). The average stimulation parameters in SN were 1.2 ± 0.5 mA (range: 0.7–2 mA) applied symmetrically on either side. At phase I, patients with PD were evaluated and then randomized to conventional STN DBS or STN+SN DBS. Phase II started 3 weeks after, with crossover reprogramming for the following 3 weeks. There was no washout period in between the two phases (**Figure 1**). All visits were performed with MED ON, which was kept constant throughout the whole course of the study. Stimulation parameters were fixed during phase I and phase II of the study, besides in one patient, in which stimulation amplitude in the SN had to be reduced after 2 days due to dyskinesias (Hidding et al., 2019).

The study visits took place at the university hospital regularly in the morning. The patients had taken the last levodopa dosage at home.

To assess gait kinematics of controls and patients with PD, we used the GAITRite® Walkway System. The duration of all gait task performances for gait analysis was 27.4 ± 5.3 min. The GAITRite® consists of a walkway with the overall dimensions of 90 cm × 7 m × 3.2 mm. We analyzed the *temporal* parameters as velocity (cm/s), cadence (steps per minute), single support (percentage of the gait cycle time of the same foot), and the coefficient of variation (CV) of the stride time (Hausdorff et al., 1998) as well as the *spatial* parameters as step length (cm) and base width (cm) (Bilney et al., 2003). To evaluate gait asymmetry, we calculated the step length symmetry ratio (i.e., the ratio of the mean step length of best and worst side).

During each assessment, participants were asked to walk over the GAITRite® Walkway System performing three different gait tasks as follows: (1) straightforward gait at self-paced, normal walking speed, (2) straightforward gait with fast walking speed, and (3) gait with the increased cognitive load as dual-task performance (DT) when patients walked while performing a mental arithmetic task, turning at the end of the walkway and walking back. Each gait task was performed while wearing shoes and barefoot; for each task, the walk was repeated three times. For a better comparison between different gait tasks, we calculated gait metrics in the DT scenario using only the first straightforward part of the task.

Implantation of the Permanent DBS Electrodes

The DBS electrode placement was guided by intraoperative microelectrode recording (MER) and test stimulation. Three parallel tracks were used to map the subthalamic region with tungsten electrodes (NeuroProbe electrodes, Alpha Omega Inc., Nazareth, Israel; impedance: 685 ± 245 kOhm). The subthalamic sensorimotor region was identified by cell responses to passive and active movements and a high prevalence of oscillating neuronal activities in the beta-frequency range (13–30 Hz). The differentiation of STN from SN was based on the established electrophysiological criteria (Sharott et al., 2014; Hidding et al., 2017). The optimal target site for electrode implantation was further determined by the clinical evaluation of macrostimulation responses (Moll et al., 2014; Potter-Nerger et al., 2017).

Stereotactic Reconstruction of Most Ventral Electrode Contacts

The reconstruction of the active DBS lead contacts (electrode model 3389, Medtronic, Minneapolis, MN, USA, in 8 cases, and electrode model 2201 and model 2202, Boston Scientific, Valencia, CA, USA, in 2 cases and 1 case, respectively) was performed by the co-registration of the preoperative T1 MRI scans and postoperative CT scans using iPlan (iPlan Stereotaxy; Brainlab, Feldkirchen, Germany). Further details concerning the localization of active electrode contacts were reported previously (Hamel et al., 2003; Fischer et al., 2016; Hidding et al., 2017). According to stereotactic atlases, high-resolution MRI, and MER-guided mapping, the upper border of the SNr is positioned 4.5–6 mm below the plane in between anterior and posterior commissure (AC and PC; **Figure 1**; **Table 1**) (Weiss et al., 2013).

Statistics

Since four patients withdrew from the study due to intolerance of STN+SN DBS, analyses were performed in the remaining 11 patients completing the whole course of the study.

In a first step, we compared age-matched, healthy controls and patients with PD in the STIM OFF condition by analyzing two-way repeated-measures ANOVAs with the intrasubject factors such as 1. footwear (barefoot or shoes) and 2. gait task (normal gait, fast gait, and dual task) and with the intersubject factor group (controls vs. patients with PD in STIM OFF).

In a second step, we assessed the effect of DBS by performing three-way repeated-measures ANOVAs with the intrasubject factors: 1. footwear (barefoot or shoes), 2. stimulation condition (STIM OFF, STN DBS, and combined stimulation STN+SN DBS), and 3. gait task (normal gait, fast gait, and dual task) for gait kinematics.

Greenhouse–Geisser-corrected *p*-values were calculated if the violation of sphericity was obvious in Mauchly's sphericity test. Alpha level was set at 0.05. *Post hoc* Wilcoxon signed-ranks tests were performed to compare the effects of different stimulations

TABLE 2 | Results of three-way repeated-measures ANOVAs.

			Unshod				Shod				Within-subjects contrasts for controls			Within-subjects contrasts for patients with PD				
Gait parameter		**Gait task**	**Controls**	**OFF**	**STN**	**STN+SN**	**Controls**	**OFF**	**STN**	**STN+SN**	**Unshod vs. shod**	**Dual vs. normal**	**Normal vs. fast**	**Unshod vs. shod**	**OFF vs. STN**	**STN vs. STN+SN**	**Dual vs. Normal**	**Normal vs. Fast**
Velocity	↓ Pace	Dual	111.2 ± 16.7	82.8 ± 30.6	90.8 ± 25.5	95.3 ± 27.8	119.4 ± 21.4	83.5 ± 25.7	96.4 ± 28.7	101.4 ± 27.7	**$F = 16.31$**	**$F = 23.39$**	**$F = 88.33$**	$F = 0.029$	$F = 0.72$	$F = 2.91$	**$F = 20.55$**	**$F = 159.99$**
		Normal	131.8 ± 13.4	108.5 ± 17.7	110.1 ± 23.3	118.4 ± 21.1	142.0 ± 15.2	112.1 ± 18.8	114.5 ± 18.9	119.5 ± 22.3	**$p = 0.002$**	**$p = 0.001$**	**$p < 0.001$**	$p = 0.869$	$p = 0.417$	$p = 0.119$	**$p = 0.001$**	**$p < 0.001$**
		Fast	189.4 ± 25.5	155.8 ± 24.8	156.1 ± 26.3	165.6 ± 29.1	203.6 ± 27.8	150.1 ± 26.6	151.7 ± 20.4	160.0 ± 20.0	**$\eta^2 = 620$**	**$\eta^2 = 0.701$**	**$\eta^2 = 0.898$**	$\eta^2 = 0.003$	$\eta^2 = 0.067$	$\eta^2 = 0.225$	**$\eta^2 = 0.673$**	**$\eta^2 = 0.941$**
Step length	↓ Pace	Dual	62.7 ± 5.1	49.9 ± 11.1	55.6 ± 10.5	55.6 ± 10.5	67.4 ± 6.5	53.1 ± 9.0	58.0 ± 8.0	61.7 ± 8.9	**$F = 70.59$**	**$F = 35.54$**	**$F = 57.13$**	**$F = 15.88$**	$F = 0.65$	**$F = 8.14$**	**$F = 26.68$**	**$F = 61.61$**
		Normal	68.9 ± 5.4	58.7 ± 5.8	59.5 ± 7.6	62.9 ± 7.5	76.4 ± 5.5	63.6 ± 5.4	63.8 ± 5.0	67.0 ± 7.2	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p = 0.003$**	$p = 0.440$	**$p = 0.017$**	**$p < 0.001$**	**$p < 0.001$**
		Fast	80.4 ± 7.2	70.4 ± 6.9	69.8 ± 5.5	72.6 ± 6.3	86.1 ± 7.6	74.2 ± 6.2	72.8 ± 4.4	77.6 ± 5.1	**$\eta^2 = 0.876$**	**$\eta^2 = 0.780$**	**$\eta^2 = 0.851$**	**$\eta^2 = 0.614$**	$\eta^2 = 0.061$	**$\eta^2 = 0.449$**	**$\eta^2 = 0.727$**	**$\eta^2 = 0.727$**
Cadence	↓ Pace	Dual	106.19 ± 9.6	97.4 ± 20.0	101.6 ± 17.5	101.8 ± 16.0	105.4 ± 13.4	93.3 ± 20.4	98.3 ± 19.3	97.8 ± 18.4	$F = 0.66$	**$F = 6.05$**	**$F = 76.25$**	**$F = 13.64$**	$F = 0.72$	$F = 0.63$	**$F = 9.78$**	**$F = 93.16$**
		Normal	114.1 ± 7.7	110.9 ± 13.4	110.4 ± 14.6	112.7 ± 11.9	111.9 ± 6.1	105.5 ± 12.9	107.3 ± 12.5	106.7 ± 12.6	$p = 0.436$	**$p = 0.034$**	**$p < 0.001$**	**$p = 0.004$**	$p = 0.417$	$p = 0.808$	**$p = 0.011$**	**$p < 0.001$**
		Fast	142.6 ± 14.5	132.5 ± 13.9	133.6 ± 14.7	136.7 ± 16.3	141.9 ± 13.7	120.7 ± 14.2	124.6 ± 11.8	123.8 ± 13.8	$\eta^2 = 0.062$	**$\eta^2 = 0.377$**	**$\eta^2 = 0.884$**	**$\eta^2 = 0.577$**	$\eta^2 = 0.067$	$\eta^2 = 0.006$	**$\eta^2 = 0.494$**	**$\eta^2 = 0.903$**
Single support	↓ Pace	Dual	37.3 ± 1.7	35.3 ± 2.9	36.4 ± 2.3	37.2 ± 2.0	36.3 ± 2.1	33.6 ± 1.9	35.1 ± 1.9	35.8 ± 1.6	**$F = 13.99$**	**$F = 38.73$**	**$F = 179.96$**	**$F = 35.73$**	$F = 3.19$	**$F = 8.43$**	**$F = 35.31$**	**$F = 134.9$**
		Normal	38.8 ± 1.0	38.0 ± 1.5	38.4 ± 1.7	39.1 ± 1.4	37.9 ± 1.9	36.5 ± 1.4	36.7 ± 1.5	36.8 ± 1.6	**$p = 0.004$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	$p = 0.105$	**$p = 0.016$**	**$p < 0.001$**	**3p < 0.001**
		Fast	41.6 ± 1.1	40.6 ± 1.6	40.7 ± 1.7	41.4 ± 1.5	40.3 ± 1.8	38.5 ± 1.8	38.3 ± 1.9	38.9 ± 1.7	**$\eta^2 = 0.583$**	**$\eta^2 = 0.795$**	**$\eta^2 = 0.947$**	**$\eta^2 = 0.781$**	$\eta^2 = 0.242$	**$\eta^2 = 0.457$**	**$\eta^2 = 0.779$**	**$\eta^2 = 0.931$**
CV of std of stride time	↓ Pace	Dual	3.3 ± 1.1	6.6 ± 2.5	5.7 ± 1.8	5.8 ± 2.0	2.8 ± 1.4	7.2 ± 4.5	5.2 ± 1.6	5.6 ± 2.4	**$F = 11.45$**	**$F = 7.28$**	**$F = 5.68$**	$F = 2.98$	$F = 2.25$	$F = 0.92$	**$F = 12.33$**	$F = 0.72$
		Normal	2.4 ± 0.5	4.2 ± 1.6	4.3 ± 1.6	4.6 ± 1.7	1.9 ± 0.7	3.9 ± 1.0	3.5 ± 1.3	3.6 ± 1.0	**$p = 0.007$**	**$p = 0.022$**	**$p = 0.038$**	$p = 0.115$	$p = 0.164$	$p = 0.361$	**$p = 0.006$**	$p = 0.415$
		Fast	3.3 ± 1.2	4.5 ± 1.8	4.4 ± 1.5	4.9 ± 2.0	2.7 ± 1.1	3.5 ± 1.3	4.1 ± 1.1	3.8 ± 1.2	**$\eta^2 = 0.534$**	**$\eta^2 = 0.421$**	**$\eta^2 = 0.362$**	$\eta^2 = 0.230$	$\eta^2 = 0.184$	$\eta^2 = 0.084$	**$\eta^2 = 0.552$**	$\eta^2 = 0.067$
Step length symmetry ratio	↓ Pace	Dual	1.03 ± 0.03	1.09 ± 0.07	1.05 ± 0.04	1.04 ± 0.04	1.03 ± 0.04	1.12 ± 0.08	1.04 ± 0.02	1.04 ± 0.04	$F = 0.02$	$F = 0.01$	$F = 4.65$	$F = 0.01$	**$F = 10.72$**	$F = 0.017$	**$F = 5.93$**	$F = 0.03$
		Normal	1.03 ± 0.02	1.06 ± 0.05	1.04 ± 0.03	1.04 ± 0.04	1.03 ± 0.02	1.05 ± 0.03	1.04 ± 0.03	1.05 ± 0.04	$p = 0.883$	$p = 0.951$	$p = 0.056$	$p = 0.942$	**$p = 0.008$**	$p = 0.899$	**$p = 0.035$**	$p = 0.855$
		Fast	1.04 ± 0.03	1.06 ± 0.028	1.06 ± 0.03	1.05 ± 0.02	1.03 ± 0.02	1.06 ± 0.04	1.04 ± 0.02	1.04 ± 0.03	$\eta^2 = 0.002$	$\eta^2 = 0.000$	$\eta^2 = 0.318$	$\eta^2 = 0.001$	**$\eta^2 = 0.517$**	$\eta^2 = 0.002$	**$\eta^2 = 0.372$**	$\eta^2 = 0.004$
Base width	↓ Pace	Dual	10.09 ± 2.2	13.8 ± 5.8	12.8 ± 5.6	13.8 ± 5.7	9.7 ± 2.3	14.2 ± 6.1	12.2 ± 4.3	13.1 ± 5.2	$F = 0.03$	$F = 0.27$	$F = 0.53$	$F = 1.26$	$F = 3.09$	$F = 1.22$	**$F = 10.58$**	$F = 0.28$
		Normal	9.8 ± 1.6	11.7 ± 3.9	11.3 ± 3.3	11.1 ± 3.4	9.5 ± 1.2	12.0 ± 4.0	10.8 ± 3.7	11.3 ± 3.8	$p = 0.864$	$p = 0.614$	$p = 0.485$	$p = 0.288$	$p = 0.109$	$p = 0.295$	**$p = 0.009$**	$p = 0.610$
		Fast	9.5 ± 1.9	11.4 ± 5.0	11.0 ± 4.1	11.4 ± 4.2	10.1 ± 1.4	11.3 ± 4.1	10.4 ± 3.7	11.4 ± 3.4	$\eta^2 = 0.003$	$\eta^2 = 0.026$	$\eta^2 = 0.050$	$\eta^2 = 0.112$	$\eta^2 = 0.236$	$\eta^2 = 0.109$	**$\eta^2 = 0.514$**	$\eta^2 = 0.027$

Comparison of gait parameters walking barefoot and with shoes during the three gait tasks under the three stimulation conditions. The stimulation conditions were as follows: OFF, DBS switched off; STN, conventional deep brain stimulation of the subthalamic nucleus (STN DBS); STN+SN, combined STN+SN DBS. Gait tasks were as follows: Dual, gait during the dual task; Normal, normal gait; Fast, fast gait. Values reported are mean ± SD calculated for both legs. The p-values < 0.05 are highlighted in bold.

or gait tasks (IBM SPSS Statistics version 25.0, SPSS, Inc., Chicago, IL, USA).

In a third step, *post hoc* repeated-measures correlations were performed using the rmcorr R package (R version 3.5.0; rmcorr package) (Bakdash and Marusich, 2017). This method was applied to assess consistencies between the gait parameters and the clinical scores at the three DBS stimulation conditions.

RESULTS

The Effect of Footwear on Gait Kinematics in Controls and Patients With PD

Shod or unshod gait induced distinct changes of gait characteristics in healthy controls and patients with PD in STIM OFF (**Table 2**). Of note, baseline gait characteristics between the two groups differed. As expected, in healthy controls, gait velocity was higher ($p = 0.003$), step length ($p = 0.001$) and relative single support time ($p = 0.033$) were longer compared to patients with PD, whereas gait asymmetry ($p = 0.052$) and gait variability ($p = 0.006$) were smaller compared to patients with PD in different gait tasks. During fast gait, cadence ($p = 0.004$) was higher in healthy controls compared to PD, while base width ($p = 0.029$) was smaller in the dual-task scenario in controls compared to patients with PD.

To evaluate the effect of footwear in different gait tasks in both groups in detail, two-way repeated-measures ANOVAs with the intrasubject factors such as 1. footwear and 2. gait task and with the intersubject factor group (control vs. PD in STIM OFF) were performed.

The factor footwear impacted *gait velocity* only in healthy controls (footwear × subject interaction: $F = 4.56$, $p = 0.045$, $\eta^2 = 0.186$) with increased gait speed with shoes during normal and fast gait tasks. *Gait velocity* was modulated by gait task ($F = 138.15$, $p < 0.001$, $\eta^2 = 0.874$) in all subjects, with the highest speed in the fast gait task ($p < 0.001$) and slowest gait speed in the DT ($p = 0.003$) compared to normal gait.

Step length was significantly impacted by footwear ($F = 40.54$, $p < 0.001$, $\eta^2 = 0.670$) in all subjects with larger step lengths with shoes ($p = 0.003$) and smaller step lengths when walking barefoot. Gait task impacted step length ($F = 99.19$, $p < 0.001$, $\eta^2 = 0.832$) with larger steps during fast gait ($p < 0.001$) and smaller steps during DT ($p = 0.001$) compared to normal gait. As already shown in previous studies, step length was higher in healthy controls compared to patients with PD in different gait tasks.

Cadence was significantly affected by footwear ($F = 9.24$, $p = 0.006$, $\eta^2 = 0.316$) through all gait conditions, which was particularly obvious in patients with PD (footwear × subject interaction: $F = 4.58$, $p = 0.045$, $\eta^2 = 0.186$) with a significantly lower cadence during shod gait and higher cadence when walking barefoot ($p = 0.018$). The gait task also affected cadence ($F = 86.75$, $p < 0.001$, $\eta^2 = 0.813$) with higher cadence during fast gait and lower cadence during DT compared to normal gait in all subjects.

The relative *single support* (as a percentage of gait cycle time) was significantly modulated by footwear ($F = 24.59$, $p < 0.001$, $\eta^2 = 0.551$). In controls, the relative single support time was longer than in patients with PD. As expected, the gait task ($F = 121.16$, $p < 0.001$, $\eta^2 = 0.858$) influenced the relative single support time with prolongation during fast gait ($p < 0.001$) and reduction while DT ($p = 0.032$) compared to a normal walk in all subjects.

The temporal *gait variability* as measured by the CV of the stride time was not affected by footwear in any gait task. However, gait variability changed within different gait tasks ($F = 10.34$, $p < 0.001$, $\eta^2 = 0.341$) particularly in patients with PD (gait task × subject interaction: $F = 5.44$, $p = 0.021$, $\eta^2 = 0.214$) with the highest gait variability during DT ($p = 0.017$) compared to normal or fast gait ($p = 0.061$).

The *asymmetry index* of the step length was not affected by the factor footwear in different gait tasks in any subjects. As expected, gait asymmetry was in principal lower in controls compared to patients with PD ($p = 0.045$). There was a group-dependent effect of the factor gait task (gait task × subject interaction: $F = 4.37$, $p = 0.019$, $\eta^2 = 0.179$) with a significant increase of gait asymmetry during DT compared to normal gait in patients with PD, which was not obvious in controls.

The gait *base width* was principally smaller in controls compared to patients with PD ($p = 0.042$). Base width was not modulated by footwear in any subject but modulated by gait task ($F = 7.54$, $p = 0.004$, $\eta^2 = 0.274$), particularly in patients with PD with a broad-based gait during DT (gait task × subject interaction: $F = 6.0$, $p = 0.01$, $\eta^2 = 0.231$).

The Effect of DBS on Shod and Unshod Gait Kinematics in Patients With PD

The DBS affected certain gait kinematics in patients with PD in different gait tasks. Three-way repeated-measures ANOVAs with the intrasubject factors such as 1. footwear, 2. stimulation, and 3. gait task revealed the main finding of the DBS-specific effects on gait kinematics particularly in gait tasks with increased cognitive load were recorded. Findings are shown in **Figure 2** and **Table 2**.

Gait velocity was significantly modulated during different gait tasks ($F = 103.91$, $p < 0.001$, $\eta^2 = 0.912$) with increased gait speed during the fast gait task and slower speed during DT compared to normal gait. DBS seemed to change gait velocity ($F = 2.86$, $p = 0.081$, $\eta^2 = 0.223$), but the effect was not significant. Gait velocity was not affected by footwear throughout all tasks.

Step length was significantly impacted by DBS ($F = 5.62$, $p = 0.012$, $\eta^2 = 0.360$) with significant interaction with gait task ($F = 3.69$, $p = 0.012$, $\eta^2 = 0.270$), indicating gait task-dependent step length increment. We observed a significantly higher step length during STN+SN DBS compared to STIM OFF ($p = 0.019$) and STN DBS ($p = 0.032$), particularly during DT. Thus, STN+SN DBS improved specifically step length in the gait task with increased cognitive load. As in untreated patients with PD in STIM OFF, we observed, in DBS conditions, an effect of footwear ($F = 15.88$, $p = 0.003$, $\eta^2 = 0.614$) with larger step lengths with shoes and smaller step lengths when walking barefoot. There were no significant interactions of footwear with DBS condition or gait task, indicating an overall similar effect of footwear-related step length increment across all stimulation conditions and gait

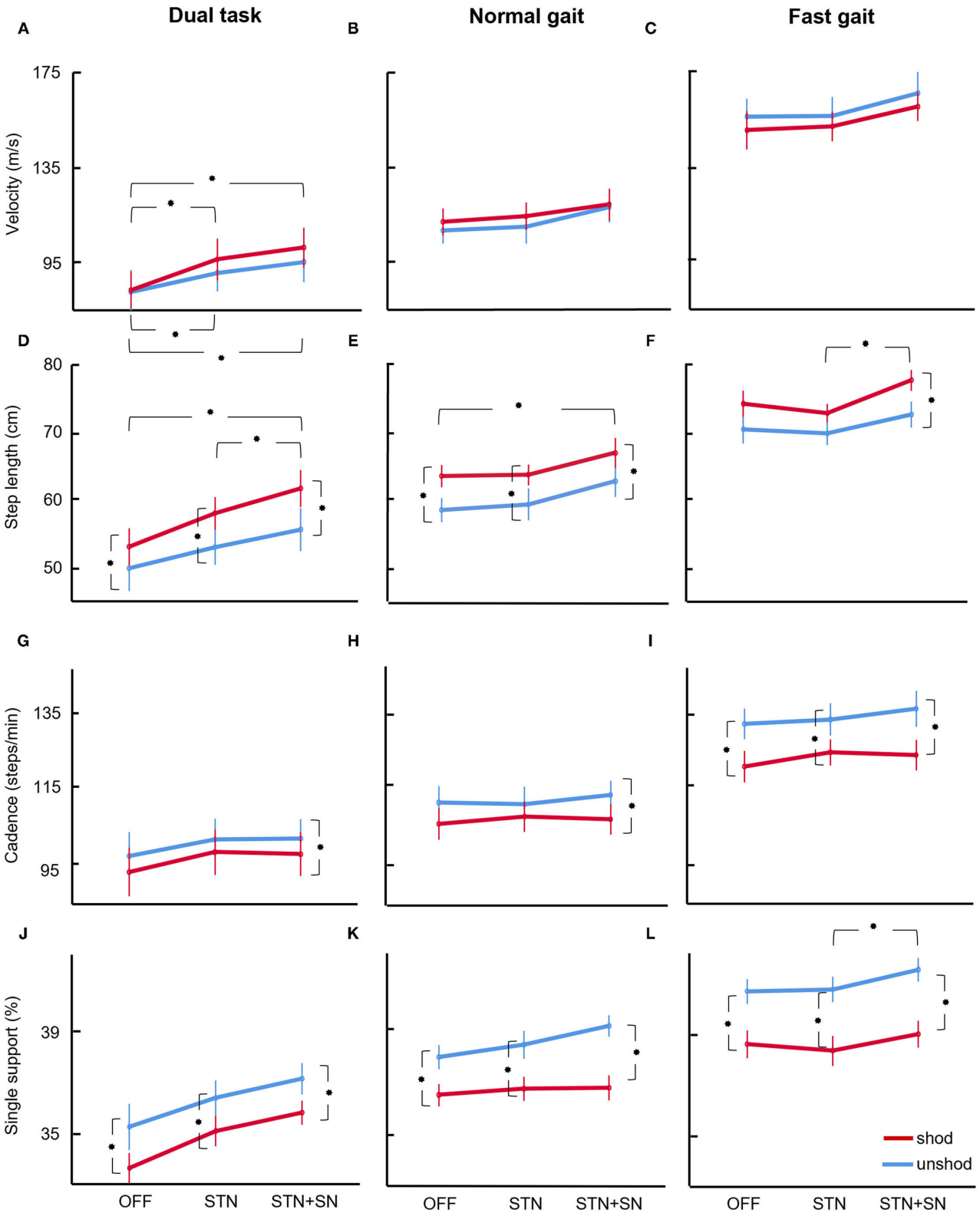

FIGURE 2 | ANOVA results. Results for ANOVA on gait parameters velocity (panels **A–C**), step length (panels **D–F**), cadence (panels **G–I**), and single support (panels **J–L**) are shown for patients with PD OFF DBS, and under STN or STN+SN DBS for the paradigms normal gait, fast gait, and dual task. Line plots are ranked by task pace, i.e., from the slowest pace during the dual task **(left)** to the fastest pace during the fast gait task **(right)**. Values reported are mean and SE bars. Stars denote significant *post hoc* Wilcoxon signed-ranks tests between gait parameters in the unshod and shod conditions and in the three stimulation conditions ($p < 0.05$).

tasks. Gait task impacted step length ($F = 53.35$, $p < 0.001$, $\eta^2 = 0.842$) with larger steps during fast gait and smaller steps during DT compared to normal gait.

Cadence was not significantly modulated by the DBS stimulation mode, but there was a significant effect of gait task ($F = 57.375$, $p < 0.001$, $\eta^2 = 0.852$) and footwear ($F = 13.64$, $p = 0.004$, $\eta^2 = 0.577$) with a significantly lower cadence during shod gait and higher cadence when walking barefoot. This decrease in cadence by wearing footwear was an overall effect across all stimulation or gait tasks since interactions within the model were not significant.

The relative *single support* (as percentage of gait cycle time) was modulated by all three factors, by DBS ($F = 7.62$, $p = 0.003$, $\eta^2 = 0.432$), footwear ($F = 35.75$, $p < 0.001$, $\eta^2 = 0.781$), and gait task ($F = 81.43$, $p < 0.001$, $\eta^2 = 0.891$). As expected, the single support was modulated through the gait tasks with prolongation during fast gait and reduction while DT compared to a normal walk. In contrast, DBS lengthened single support, particularly during STN+SN DBS compared to STIM OFF ($p = 0.027$) and STN DBS ($p = 0.047$). This single support extension was depending on the gait task (DBS × gait task interaction: $F = 5.26$, $p = 0.017$, $\eta^2 = 0.345$) with the most obvious findings during DT.

The temporal *gait variability* as measured by the CV of the stride time was not significantly affected by DBS or footwear. However, gait variability changed within different gait tasks ($F = 8.96$, $p = 0.008$, $\eta^2 = 0.473$) with the highest gait variability during DT compared to normal or fast gait.

The *asymmetry index* of the step length was not affected by the factor footwear or gait task. However, DBS impacted gait symmetry significantly ($F = 5.02$, $p = 0.017$, $\eta^2 = 0.334$), particularly in specific gait tasks (DBS × gait task interaction: $F = 4.98$, $p = 0.029$, $\eta^2 = 0.332$). DBS within STN and STN+SN improved and reduced gait asymmetry compared to STIM OFF, particularly in the DT ($p = 0.057$).

The gait *base width* was only significantly modulated by gait task ($F = 9.78$, $p = 0.001$, $\eta^2 = 0.495$) but not by DBS or footwear. In the DT, the base width was widened, indicating a more unstable gait pattern compared to a normal or fast gait.

Gait characteristics of objective gait analyses as single support time, step length, and velocity correlated with the clinical scores of FOG, balance, and motor scores, particularly in the DT condition underlining the close relationship of objective gait metrics and clinical scores (**Supplementary Figure 1**).

DISCUSSION

In this study, we found the modulation of gait kinematics by footwear and DBS within the specific gait tasks in patients with PD. Footwear impacted gait characteristics in patients with PD with longer step length and lower cadence throughout all DBS conditions and gait tasks. In contrast, STN DBS and STN+SN DBS induced circumscribed changes of certain gait parameters depending on the specific gait task. DBS induced step length increment, gain of relative single support time, and reduction of gait asymmetry depending on the gait task. These changes were particularly obvious during STN+SN DBS in DT conditions, thus in gait tasks with increased cognitive load.

There are limitations to the study. The sample size of patients with PD was small since, during surgery processes for conventional STN DBS, the most caudal electrode contact reaches the SN only in a few patients. We decided to evaluate the patients in daily MED ON conditions to assess patients with PD in the everyday condition; however, we might have ceiling effects and miss further differences between different DBS conditions. Another limitation might be a lack of the use of a standardized shoe in all patients; the patients were asked to wear their own, comfortable outdoor shoes. Besides, gait analyses on the GAITRite® carpet offered short time stamps of the gait performance in the laboratory conditions and might not reflect everyday gait performance in the long term.

Footwear as a peripheral, proprioceptive factor and DBS as a central, neuromodulatory technique affect the human gait network at different sites. The spinal "central pattern generator" and the "MLR" are controlled by supraspinal networks and peripheral, sensory feedback from various somatosensory systems (Takakusaki, 2013). In PD, gait network activity is disturbed with activity changes at different sites (Grabli et al., 2012). It is interesting to what extent modulation at peripheral and basal ganglia sites within the gait network affects the clinical outcome.

Barefoot walking has been assessed extensively in the healthy younger and older population. One of the most consistent findings during unshod gait is a reduction of step length and an increase of cadence (Franklin et al., 2015). These findings could be observed in our patients with PD group independent of the DBS mode or gait task, and thus, footwear impacted generally step length and cadence. There are several hypotheses on this kinematic finding when walking with shoes. On the one hand, the increased distal mass of the foot when wearing footwear might induce a higher pendulum effect and inertia during the swing phase (Oeffinger et al., 1999). Another hypothesis is the modulation of sensory feedback by footwear (Franklin et al., 2015) since cutaneous receptors in the feet are assumed to play an important role in gait and postural control (Viseux et al., 2019) according to the gait network model with sensory afferents projecting and modulating the spinal central pattern generators.

To summarize considerations about footwear, it is difficult to advise patients with PD to walk barefoot or with shoes at home or during rehabilitative training sessions, since both gait modes have their specific advantages. Barefoot walking might enhance proprioceptive feedback besides its favorable foot mechanics, foot awareness, or strengthening. Appropriate footwear seems to stabilize gait and can be scientifically used as a vehicle for monitoring gait or to improve FOG by cueing (Barthel et al., 2018b). In terms of gait analysis, one needs to consider footwear as a factor in a longitudinal study with repeated measurements over time.

The effects of DBS have been assessed quite intensively. We found that DBS induced step length increment, gain of relative single support time, and reduction of gait asymmetry depending on the gait task. These quantitative measures are supposed to reflect indirect biomarkers for the clinical phenomenon of FOG

in the interictal phase (O'Day et al., 2020) and indicate potential effects of DBS on FOG.

In previous studies, the effect of STN DBS on gait and FOG was variable (Potter-Nerger and Volkmann, 2013), with gait improvement in about one-third of patients with PD, remaining effective for 3–5 years (Schlenstedt et al., 2017). Recent efforts have been made to stimulate simultaneously the STN and SN (STN+SN DBS) (Weiss et al., 2011a,b, 2013; Scholten et al., 2017). Although the different, simultaneous mechanisms of action of DBS at cellular, populational, and network level are still debated, the overall effect might be a "functional inhibition" since clinically DBS effects are comparable to those of the previous stereotactic lesions. STN+SN DBS was introduced based on the anatomical considerations of dense basal ganglia interconnections to brain stem centers *via* SNr (Nandi et al., 2002), which might play a major role as a final common pathway (Georgiades et al., 2019) in the mediation of gait symptoms and FOG. The inhibitory high-frequency co-stimulation of the SN (Weiss et al., 2011a,b, 2013) was proposed to release the excessive basal ganglia inhibitory tone on the MLR, which in turn mediates the actual gait program to spinal locomotor centers coordinating bilateral lower limb movements (Lewis and Shine, 2016). Another approach was the use of low-frequency DBS within the pedunculopontine nucleus (PPN), which was assumed to reactivate the pathologically suppressed PPN activity within the MLR (Jenkinson et al., 2009; Thevathasan et al., 2018); however, the clinical results remained inconsistent (Thevathasan et al., 2012; Bourilhon et al., 2021), so that this procedure remains an experimental approach.

In our cohort of patients with PD, we assessed STN+SN DBS in postoperative patients in gait tasks with low and high cognitive load. Our results revealed a favorable effect of STN+SN DBS on gait compared to STN DBS as described previously (Weiss et al., 2013). We found improvement in spatial and temporal gait characteristics with STN+SN DBS, which were emphasized in gait tasks with the increased cognitive load as performing dual tasks. This particular improvement in cognitive gait aspects by STN+SN DBS might be due to the role of SNr in cognitive processes since SNr is proposed to be involved in cognitive, attentional control of purposeful movements and gaze to enhance the valuable outcome of the selected action (Sato and Hikosaka, 2002). The projections of the SNr connect not only the caudate nucleus and superior colliculus but also the thalamocortical and brain stem nuclei. These nigral circuits are proposed to be involved in cognitive, attentional control of purposeful movements to enhance the success of the selected action. To further evaluate the beneficial effects of STN+SN DBS in clinical routine, multicenter studies with larger collectives are needed.

In summary, footwear and DBS affect spatial and temporal kinematics of gait. The effect of footwear with the enhancement of step length and decrease of cadence needs to be considered when planning longitudinal studies or rehabilitative training settings. DBS improves gait kinematics, particularly STN+SN DBS is useful in the improvement of gait characteristics in conditions with increased cognitive load. Clinical benefits, side effects, and changes of quality of life in the long term still need to be assessed in more detail.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Ärztekammer Hamburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

For the research project, AG and MP-N contributed to the conception. MH, AG, UH, CG, WH, CM, and MP-N organized the project. MH, AG, UH, WH, CM, and MP-N contributed to the execution of the project. For statistical analysis, AG and MP-N contributed to the design; MH and AG contributed to the execution; MH, AG, and MP-N contributed to the review and critique. For the manuscript, MH and MP-N contributed to the writing of the first draft; MH, AG, UH, CG, WH, CM, and MP-N contributed to the review and critique. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Supplementary Figure 1 | Repeated measures correlations. This method was applied to assess consistencies between the gait parameters velocity **(A–C)**, step length **(D–F)**, cadence **(G–I)**, and single support **(J–L)** in the dual task with shoes and the clinical scores FOG, Berg Balance, and MDS-UPDRS part III at the three DBS conditions (OFF DBS, STN, and STN+SN DBS). Repeated measures correlation (i.e., rmcorr) is a statistical technique for determining the common within-individual association for paired measures assessed on more occasions for multiple individuals (Bakdash and Marusich, 2017). The rmcorr accounts for non-independence among observations using the analysis of covariance (ANCOVA) to statistically adjust for interindividual variability. Unlike simple correlations, rmcorr does not violate the assumption of independence of observations. Colors coded are the single patients at the three DBS conditions. The separate parallel lines show the rmcorr fit for each individual patient. The sign of the rmcorr coefficient (i.e., positive or negative) is indicated by the direction of the common regression slope plotted as an interrupted line. Inset values give the statistics for the corresponding rmcorr.

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People With Parkinson's Disease and Freezing of Gait Show Abnormal Low Frequency Activity of Antagonistic Leg Muscles

Maria-Sophie Breu[1,2], Marlieke Schneider[1,2], Johannes Klemt[1,2], Idil Cebi[1,2], Alireza Gharabaghi[3] and Daniel Weiss[1,2]**

[1] Centre of Neurology, Department of Neurodegenerative Diseases, University of Tübingen, Tübingen, Germany, [2] Hertie Institute for Clinical Brain Research, Tübingen, Germany, [3] Centre for Neurosurgery, Institute for Neuromodulation and Neurotechnology, University of Tübingen, Tübingen, Germany

Objective: Freezing of gait is detrimental to patients with idiopathic Parkinson's disease (PD). Its pathophysiology represents a multilevel failure of motor processing in the cortical, subcortical, and brainstem circuits, ultimately resulting in ineffective motor output of the spinal pattern generator. Electrophysiological studies pointed to abnormalities of oscillatory activity in freezers that covered a broad frequency range including the theta, alpha, and beta bands. We explored muscular frequency domain activity with respect to freezing, and used deep brain stimulation to modulate these rhythms thereby evaluating the supraspinal contributions to spinal motor neuron activity.

Methods: We analyzed 9 PD freezers and 16 healthy controls (HC). We studied the patients after overnight withdrawal of dopaminergic medication with stimulation off, stimulation of the subthalamic nucleus (STN-DBS_{only}) or the substantia nigra pars reticulate (SNr-DBS_{only}), respectively. Patients performed a walking paradigm passing a narrow obstacle. We analyzed the frequency-domain spectra of the tibialis anterior (TA) and gastrocnemius (GA) muscles in 'regular gait' and during the 'freezing' episodes.

Results: In stimulation off, PD freezers showed increased muscle activity of the alpha and low-beta band compared to HC in both TA and GA. This activity increase was present during straight walking and during the freezes to similar extent. STN- but not SNr-DBS decreased this activity and paralleled the clinical improvement of freezing.

Conclusion: We found increased muscle activation of the alpha and lower beta band in PD freezers compared to HC, and this was attenuated with STN-DBS. Future studies may use combined recordings of local field potentials, electroencephalography (EEG), and electromyography (EMG) to interrogate the supraspinal circuit mechanisms of the pathological activation pattern of the spinal pattern generator.

Keywords: Parkinson's disease, EMG, freezing of gait (FOG), low frequency activation, DBS (deep brain stimulation)

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****Correspondence:***
Maria-Sophie Breu
maria-sophie.breu@med.uni-tuebingen.de
Daniel Weiss
daniel.weiss@uni-tuebingen.de

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Abbreviations: DBS, deep brain stimulation; PD, Parkinson's disease; HC, healthy controls; STN, subthalamic nucleus; SNr, substantia nigra pars reticulate; MLR, mesencephalic locomotor region; PMRF, ponto-medullary reticular formation; EEG, electroencephalography; EMG, emelctromyography; ULF, upper limb freezing; TA, tibialis anterior; GA, gastrocnemius; PPN, pedunculo-pontine nucleus; TO, toe-off; HS, heel-strike; MS, midswing; FFT, fast Fourier transform.

INTRODUCTION

Freezing of gait (FoG) in Parkinson's disease (PD) represents the defective spinal motor output depending on the supraspinal cortical, subcortical, and brainstem contributions (Lewis and Shine, 2016; Snijders et al., 2016; Weiss et al., 2020). As such the motor, cognitive, and emotional systems (Shine et al., 2013; Ehgoetz Martens et al., 2018) modulate the effective spinal motor output according to the environmental and internal requirements (Drew et al., 2004; Snijders et al., 2016). In particular, the spinal pattern generator is modulated by the descending drives of the pyramidal tract and the nigro-ponto-reticulospinal pathway (Nutt et al., 2011; Snijders et al., 2016).

The rhythmic alternation of stepping during regular gait is generated in the spinal cord in humans (Guertin, 2009). Historically, early experimental studies in decerebrate cats suggested that the spinal pattern generator generates rhythmic locomotion, even in the absence of supraspinal input. The cats were able to walk, trot and gallop when put on a treadmill, but the gait was mechanical and inflexible (Mori, 1987; Snijders et al., 2016). Further, experimental models found that the descending drives to spinal motor neurons stem from nuclei of the mesencephalic locomotor region (MLR) including the pedunculopontine and cuneiform nucleus and the reticulospinal projections (Jordan et al., 2008; Takakusaki, 2013; Snijders et al., 2016). Previous experimental and clinical research supported that human gait can be modulated both on the level of the substatia nigra, pars resticulate (SNr) based on the monosynaptic GABAergic projection from the SNr (Weiss et al., 2013; Scholten et al., 2017; Heilbronn et al., 2019; Valldeoriola et al., 2019) to the pedunculo-pontine nucleus (PPN) (Ferraye et al., 2010; Garcia-Rill et al., 2019). Experimental research suggested that both dopaminergic depletion and pharmacological des-inhibition increased GABAergic SNr activity resulting in a pro-akinetic net effect (Burbaud et al., 1998; Breit et al., 2006). Instead, pharmacological or electrical SNr inhibition led to prokinetic effects including those on gait (Wichmann et al., 2001; Lafreniere-Roula et al., 2010; Sutton et al., 2013; Milosevic et al., 2018). Experimental research established a reciprocal link between SNr and PPN, showing the reciprocal regulation of single cell activity of the two nuclei (Breit et al., 2001, 2006). In human PD, nigral stimulation modulated clinical and kinematic gait measures (Scholten et al., 2017; Heilbronn et al., 2019) and FoG. Yet, it has to be kept in mind that these conclusions stem from piloting observations and have to be confirmed in larger clinical trials (Snijders et al., 2016; Garcia-Rill et al., 2019; Weiss et al., 2020).

Less so the model work but more the clinical and neurophysiological human PD gait research pointed to the fact that the subthalamo-cortical circuits may be more meaningful in PD gait than was anticipated in experimental work. In particular, patients with L-Dopa sensitive FoG may show considerable therapeutic benefit from subthalamic nucleus deep brain stimulation (STN-DBS) (Schlenstedt et al., 2017; Barbe et al., 2020; Cebi et al., 2020). The STN holds both inhibitory indirect and hyperdirect projections to the primary motor cortex (Delwaide et al., 2000; Gradinaru et al., 2009), and high-frequency stimulation of the STN modulated activity and excitability of the primary motor cortex (Kuriakose et al., 2010; Udupa et al., 2016) as well as of the associated premotor and prefrontal cortical areas (de Hemptinne et al., 2015; Weiss et al., 2015). However, stimulation of the STN does not exclusively act on the subthalamo-cortical circuit, but also entrains brainstem connections including in PD gait (Pötter et al., 2008). The subthalamic contributions to PD gait and freezing phenomena have more recently been highlighted with neurophysiological techniques studying oscillatory activity of STN local field potentials and cortical activity. Traditionally, enhanced broad alpha and beta band activity (8–35 Hz) from STN-LFPs correlated with bradykinesia and rigidity (Brown, 2003; Kühn et al., 2006, 2009) and were suppressed with effective STN-DBS therapy (Kühn et al., 2008; Eusebio et al., 2012). More recent studies linked oscillatory activity with freezing phenomena. As such, PD freezers showed elevated activation around 18 Hz at movement initiation (Storzer et al., 2017) compared to non-freezers. Additionally, pathologically prolonged broad band beta burst duration (Tinkhauser et al., 2017) was associated to freezing, since beta burst duration (13–30 Hz band) was more prolonged in PD freezers compared to non-freezers during regular gait and more pronounced during the freezing episodes (Anidi et al., 2018).

In addition to STN, the cortex is involved in freezing phenomena as indicated from oscillatory activity and cortical stimulation studies, as reviewed elsewhere (Weiss et al., 2019). Briefly, upper limb freezing (ULF) showed enhanced activity around and below 10 Hz during a freeze in the alpha band (Scholten et al., 2016a). Moreover, cortical abnormalities of both cortico-cortical synchronization (Scholten et al., 2016b) and beta band decoupling abnormalities prior to a freeze indicated premonitory cortical susceptibility to freezing (Scholten et al., 2020). There were similar findings in FoG, when cortico-subthalamic decoupling in the low frequency band (4–13 Hz) became evident not only during freezing episodes, but also preceded a freeze (Pozzi et al., 2019). Finally, similar abnormalities were found in the PPN when freezing episodes showed attenuated alpha activity (Thevathasan et al., 2012), and electromyography (EMG) studies showed enhanced activity below 10 Hz in the PD off state in general (Salenius et al., 2002; Weiss et al., 2012). More specific, activity around and below 10 Hz was found in freezers and during ULF, and was suppressed by STN-DBS (Scholten et al., 2016a).

Little is known about the pathological changes in the frequency domain in muscular activity in PD patients when exhibiting FoG. Based on the current literature, we explored muscular activity in broad frequency range from 1 to 45 Hz comprising the above mentioned frequency bands, and compared to healthy controls (HC). Derived from these findings, we further explored if activation abnormalities of the alpha and beta frequency were related to freezing episodes. Then, we used DBS therapy to differentially modulate the basal ganglia contributions to the spinal motor neurons, applying both STN and SNr stimulation, respectively. We posited that – if the supraspinal contribution of each nucleus was relevant to spinal motor activity and FoG – neuromodulation of either target should modulate both the clinical expression of freezing

and the activity of the antagonistic tibialis anterior (TA) and gastrocnemius (GA) muscles.

MATERIALS AND METHODS

Subject Characteristics

We included 16 patients with idiopathic PD and DBS and 16 age- and gender-matched HC. From these, we selected 11 PD patients with clinically confirmed FoG episodes (Snijders et al., 2012). We excluded two further PD patients from analysis, one owing to technical problems during the recording and another owing to the inability to walk during the experimental session. Finally, we analyzed data from 9 PD freezers (3 female, age 66.4 ± 7.2 years) and 16 HC (6 female, age: 58.5 ± 4.6 years). Detailed patient characteristics are given in **Table 1**.

Inclusion criteria were idiopathic PD with akinesia-rigidity type and time since DBS implantation more than 3 months. Exclusion criteria were Mini Mental Status Examination < 22, Beck's Depression Inventory > 13, and other neurological or neuromuscular disease except PD. The local Ethics committee of the University of Tübingen approved the study (application no. 732/2012BO2) and all subjects provided written consent to participate in the study.

Experimental Setup

Paradigm

During the experimental session, patients walked repeatedly on a straight over ground walkway of 9 m forth and back. We installed two obstacles at 1/3 and 2/3 along the hallway to narrow the pathway in order to provoke FoG episodes (Rahman et al., 2008). The patients self-initiated walking and walked in their self-selected, comfortable pace for about 3 min, or at least as long as possible, the minimum walking period analyzed in a single patient was 70 s. All patients walked freely except patient PD2, who wished to use a walking aid uniformly in all therapy conditions. Patients were studied in three stimulation conditions after overnight withdrawal of dopaminergic medication (MedOff). Therefore, we recorded patients in stimulation off ('StimOff'), stimulation of only STN: STN_{only} (briefly 'STN'), and stimulation of only SNr: SNr_{only} (briefly 'SNr'), and the three conditions were delivered in randomized order. Electrode localization of the active contacts was located in the STN (electrode model 3389, Medtronic, Minneapolis, MN, United States), additionally in 8 out of 9 patients the lowermost electrode contact reached the SNr area {at least −5 mm below the midcommisural point [MCP, mean coordinates of the cohort: left SNr: −11.0 (±0.6), −3.6 (±0.4), −7.1 (±0.5), right SNr: 10.3 (±0.5), −3.6 (±0.4), −6.2 (±0.3); left STN: −13.0 (±0.6), −1.4 (±0.4), −3.3 (±0.4); right STN: 12.1 (±0.4), −1.2 (± 0.4), −2.2 (±0.4); (x, y, z)]}, verified by co-registration of the preoperative MRI and postoperative CT images (Brainlab, München, Germany). Patients and experimenters were not blinded, and each stimulation condition was active for at least 20 min prior to the recording in order to achieve sufficient efficacy and to limit carry-over effects (Cooper et al., 2013; Weiss et al., 2013). Since the recordings took place in MedOff, we did not consider longer periods.

Kinematic and Electrophysiological Recordings

During walking, we recorded the synchronized videotapes as well as the kinematic and EMG time series. Therefore, patients wore small, lightweight body-fixed kinematic sensors attached to the left and right ankles (about 20 mm above the malleolus), and to the lumbar spine (APDM, Portland, OR, United States). Data was sampled at 128 Hz and transferred to Matlab (Release R2015b, The Mathworks, Inc., Natick, MA, United States) for the *post hoc* offline analysis. Detailed analyses of the kinematic features and the methodological approach were published elsewhere (Scholten et al., 2017). Briefly, gait kinematics including step length were only analyzed during effective walking, excluding freezing episodes. The events were calculated using the acceleration in the anterior–posterior direction and the angular velocity in the sagittal plane. First we identified the midswing (MS) as peak value exceeding 50°/s in the sagittal plane of the gyroscope signal. Next we identified toe-off (TO) and heel-strike (HS) in the time interval 750 ms before and after MS. TO was defined as minimum anterior–posterior acceleration in the time interval before MS, and HS was defined as the minimum value of angular velocity in the sagittal plane before the maximum anterior–posterior acceleration in the time interval after MS. Using the gait events, we computed temporal and spatial gait outcome measures for each condition.

Furthermore, we recorded bipolar EMG with active surface electrodes (actiCAP active Electrodes, Brain Products, Gilching, Germany) of the bilateral TA and GA muscles. We decided to use active electrodes which enabled the digitization of time series at electrode level and, from there, wireless transmission to the electroencephalography (EEG) recorder (EMG was recorded with an EMG input box connected and synchronized to our EEG-recording system), which helped prevent to expose the time series to cable swinging that would arise during gait (MOVE and active electrodes system, Brain Products, Gilching, Germany). The electrophysiological data was sampled at 1 kHz. Electrodes of the TA were placed 1/3 below the tip of the fibula on an imaginary line connecting fibula and the medial malleolus, the electrodes of the GA were placed over the most prominent bulge of the inner head. We used an inter electrode distance of 20 mm in accordance to the SENIAM Guidelines (Hermens et al., 2000).

Clinical Assessments

All patients reported narrative scores on FoG (NFOG-Q) 1 day prior to the recording. Moreover, we assessed the motor score in UPDRS III in each therapy condition (see **Table 1**). We deduced the objective freezing-related clinical information from the videos and kinematic survey while walking, i.e., number of freezing episodes, absolute time of freezing and the time percentage frozen (absolute time of freezing throughout the walking task over absolute duration of the walking task, see **Table 2**, individual parameters see **Table 3**).

Analyses

Data Segmentation, Preprocessing, and Spectral Analysis

For data analysis we selected the time series while walking straight ahead, and rejected the turning episodes. Next, we segmented for time series related to either 'regular gait' or 'freezing episodes.'

TABLE 1 | Patient characteristics of the final analysis cohort; NFOG-Q, New Freezing of Gait Questionnaire (Seuthe et al., 2021); STN-DBS, deep brain stimulation of the subthalamic nucleus; SNr-DBS, deep brain stimulation of the substantia nigra pars reticulata.

ID	Gender	Age	Disease duration (years)	Months with DBS	Disease dominant side (L/R)	NFOG -Q	Motor score (UPDRS III, item 18–31) OFF/STN/ SNr	MMST	STN-DBS parameters				SNr-DBS parameters			
									Voltage (left/ right)	Frequency (Hz)	pulse width (μs)	Active contacts (left/ right)	Voltage (left/ right)	Frequency (Hz)	Pulse width (μs)	Active contacts (left/ right)
2	M	69	17	13	L	13	49/49/49	27	2.7/3.0	130	60	2–3+/ 10–11+	2.5/2.5	130	60	0–1+/ 8–9+
4	M	64	16	86	L	4	73/40/61	30	5.3/3.0	125	60	2–3+/ 6–7+	3.5/3.5	125	60	0–1+/ 4–5+
5	M	71	16	27	R	4	50/28/x	30	3.6/3.6	130	60	2–3+/ 10–11+	x/x	x	x	x
8	M	64	9	14	R	10	50/28/32	27	2.8/3.5	130	60	2–3+/ 10–11+	2.5/1.9	130	60	0–1+/ 8–9+
9	F	56	21	61	R	4	54/31/40	30	5.5/3.5	130	60	2–3+/ 6–7+	2.9/2.9	130	60	0–1+/ 4–5+
10	M	55	17	4	R	15	48/28/31	28	4/4.5	130	60	2–3+/ 10–11+	2.7/2.7	130	60	0–1+/ 8–9+
13	F	76	13	6	L	6	46/34/41	27	2.1/2.1	125	60	2–3+/ 10–11+	1.6/1.6	125	60	0–1+/ 8–9+
14	F	76	19	10	R	12	38/25/35	28	3.2/2.0	130	60	2–3+/ 10–11+	2.2/2.2	130	60	0–1+/ 8–9+
15	M	67	16	11	R	7	62/28/67	29	5.4/5.1	130	60	2–3+/ 10–11+	1.3/1.3	130	60	0–1+/ 8–9+

In PD 5 electrode contacts did not reach SNr.

TABLE 2 | Freezing characteristics in different therapeutic conditions.

Condition	No of patients	No of freezing episodes	Absolute time frozen (seconds)	Time percentage frozen (%)
Off	4	15	144	39
STN	1	2	23	31
SNr	3	9	172	23

Time percentage frozen is given as median value.

We verified FoG episodes from the video recordings according to the existing consensus definition that defines FoG as 'a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk' (Nutt et al., 2011), including shuffling episodes as well as complete movement arrests. To entirely remove complete freezing episodes from the 'regular gait' time series, we rejected the clinically defined FoG episode and 1 s before the episode.

We filtered the EMG data with a band pass finite impulse response filter from 10 to 200 Hz, notch filtered for the 50 Hz line artifact, and full-wave rectified the EMG time series (Mima and Hallett, 1999).

EMG signals were first partitioned into disjoint segments. Each time segment had a duration of 2 s resulting in a frequency resolution of 0.5 Hz. Every 200 ms the power spectral density of the muscular activity was computed of the segment using the fast Fourier transform (FFT; Matlab fft.m function). The FFT returns for each frequency bin a complex number, from which we extract the amplitude by taking the magnitude squared of this number to obtain the power spectral density expressed in $\mu V2/Hz$. We then averaged over all segments. We report the relative power spectral density after normalizing the absolute values to the summed power from 1 to 45 Hz.

Frequency spectra were computed for TA and GA separately for the left and right leg for PD and HC, as well as for the disease dominant and the non-dominant side separately in PD. Since we did not find statistical differences between the two groups in both comparisons (cluster-based permutation test), we report the average of both legs in all analyses.

Statistical Analysis

Descriptive are given as mean ± standard deviation, except for the time percentage frozen given as median value, due to a non-parametric data distribution.

In the first part of our analysis we aimed to compare frequency spectra from 1 to 45 Hz. We decided to explore a broad frequency range of interest based on the fact that (i) frequency domain analysis in ambulatory EMG has only sparsely been studied before, and (ii) in cortical and basal ganglia showed diverse abnormalities in this broad frequency range with regard to motor symptoms, freezing or cognitive processes including the theta, alpha, and also broad beta band (de Hemptinne et al., 2015; Tinkhauser et al., 2017; Anidi et al., 2018; Fischer et al., 2018; Hell et al., 2018; Pozzi et al., 2019). First we compared the frequency spectrum of PD freezers in 'StimOff' and during 'regular gait' with HC in TA and GA. Furthermore, we compared in PD

TABLE 3 | Single patient description of freezing episodes during straight walking (excluding U-turns at the end of the walkway).

ID	No of FoG Stim Off	No of FoG STN	No of FoG SNr	Absolute Time Frozen (seconds) Stim Off	Absolute Time Frozen (seconds) STN	Absolute Time Frozen (seconds) SNr	Duration single freezing episode (seconds) Stim Off min/max	Duration single freezing episode (seconds) STN min/max	Duration single freezing episode (seconds) SNr min/max	Time percentage frozen (%) Stim Off	Time percentage frozen (%) STN	Time percentage frozen (%) SNr
2	3	2	3	33	23	123	3/17	5/18	7/94	76	31	86
5	1	0	0	3	0	0	3	0	0	37	0	0
8	4	0	5	21	0	38	5/6	0	4/10	21	0	23
13	7	0	1	87	0	11	2/42	0	11	40	0	17

freezers in 'StimOff' the frequency spectra (1–45 Hz) of 'regular gait' and 'freezing' in TA and GA. Then, we analyzed the effect of stimulation of either target (STN_{only}, SNr_{only}, respectively) on muscle activity, comparing the frequency domain spectra of PD freezers in 'regular gait' 'StimOff' with 'STN,' and 'StimOff' with 'SNr' for TA and GA.

For statistical comparison of the frequency-domain spectra, we used a cluster-based permutation test as implemented in the Fieldtrip toolbox to address for multiple comparisons (Maris and Oostenveld, 2007). This test is based on the Monte Carlo permutation principle and identifies significant changes between conditions using clusters of adjacent frequencies. We performed 5000 randomizations and considered an adjusted two-sided alpha level of $p < 0.05$ significant.

Individual Alpha/Low Beta Peak

Based on the results from the spectral frequency-domain analysis we defined the individual alpha/low beta peak frequency for 'regular gait' as well as for 'freezing' episodes in 'StimOff' in PD freezers. We first identified the peak frequency for TA and GA separately in the frequency range of interest as identified in the cluster analyses. Then, we calculated the individual mean alpha/low-beta peak amplitude of the GA/TA peaks. We used the individual peak frequency from 'freezing' episodes in 'StimOff' to extract the individual alpha/low beta power to compare the differences between 'regular gait' and 'freezing' episodes in PD freezers in 'StimOff.' Additionally the individual alpha/low beta power at the individual peak frequency from 'regular gait' in 'StimOff' was used for statistical comparison of 'StimOff' vs. 'STN', and 'StimOff' vs. 'SNr.' Data were non-parametric distributed and statistical differences were analyzed with a Wilcoxon signed ranks test.

Correlation Analyses

We correlated spectral measures (individual peak frequency) with clinical outcome parameters such as: FoG (NFOG-Q, UPDRS III item 14 (freezing episodes), number of freezing episodes during straight walking, percentage frozen during the complete walking paradigm. To evaluate the specificity of the observed associations with FoG, we performed control analysis by correlating the spectral measures of other PD motor symptoms including rigidity (UPDRS III item 22) and bradykinesia of the legs (UPDRS III item 26). Correlations were performed for each condition separately (StimOff, STN, and SNr') and calculated with Spearman tests using SPSS 22.0. All tests were decided on a two-sided significance level of $p < 0.05$.

RESULTS

Frequency Domain Analysis of Muscular Activity

Healthy Controls vs. Parkinson's Disease in 'Stimulation Off'

Parkinson's disease patients in 'StimOff' showed higher power of both the TA and the GA compared to HC in the cluster-based statistical comparison from 1 to 45 Hz during 'regular gait.' In TA, this was represented in the alpha and low-beta range (6–26.5 Hz; $p = 0.0004$). In GA, it covered a broad frequency range from 6.5 to 45 Hz ($p = 0.0004$) (**Figure 1**).

To exclude that the low-frequency cut-off filter < 10 Hz affected our findings, we added a control analysis, i.e., we re-calculated the muscular frequency domain spectra after bandpass filtering from 1 to 200 Hz (refer **Supplementary Figure 1**). Statistical analysis revealed similar results: PD patients in 'StimOff' showed higher power of both the TA and the GA compared to HC in the cluster-based statistical comparison from 1 to 45 Hz during 'regular gait.' In TA, this was represented in the alpha and low-beta range (5.5–26 Hz; $p = 0.0004$), in GA from 6 to 45 Hz ($p = 0.0004$).

We asked next, whether the increased activity increase of the alpha and beta band observed in PD freezers in 'StimOff' was related to FoG or to the PD motor 'off state' more generally. To this end, we studied the spectra in 'StimOff' and compared first the frequency domain spectra between 'regular gait' vs. 'freezing' episodes. Then, we studied whether neurostimulation of STN or SNr modulated the muscular low-frequency activity.

'Regular Gait' vs. 'Freezing Episodes' in 'Stimulation Off'

The frequency domain spectra pointed to higher activity in both TA and GA during 'freezing' episodes compared to 'regular gait' in 4 PD freezers, however, this did not reach statistical significance in the cluster-based comparison of the frequency domain spectra from 1 to 45 Hz (TA: $p = 0.1264$; GA: $p = 0.1204$) (**Figures 2A,B**). When specifically comparing the individual peak maxima of the alpha/low beta frequency range as our main frequency range of interest (6–26.5 Hz as derived from our previous analysis PD StimOff vs. HC), we found higher peak maxima in 'freezing' compared to 'regular gait,' however, again this did not reach statistical significance (TA: $p = 0.250$; GA: $p = 0.375$, Wilcoxon signed rank test) (**Figures 2C,D**).

In further subanalysis we compared 'all freezing episodes', regardless of whether they occurred during regular gait or during a U-turn in 'StimOff' and 'regular gait'. This accounted for 24 freezing episodes in 5 patients and an absolute time frozen of 266 s. Again, the frequency domain spectra pointed to higher activity in both TA and GA during 'all freezing episodes' compared to 'regular gait,' however, this did not reach statistical significance in the cluster-based comparison of the frequency domain spectra from 1 to 45 Hz (TA: $p = 0.7030$; GA: $p = 0.2244$) (**Figures 2E,F**).

'Subthalamic Nucleus' or 'Substantia Nigra Pars Reticulate' vs. 'Stimulation Off'

Next, we studied whether muscular activity during 'regular gait' in 'StimOff' was modulated by either 'STN' or 'SNr' stimulation. STN showed lower activity in TA between 5 and 21 Hz and in GA from 7 to 23 Hz, however this did not reach statistical significance in the cluster-based comparison from 1 to 45 Hz ('StimOff' vs. 'STN': TA: $p = 0.6111$, GA: $p = 0.8362$; 'StimOff' vs. 'SNr': TA: $p = 0.3639$, GA: $p = 0.1784$) (**Figures 3A–D**).

As derived from the contrast PD StimOff vs. HC, we further analyzed as additional non-parametric analysis the individual

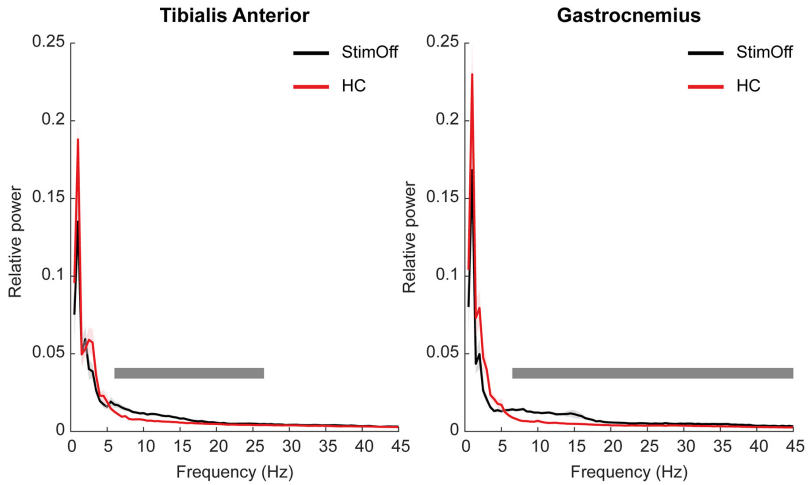

FIGURE 1 | Power spectrum and standard error of the mean (SEM) of TA (**A,** left panel) and GA (**B,** right panel) during 'regular gait' in 9 PD patients with DBS turned off ('StimOff') and healthy controls (HC). PD patients in 'StimOff' showed higher power of TA in the alpha and low-beta range (6–26.5 Hz; $p = 0.0004$) and a higher power in the GA muscle (6.5–45 Hz; $p = 0.0004$, cluster based permutation test).

peak maxima from 6 to 26.5 Hz. We found that 'STN' (TA: $p = 0.015$, GA: $p = 0.015$, Wilcoxon signed rank test), but not 'SNr' (TA: $p = 0.093$, GA: $p = 0.161$) decreased the peak maxima in the alpha/low-beta range in both TA and GA compared to 'StimOff' (**Figures 4A–D**).

Correlations of Alpha/Low-Beta Peak Maxima With Clinical Motor Scores and Freezing of Gait Measures

We correlated the individual alpha/low beta peak maxima in 'StimOff' with clinical measures of FoG and control variables. As freezing measures there was a correlation of time percentage frozen and the alpha/low-beta peak maxima of the GA in 'StimOff' ($r = 0.763$, $p = 0.017$, uncorrected; **Figure 5**) but not of the TA ($p = 0.631$). There was no correlation of NFOG-Q (TA: $p = 0.439$; GA: $p = 0.841$), UPDRS III freezing (item 14) (TA: $p = 0.489$, GA: $p = 0.768$), and the number of FoG episodes (TA: $p = 0.452$, GA: $p = 0.965$). As control analyses, we did not find correlations with rigidity (UPDRS III item 22) (TA: $p = 0.795$, GA: $p = 0.931$) and diadochokinesia (UPDRS III item 26) (TA: $p = 0.628$, GA: $p = 0.742$).

Gait Characteristics

On average, HC walked for 198 ± 55 s (mean ± standard deviation) with a cadence of 105 ± 10 steps per minute and a step length of 0.46 ± 0.05m. PD patients in 'StimOff' walked on average 126 ± 53 s with a cadence of 106 ± 16 steps per minute and a step length of 0.23 ± 0.09 m. In 'STN,' PD patients walked on average 157 ± 36 s with a cadence of 101 ± 15 steps per minute and a step length of 0.28 ± 0.08 m. In 'SNr,' PD patients walked 151 ± 57 s, with a cadence of 108 ± 18 steps per minute, and a step length of 0.21 ± 0.08 m.

We performed a statistical comparison that revealed significant differences in stride length between HC and PD in 'StimOff' ($p = 0.00006$, Mann–Whitney-*U*-Test). Since gait speed is known to have an impact on additional kinematic parameters (Fukuchi et al., 2019), we additionally calculated the over ground walking speed in HC: 0.7 ± 0.1 m/s, and in PD in 'StimOff': 0.4 ± 0.1 m/s ($p = 0.00007$, Mann–Whitney-*U*-Test), which also differed significantly between the two groups. These kinematic differences might also affect underlying electrophysiological differences between HC and PD in 'StimOff.' Therefore, we correlated individual gait speed to (i) the frequency of the individual alpha peak ($\rho = -0.51$, $p = 0.16$) and (ii) to the relative power of the individual alpha peak (both muscles: $\rho = -0.42$, $p = 0.26$; TA $\rho = -0.07$, $p = 0.87$; GA ρ: -0.45, $p = 0.13$). All correlations were negative and do not suggest that lower EMG power relates to gait speed.

DISCUSSION

In this study, we studied PD freezers while walking with ambulatory EMG-recordings of the antagonistic leg muscles. We found that PD freezers showed enhanced activity of TA and GA in a low frequency range of alpha and beta band, presumably in both TA and GA compared to HC during regular walking. Furthermore PD freezers showed a similar activation profile during regular walking and actual freezes. Interestingly, STN stimulation decreased this pathological activity together with improved clinical outcomes in freezing.

Pathological Muscular Activity and Its Relation to Freezing in Parkinson's Disease

In healthy people EMG activity of hand movement and fine motor task is mostly located in the beta band (15–30 Hz) or Piper rhythm (35–60 Hz) (Brown, 2000), in contrast to PD patients, who showed predominant activation around or below 10 Hz in EMG in dopaminergic off state. Effective L-Dopa or STN-DBS therapy lead to suppression of this pathological activity (Salenius et al., 2002; Weiss et al., 2012). However, the relation of these activation abnormalities to PD gait remained unknown.

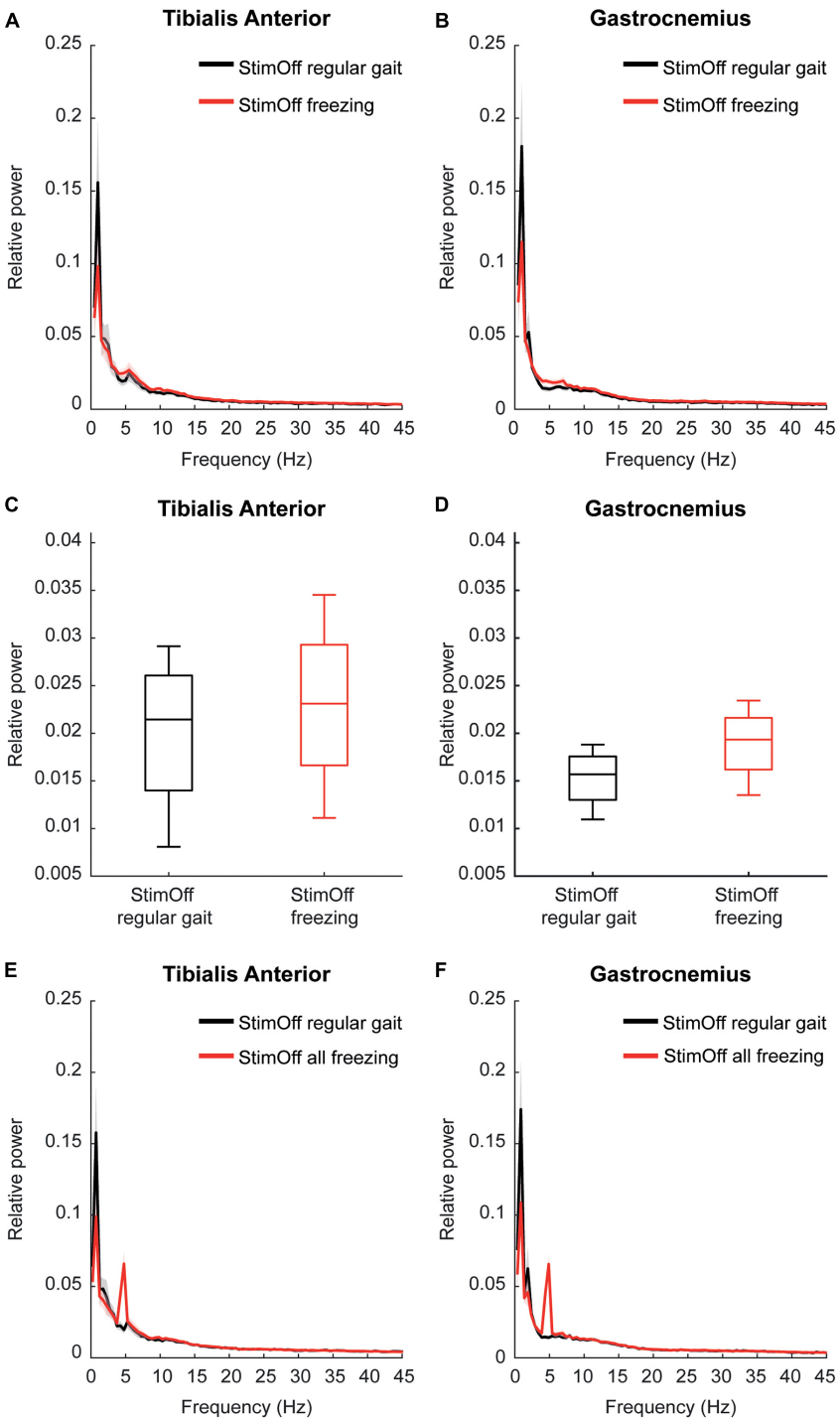

FIGURE 2 | (A,B) Power spectrum and SEM of TA (upper left panel) and GA (upper right panel) in 4 PD patients with 'StimOff' comparing 'regular gait' and 'freezing.' Freezing episodes showed higher median power in TA and GA between 5 and 10 Hz, however, this difference did not show significance and has to be considered with caution owing to the limited number of patients showing freezing episodes during straight walking. **(C,D)** Alpha/low-beta power observed in 'StimOff' during regular gait and freezing episodes in TA (middle left panel) and GA (middle right panel). There was no significant difference between the two conditions. Data is presented in boxplots giving the median, 25, 75th percentile, min and max. **(E,F)** Power spectrum and SEM of TA (lower left panel) and GA (lower right panel) in 5 PD patients with 'StimOff' comparing 'regular gait' and ' all freezing' episodes. Freezing episodes showed higher median power in TA and GA between 5 and 10 Hz, however, this difference did not show significance and has to be considered with caution owing to the limited number of patients showing freezing episodes. Please note the prominent peak at 5 Hz in TA and GA. Visual inspection of the video recordings as well as of the EMG raw data did not reveal tremor-associated activation. Further, the individual frequency spectra of the 5 subjects did not show similar peak activation but a broader low-frequency activation band known from freezing episodes (Moore et al., 2008; Vercruysse et al., 2012) as opposed to tremor that occurs in a stable circumscribed frequency bin in the individual subject.

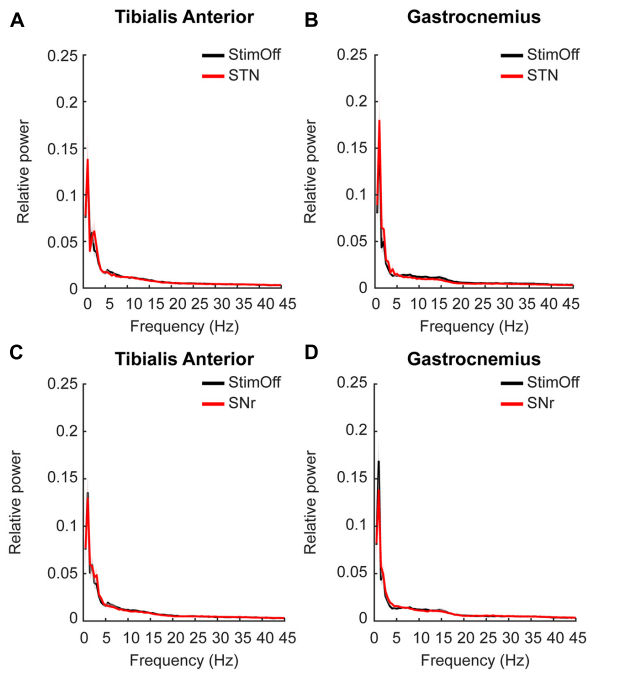

FIGURE 3 | (A,B) Power spectrum and SEM of TA (upper left panel) and GA (upper right panel) during 'regular gait' in PD patients with 'StimOff' vs. 'STN'. There was no significant difference in the power spectra of the two conditions. **(C,D)** Power spectrum of TA (lower left panel) and GA (lower right panel) during 'regular gait' in PD patients with 'StimOff' vs. 'SNr.' There was no significant difference in the power spectra of the two conditions.

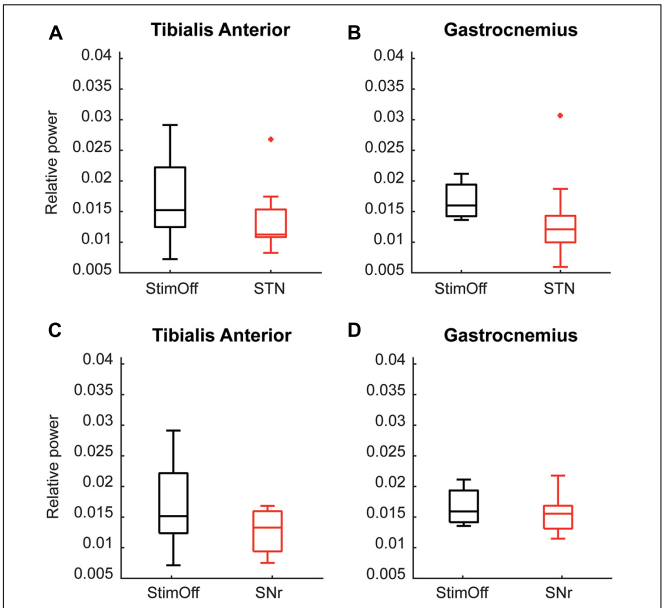

FIGURE 4 | (A,B) Data is presented in boxplots giving the median, 25th, 75th percentile, min and max. Alpha/low beta power observed in 'StimOff' can be significantly lowered by 'STN' in both the TA (upper left panel, $p = 0.015$) and GA (upper right panel, $p = 0.015$). **(C,D)** Data is presented in boxplots giving the median, 25th, 75th percentile, min and max. There was no significant difference of the alpha/low beta power observed in 'StimOff' vs. 'SNr' in both the TA (lower left panel) and GA (lower right panel). $^{+}$Indicates statistically significat differences.

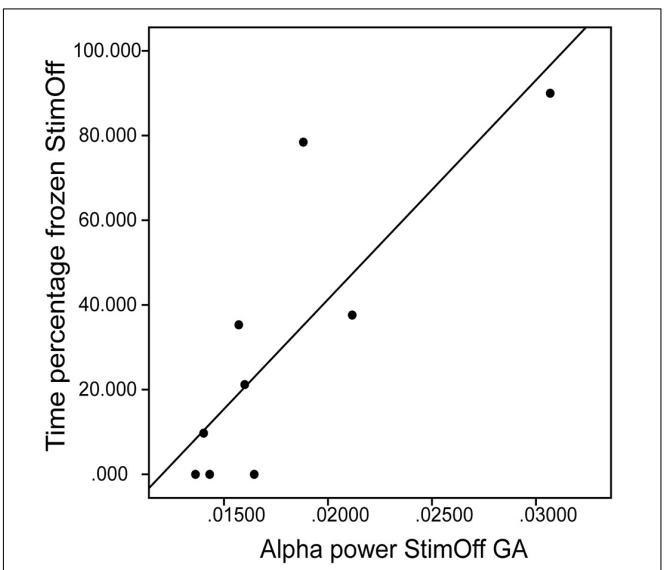

FIGURE 5 | Correlation between the alpha/low beta peak maxima of the GA (*x*-axis) and the time percentage frozen in 'StimOff' ($r = 0.763$, $p = 0.017$). Higher alpha/low beta peak maxima are associated with longer freezing duration.

We found that PD freezers show elevated activity from 6 to 45 Hz in the antagonistic leg muscles during effective regular gait, and this was centered in the low frequency range of the alpha and low beta bands. This was present during both regular gait and during the freezes to similar extent. Since the activity was not specific to the freeze itself but existed already during preserved gait, muscular activation at lower frequency around and below 10 Hz may be a general feature of the PD off state mirroring pathological supraspinal activation patterns on the level of the spinal cord (Salenius et al., 2002; Weiss et al., 2012; Flood et al., 2019).

Nevertheless, the finding raises considerations on whether activation at lower frequency contributes to freezing, such that it could represent a more unstable motor system which yields susceptibility to encounter freezing episodes (Scholten et al., 2016b). Activation abnormalities around and below 10 Hz were identified as a pathological feature of the multistage locomotor network comprising cortex (Marsden et al., 2001; Scholten et al., 2016a), basal ganglia (Hammond et al., 2007; de Solages et al., 2010; Chen et al., 2019), brainstem (Thevathasan et al., 2012), and spinal pattern generator (Marsden et al., 2001; Weiss et al., 2012; Scholten et al., 2016a). From these data and the present study it is plausible to reason that these activation abnormalities relate to freezing, since freezers show premonitory activation abnormalities already outside or immediately preceding a freeze in contrast to non-freezers (Singh et al., 2013; Toledo et al., 2014; Storzer et al., 2017). Instability of the motor system may be a pre-requisite to freezing there mirroring the susceptibility of a PD patient to loose effective spinal motor output (Scholten et al., 2016b, 2020). During a freeze itself, the pathological rhythm can either stay unchanged or even increase (Scholten et al., 2016a; Anidi et al., 2018; Chen et al., 2019; Pozzi et al., 2019).

In this sense, we speculate that low-frequency activation of the spinal pattern generator of PD freezers could be interpreted as an abnormally slow and prominent rhythm. This might oppose the rapid adjustment of antagonistic muscle activity as is needed for the recurrent cycling of activation and deactivation cascades throughout the cyclic gait phases. Mathematically spoken, motor output in the high beta and gamma range > 20 Hz would allow for much faster reprogramming and adaptation of the spinal pattern generator (Schoffelen et al., 2005) as opposed to the activation abnormalities at slower rhythms observed in this freezer group. This would lead – depending on the individual cadence – to a much slower adaptation and also performance of the alternating activation – deactivation changes of the antagonistic leg muscles throughout the full gait cycle, which can only interact in the slow alpha and low-beta rhythms in PD. In healthy subjects activation of the TA will take for about 10% of the gait cycle, from initiation to full recruitment (Hart et al., 2006). Considering a cadence of around 105 steps per minute in our cohort of healthy controls indicates a duration of the gait cycle of 0.57 s and a necessity of adaptions within 57 ms. The prominent slow alpha and low-beta rhythms in PD patients will not allow for more than a temporal resolution of around 50–100 ms, which is inherently slow to allow rapid adjustments of the gait cycles and leads to abnormal temporal activation patterns in PD freezers (Nieuwboer et al., 2004). Moreover, the ability to adapt gait to the external or internal requirements is limited at such slow frequencies, and this may comply with the clinical observation that gait performance can be disrupted with cognitive interference (Nutt et al., 2011; Nonnekes et al., 2015). Instead, it was stabilized with rhythmic cueing, as was the oscillatory beta activity time-locked to the gait cycle (Fischer et al., 2018).

Besides the enhanced alpha and low beta activity our data also reveal higher power spectra > 20 Hz in GA, which could be due to (i) either postural differences in PD patients, caused by a more flexed posture (Nieuwboer et al., 2004) and a tendency to shift the center of gravity forward when walking, resulting in toe walking or (ii) reflect compensatory mechanisms caused by cortical drives to the spinal cord which are located in a higher frequency range (Schoffelen et al., 2005). To this point it is rather difficult to disentangle whether this high frequency activation in GA is a causal or compensatory mechanism in the first place.

Subthalamic Stimulation Reduces Muscle Activation at Low Frequencies and Clinical Freezing Outcomes

Subthalamic nucleus -stimulation in PD is a potent treatment for L-Dopa sensitive FoG. Clinical studies reported on reduced occurrence of FOG and sever falls in PD freezers after undergoing STN-DBS (Schlenstedt et al., 2017; Barbe et al., 2020; Cebi et al., 2020). However, to prevent adverse outcomes of STN-DBS it is important to avoid co stimulation of the pallido-thalamic tract crossing on the level of the zona incerta as was for example found in antero-medially displaced electrodes or by delivering large amounts of energy and increasing the electrical field (Moreau et al., 2008; Fleury et al., 2016). When applying effective STN-stimulation along with clinical improvement also pathological changes of gait parameters in PD freezers, such as stride length and stride amplitude improve (Pötter-Nerger and Volkmann, 2013; Scholten et al., 2017). Notably, high frequency stimulation of the STN also led to a reduction of beta-band activity in STN-LFPs. In our experiment the kinematic parameters do not reveal significant differences between 'STN' and 'StimOff.' Scholten et al. (2017) report results of a larger group of PD freezers in which gait parameters, temporal and spatial, showed improvement with STN- or SNr-stimulation. Especially the stride length improved when applying STN-DBS. In the subgroup we choose for our data analysis also the stride length improves in STN-condition, but the changes are not statistically significant, probably due to the smaller size of the cohort. Additionally also the absolute number of freezing episodes across subjects and the absolute time frozen improved when we applied STN-DBS in contrast to the 'StimOff'-condition, and this clinical improvement was associated with a reduction of pathological activity at low frequency in TA and GA. The modulation effect on oscillatory patterns of STN-DBS is not locally limited to the STN, but may impact on the functionally connected areas, in particular the subthalamo-cortical circuits (de Hemptinne et al., 2015; Weiss et al., 2015). On the one hand STN has an excitatory net effect on SNr and GPi, resulting in more inhibitory control on PPN/MLR which was brought in context to FoG (Shine et al., 2013; Weiss et al., 2019). STN-DBS is attenuating the exaggerated glutamatergic output (Benabid et al., 2003) and the pathological beta oscillations (Kühn et al., 2008; Eusebio et al., 2012). This means that STN-DBS could potentially act on releasing the pallidothalamic inhibition of the primary motor cortex, or by modulating the cortex more directly via the hyperdirect connections. However, toning down pathological STN activity could also change SNr activity through the monosynaptic connections (Milosevic et al., 2018; Weiss et al., 2019). Thus, observing a change of muscular activity with STN-DBS would not necessarily mean that the effect is transmitted via the 'ascending' cortical and then corticospinal pathway, but would still allow for contributions of the 'descending' nigropontine route. However, our second finding that SNr_{mono} stimulation did not affect both muscular activity and clinical FoG measures argues against this alternative interpretation. Therefore, we propose that the primary effect of high-frequency STN-DBS was delivered via the subthalamo-cortical circuits of either the indirect or the hyperdirect pathway – or maybe both (Gradinaru et al., 2009; de Hemptinne et al., 2015). STN holds projections via the subthalamo-pallido-cortical 'hyperdirect' and the striato-external pallido-subthalamo-internal pallido-cortical 'indirect' pathway, both executing inhibitory control on thalamo-cortical activation patterns and preventing effective motor output (Delwaide et al., 2000). STN-DBS can effectively modulate the oscillatory patterns of cortical areas via these pathways and electrophysiological changes are accompanied by improved clinical outcome parameters (Kuriakose et al., 2010; de Hemptinne et al., 2015; Weiss et al., 2015). Considering the fact that in our experiment clinical as well as oscillatory improvements were achieved via STN-DBS, but not SNr-DBS, it seems reasonable to consider the underlying pathological

enhance alpha and low beta activity also being primary transmitted via the subthalamo-cortical pathway and the descending projections of the pyramidal tract to spinal motor neurons. Further support for this hypothesis comes from studies on the pathology of ULF, when freezing episodes were associated with increased cortical activity (7–11 Hz), muscular activity (6–9 Hz), and increased intermuscular coherence, the latter of which was proposed as marker for cortical control of muscular activity (Scholten et al., 2016a). Nevertheless, cortical contributions do not exclude subcortical contributions to muscular activation at low frequencies. Future research using combined EMG-LFP-EEG measurement in gait paradigms will help to further investigate the underlying network interactions of pathological activation pattern in FoG (Kühn et al., 2009; Lewis and Barker, 2009; Anidi et al., 2018; Pozzi et al., 2019). Especially high resolution time-frequency analyses of LFP-EEG data could help differentiate a primary cortical or subcortical source of the muscular activation abnormalities of the alpha and beta band.

Methodological Considerations

In this study, we investigated the role of muscular activation abnormalities at alpha and beta frequencies for FoG taking advantage from ambulatory EMG recordings, and studied their supraspinal modulation with STN- and SNr-DBS. We were able to analyze data from a very homogenous group of finally 9 PD freezers with an acinetic-rigid subtype, susceptibility of FoG and electrode localization of the most caudal contact being located in SNr, a group size comparable to those of previous electrophysiological studies (Anidi et al., 2018; Pozzi et al., 2019). Although observing a large quantity of freezes under laboratory conditions has been recognized as a challenge in FoG research (Lewis and Shine, 2016; Weiss et al., 2019) we were able to gather an absolute time of 144 s frozen in 'StimOff,' which can be considered sufficient data material to stabilize the frequency domain spectra from a statistical viewpoint (Mima and Hallett, 1999). A limitation is that the data of freezing episodes stem from only 5 of the 9 subjects which limits the interpretation and generalizability of comparing the spectra of the freezing state with regular gait. The same applies for comparisons of clinical features, i.e., number of freezing episodes, absolute time frozen, etc. The descriptive indicate a marked reduction of freezing, considering the number of patients expressing FoG (4 in 'StimOff,' 1 in 'STN'), the number of freezing episodes (15 in 'StimOff,' 2 in 'STN') and the absolute time frozen (144 s in 'StimOff,' 50 s in 'STN'). Still the subgroup is quite small and performing a Wilcoxon signed rank test would not show statistical significant improvement. But we were therefore careful in interpreting our finding, and suggest to leave it to future studies to test, whether muscular activity shows a further increase during freezes as compared to regular gait. Nevertheless, the above summarized evidence across the distributed freezing-network levels draws a coherent picture that activation around and below 10 Hz in basal ganglia, brainstem, cortex, and spinal motor neurons is critical to freezing susceptibility, i.e., representing a general failure of neuronal gait integration in PD freezers that yield a risk for expressing freezing episodes on this grounds.

We performed several correlation analyses of clinical measurements and electrophysiological parameters. There was no correction for multiple comparisons, since we performed the correlation analysis with exploratory intent and did not interpret them in a confirmatory way. Instead, we suggest to reproduce these findings in independent and larger cohorts.

CONCLUSION

Here, we demonstrated with ambulatory EMG that PD freezers in medication off and stimulation off show abnormal activation of alpha and low-beta band activity when compared with healthy subjects. This was not specific to the freezing state. However, our findings and the context to the available research support that activation abnormality contributes to freezing susceptibility, since STN-DBS decreased the muscular activity together with clinical improvement of FoG. Since we found that STN-DBS but not SNr-DBS was effective to suppress this low-frequency activity, it is likely that the cortical projections of the STN – rather than the brainstem connections albeit not being exclusive – were meaningful to this effect. Future combined LFP-EEG-EMG research may shed further light on the neuronal supraspinal contributions to muscular activation abnormalities.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: privacy policy of individual patients' data. Requests to access these datasets should be directed to DW, daniel.weiss@med.uni-tuebingen.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik-Kommission am Universitätsklinikum Tübingen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS, AG, and DW: conception and design of the study. MS and JK: acquisition of data. IC: patient inclusion. MS, M-SB, and DW: analysis and interpretation of data. M-SB and DW: drafting the manuscript. All authors: critical revision and final approval of the version to be submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2021.733067/full#supplementary-material

Supplementary Figure 1 | Power spectrum and standard error of the mean (SEM) of TA **(left panel)** and GA **(right panel)** during 'regular gait' in 9 PD patients with DBS turned off ('StimOff') and healthy controls (HC) after band pass filtering of 1–200 Hz. PD patients in 'StimOff' showed higher power of TA in the alpha and low-beta range (5.5–26 Hz; $p = 0.0004$) and a higher power in the GA muscle (6–45 Hz; $p = 0.0004$, cluster based permutation test).

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REVIEW
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Review—Emerging Portable Technologies for Gait Analysis in Neurological Disorders

Christina Salchow-Hömmen[1], Matej Skrobot[1], Magdalena C. E. Jochner[1], Thomas Schauer[2], Andrea A. Kühn[1,3,4,5] and Nikolaus Wenger[1]*

[1] Department of Neurology With Experimental Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany, [2] Control Systems Group, Technische Universität Berlin, Berlin, Germany, [3] Berlin School of Mind and Brain, Charité–Universitätsmedizin Berlin, Berlin, Germany, [4] NeuroCure Clinical Research Centre, Charité–Universitätsmedizin Berlin, Berlin, Germany, [5] German Center for Neurodegenerative Diseases, DZNE, Berlin, Germany

The understanding of locomotion in neurological disorders requires technologies for quantitative gait analysis. Numerous modalities are available today to objectively capture spatiotemporal gait and postural control features. Nevertheless, many obstacles prevent the application of these technologies to their full potential in neurological research and especially clinical practice. These include the required expert knowledge, time for data collection, and missing standards for data analysis and reporting. Here, we provide a technological review of wearable and vision-based portable motion analysis tools that emerged in the last decade with recent applications in neurological disorders such as Parkinson's disease and Multiple Sclerosis. The goal is to enable the reader to understand the available technologies with their individual strengths and limitations in order to make an informed decision for own investigations and clinical applications. We foresee that ongoing developments toward user-friendly automated devices will allow for closed-loop applications, long-term monitoring, and telemedical consulting in real-life environments.

Keywords: motion tracking, human kinematics, locomotion, postural control, wearables, digital image processing, Parkinson's disease, multiple sclerosis

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****Correspondence:***
Christina Salchow-Hömmen
christina.salchow@charite.de

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1. INTRODUCTION

The widespread application of technologies for gait analysis has contributed greatly to our current understanding of healthy and pathological locomotion (Celik et al., 2021). On one hand, instrumented gait analysis complements the quantification of long-established clinical scales [e.g., Berg Balance Scale (Berg et al., 1989), Timed-up-and-go test (Podsiadlo and Richardson, 1991)] and patient self-reports [e.g., Freezing of Gait Questionnaire (Giladi et al., 2000)]. On the other hand, portable technologies for gait analysis may improve diagnosis, follow-up, and treatment of gait disorders through continuous monitoring in activities of daily living (Tzallas et al., 2014; Filli et al., 2018; Ancona et al., 2021). In concert with functional neuroimaging and neuromodulation, gait analysis technologies can enhance our knowledge of healthy and pathological gait function (Maetzler et al., 2009; Artusi et al., 2018; Buckley et al., 2019).

Gait and postural control disorders in the context of neurological diseases, such as Parkinson's Disease (PD) and Multiple Sclerosis (MS), have an immense impact on affected people's quality of life (Snijders et al., 2007). Parkinson's Disease is the second most common neurodegenerative disease in the elderly in Europe (Deuschl et al., 2020). Patients frequently suffer from slow

movements (bradykinesia), pathological gait patterns including reduced step length and freezing of gait (FoG) (Nutt et al., 2011), as well as difficulties in postural control (Schlenstedt et al., 2016). Numerous publications have shown that gait parameters extracted with optical motion capturing, force plates, or inertial sensors correlate with clinical assessments of disease severity and levodopa responsiveness in PD (Horak and Mancini, 2013). In patients with MS, leg paresis, loss of coordination, and spasticity often manifest as gait dysfunction and changes in balance control (Comber et al., 2017). MS related gait and balance impairments can occur at very early disease stages, however, so minor that they may be difficult to see with the bare eye (Kieseier and Pozzilli, 2012). Advanced movement analysis techniques can measure these subtle changes and could be used to identify the risk of mobility loss (Shanahan et al., 2018). In this narrative review on gait analysis technologies in neurological disorders, we will discuss PD and MS as illustrative examples because of their distinct gait characteristics and clinical relevance in different age groups.

Recently, there has been a growing research interest in contact-free human motion tracking with available clinical equipment (e.g., standard camera) using machine learning (ML). Telemedical patient care options play an increasing role in times of global pandemics (Sibley et al., 2021). Therefore, the literature published on the topic of reliable, easily accessible, and easy to use measurement systems for gait and balance analysis is extensive and can be overwhelming. This narrative review aims at building a technical understanding of emerging portable gait analysis technologies for neurological disorders, which can be classified into non-wearable and wearable devices (*wearables*) (de-la Herran et al., 2014). Our goal is to enable the reader to understand the strengths and limitations of available technologies and thereby support decision-making for planning applications in research and diagnostics. After briefly introducing gait and postural control measures, wearable and recent non-wearable systems from the last decade are discussed in detail for their functionality, usefulness, and usability in practice. Future applications and trends are identified.

2. MEASURES OF GAIT AND POSTURAL CONTROL

2.1. Gait Measures

Gait results from cyclical limb movement. For its analysis, parameters are often defined in the dimensions time and space, as illustrated in **Figure 1**. Despite the two displayed main phases, stance phase and swing phase, the gait cycle can be divided into up to eight phases with regard to leg position, foot position, and load (namely initial contact, loading response, mid stance, terminal stance, pre-swing, initial swing, mid swing, and terminal swing) (Taborri et al., 2016). Resulting spatiotemporal features such as gait cycle and gait velocity are commonly expressed as the average of several strides. Dynamic features of gait represent the stride-to-stride variability of these measures in the form of intra-subject standard deviation or coefficient of variation (Lord et al., 2013; Buckley et al., 2019). Further variables can be extracted such as parameters in the frequency domain or sub-task-specific parameters, e.g., the rotational velocity of turns (Horak and Mancini, 2013). The evaluation of sub-tasks in standard clinical tests may be relevant for investigating specific symptoms. For example, sequential tasks of turning and passing through narrow doors have been designed to provoke episodic FoG symptom in PD (Ziegler et al., 2010; Reches et al., 2020). In addition, kinematic parameters such as knee joint angles or range of motion (ROM) as well as kinetic parameters such as ground reaction forces (GRF) can be extracted from certain portable systems to monitor disease progression (Baker, 2013; Veeraragavan et al., 2020). A list of frequently reported gait and balance parameters is presented in **Table 1**.

With the high amount of redundant and covariant available parameters from instrumented gait analysis, methods have been suggested to summarize parameters for better interpretation: For example, the *Gait Variability Index* (GVI) was introduced by Gouelle et al. (2013) combining nine weighted gait parameters based on results of a principal component analysis (PCA) in comparison with a reference group. Morris et al. (2017) proposed a model of unrestricted gait based on data from wearables on 103 elderly controls and 67 PD patients. Four gait domains were derived from 14 gait parameters by applying a PCA: pace, rhythm, variability, and asymmetry. Further models are summarized in Celik et al. (2021). Although simplifying the complexities of instrumented gait assessment would be helpful, the prevalence of these higher-order parameters in clinical trials has been low to date, possibly due to the complexity of their analysis and interpretation.

Since the number of kinematic gait analysis technologies has grown excessively in recent years, we focus on the assessment of kinematic parameters in this review. However, additional investigations of the phasic contribution of muscles in a gait cycle can be obtained from surface electromyography (EMG), integrated into many studies on human locomotion and neurological disease characteristics (e.g. Winter, 1989; Mickelborough et al., 2004; Gnther et al., 2019; Cofré Lizama et al., 2020). A detailed overview of standardized clinical tasks and protocols for the assessment of gait, such as the timed 10m walking test or the timed-up-and-go test (TUG), can be found in Graham et al. (2008) or de-la Herran et al. (2014).

2.2. Balance Measures

Depending on the measurement modality, either the center of pressure (COP) or the center of mass (COM) is tracked in balance assessments during standing in different conditions (Buckley et al., 2019). Often utilized conditions are standing on hard surfaces vs. foam surfaces [modified clinical test of sensory interaction on balance (Horn et al., 2015)] or eyes-open vs. eyes-closed. Multiple parameters are determined describing the displacement of COP or COM over a defined amount of time as illustrated in **Figure 2**. Postural sway captures the horizontal acceleration of the person's center in all directions, most often in the mediolateral and anterior-posterior planes. Typically, sway area, sway range, sway velocity, and jerk, defined as the smoothness of the trunk sway (rate of change), are extracted and

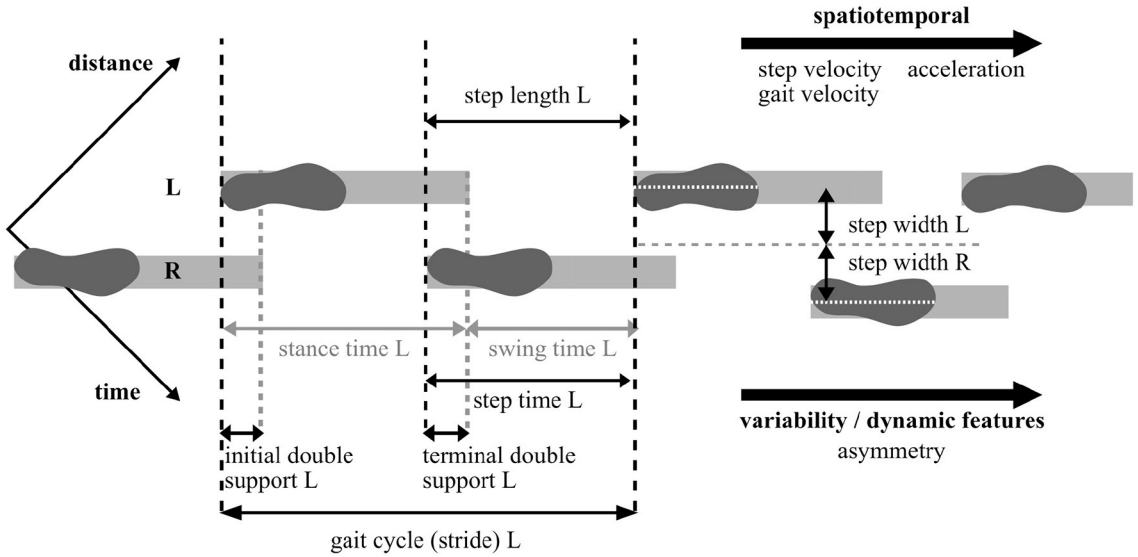

FIGURE 1 | Illustration of basic spatiotemporal and dynamic gait parameter definitions. Note that the footprint indicates the heel strike event. L, Left foot; R, Right foot.

TABLE 1 | Examples of commonly derived measures of gait and postural control from instrumented analysis technologies.

Parameter	Unit	Examples PD	Examples MS
Spatiotemporal, kinematic gait parameters			
Gait cycle / stride duration	s, ms	Blin et al., 1990; Ginis et al., 2017; Shah et al., 2020	Benedetti et al., 1999; Straudi et al., 2013; Müller et al., 2021
Cadence	steps/min	Curtze et al., 2015; Horak et al., 2016; Iijima et al., 2017	Martin et al., 2006; Straudi et al., 2013; Leone et al., 2018
Gait velocity / speed	m/s, cm/s	Herman et al., 2014; Galna et al., 2015; Fino and Mancini, 2020	Benedetti et al., 1999; Remelius et al., 2012; Müller et al., 2021
Stride / step length	m	Rochester et al., 2014; Ferrari et al., 2016; Cebi et al., 2020	Martin et al., 2006; Remelius et al., 2012; Leone et al., 2018
Double support time	% cycle, % stride	Blin et al., 1990; Curtze et al., 2015; Shah et al., 2020	Benedetti et al., 1999; Straudi et al., 2013; Leone et al., 2018
Stride / step time variability	s	Herman et al., 2014; Galna et al., 2015; Ma et al., 2020a	Moon et al., 2015; Allali et al., 2016; Kalron et al., 2018
Knee (lower leg) ROM	degree	Dewey et al., 2014; Curtze et al., 2015; Horak et al., 2016	Rodgers et al., 1999; Filli et al., 2018; Valet et al., 2021
Postural stability parameters			
Postural sway area / range	m/s, cm	Mancini et al., 2012a; Dewey et al., 2014; Horak et al., 2016	Spain et al., 2012; McLoughlin et al., 2014; Solomon et al., 2015
Postural sway jerk	m^2/s^5	Mancini et al., 2012a; Dewey et al., 2014; Horak et al., 2016	Sun et al., 2018; Arpan et al., 2020; Gera et al., 2020
RMS amplitude	m/s, cm	Mancini et al., 2012b; Nantel et al., 2012; Chen et al., 2018	Sun et al., 2018; Santinelli et al., 2019; Arpan et al., 2020

RMS, Root mean square.
Three exemplary publications are listed for each parameter. Note that the exact parameter definition might vary between references.

analyzed regarding asymmetry and variability between different conditions (Martinez-Mendez et al., 2012).

Balance and gait may represent independent domains of mobility in neurological diseases (Horak et al., 2016). Thus, no single measure of either balance or gait can fully characterize mobility impairments, although gait parameters facilitate statements on the balance capabilities of a person. Longer stance phases, expanded step width and deviations from walking a straight line were reported in people with balance disorders (Spain et al., 2014; Diaz et al., 2020).

2.3. Measures/Biomarkers in PD

Parkinsonian gait differs from the gait of the healthy elderly even in the early stages of the disease as revealed by kinematic

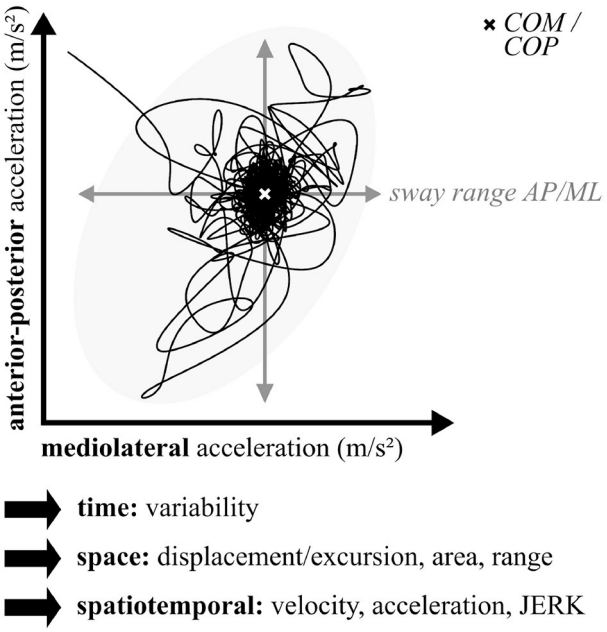

FIGURE 2 | Balance and postural sway parameters.

measures. Galna et al. (2015) found an impairment across the gait domains pace, variability, rhythm, asymmetry, and postural control in recently diagnosed PD patients compared to age-matched healthy controls. PD patients walked at a slower pace, with decreased step length, and showed increased asymmetry and step-to-step variability. Others reported a set of 20 gait kinematic variables, such as stride length or gait velocity, that differentiates parkinsonian gait from the gait of controls, and a set of variables correlating with symptom severity, potentially serving as markers of PD progression (Dewey et al., 2014). Recently, Ghislieri et al. (2021) used foot-switch sensors to assess gait parameters in PD patients and age-matched controls during walking and reported a 42%-increase in atypical gait cycles in PD, which correlated with motor symptom severity[1]. Veeraragavan et al. (2020) showed that a neural network approach with features extracted from the vertical ground reaction force can differentiate PD from controls as well as predict disease severity (Hoehn & Yahr stage). Furthermore, postural instability is increased in early PD and deteriorates within 12 months of diagnosis, thus providing a potential marker for motor function decline (Mancini et al., 2011, 2012a). Increased gait variability and sagittal trunk movement might predict an increased risk of falls (Ma et al., 2020a). Yet, no standardized set of gait kinematic biomarkers that signifies gait improvement in PD exists (Horak and Mancini, 2013).

2.4. Measures/Biomarkers in MS

Differences in gait and balance parameters between neurologically intact controls and MS patients were reported (Shanahan et al., 2018): Reduced gait speed and stride length, a prolonged double support time, as well as changes in kinematic characteristics of the hip, knee, and ankle joint were found to correlate with disease severity in patients with relapsing-remitting, primary or secondary progressive MS with no to moderate impairments[2] (Benedetti et al., 1999; Martin et al., 2006; Kelleher et al., 2010; Remelius et al., 2012). Additionally, a relationship between a reduced dorsiflexion angle at initial contact and walking induced fatigue as well as an increased power absorption at the hip, knee, and ankle have been reported in MS patients with moderate disabilities (EDSS 3–6) (McLoughlin et al., 2016). Studies on balance in MS patients with mild to moderate impairments (EDSS 0–5.5) showed an increased mediolateral sway path length, mediolateral sway range (Solomon et al., 2015), and sway area (Spain et al., 2014). This is also reflected by a wider stride width in patients with EDSS 2.5–6 compared to controls (Remelius et al., 2012). Clinical tests including turns were recommended to reveal important markers of balance confidence and walking abilities in MS (Adusumilli et al., 2018).

3. WEARABLE TECHNOLOGIES

3.1. Inertial Sensors

3.1.1. Technology

The progress in micro-electromechanical system (MEMS) technology resulted in the availability of small, lightweight, and low-cost inertial measurement units (IMUs) conquering the motion tracking market (Seel et al., 2020). Therefore, IMUs are the most widely used type of wearable sensors for gait and balance analysis (de-la Herran et al., 2014; Shanahan et al., 2018); the quantification of gait with IMUs is sometimes referred to as InertiaLocoGraphy (ILG) (Vienne-Jumeau et al., 2020). IMUs typically consist of a combination of multi-dimensional gyroscopes, accelerometers, and often magnetometer sensors allowing the estimation of joint angles, gait and angular velocities, position and orientation in space via sensor fusion techniques (Sabatini, 2006). The wireless sensors can be mounted on various parts of the patient's body, for example, foot, lower leg, pelvis, torso, or integrated into garments and insoles, in order to measure movements of a specific body segment.

Accelerometers are most commonly used in motion analysis and assess the one-, two-, or three-dimensional acceleration of the sensor in terms of externally applied acceleration forces (Diaz et al., 2020). The measured signal is the sum of (1) the linear acceleration, namely the translation- and/or rotation-related instantaneous change of velocity, and (2) the earth's gravitational acceleration, which is approximately 9.81 m/s^2 in vertical direction near the earth's surface. However, these two components can only be differentiated completely in quasi-stationary scenarios.

Gyroscopes provide the one-, two-, or three-dimensional angular velocities of the body segment to which they are attached. The design typically relies on the Coriolis effect whereby a body

[1]Unified Parkinson's Disease Rating Scale - Part III (UPDRS-III).

[2]Expanded Disability Status Scale (EDSS) 0–2.5 (Benedetti et al., 1999; Martin et al., 2006) and 2.5–6 (Remelius et al., 2012); Hauser Ambulation Index (HAI) 0–2 (group 1) and 3–4 (group 2) (Kelleher et al., 2010).

moving freely in a rotating frame of reference experiences the Coriolis force acting perpendicular to the direction of applied motion and to the axis of rotation. Segment orientations and joint angles can be determined by integration of the resulting angular rates if initial values are known and measurement biases are removed. However, the biases of MEMS-based gyroscopes are temperature-dependent and time-varying, which makes it difficult to estimate them during movements (Woodman, 2007).

To overcome the disadvantages of both sensor types, accelerometers and gyroscopes, *magnetometers* are often included in IMUs [also referred to as magneto inertial measurement units (MIMUs)] to improve orientation measurements, namely heading. Heading describes the angle of the sensor with respect to the horizontal direction of the magnetic north. In a magnetically undisturbed environment, magnetometers measure this component and a vertical component of the local earth's magnetic field. However, these readings are typically noisy and affected by magnetic disturbances originating from objects containing ferromagnetic material or emitting magnetic fields as usually the case in indoor environments (Schauer, 2017).

As the measurement signals of inertial sensors are well-known to be subject to errors such as time-variant sensor biases and measurement noise, reliable motion tracking requires computationally complex algorithms including state estimation methods and kinematic models (Seel et al., 2020). Three-dimensional strap-down integration and suitable sensor fusion algorithms combining the different signals are applied to estimate the real-time orientation of an attached IMU (Schauer, 2017), as illustrated in **Figure 3**. More precisely, the orientation of the inertial coordinate system, which is aligned with the housing of the sensor, is estimated with respect to a three-dimensional inertial reference coordinate system. The accuracy and precision of a wearable sensor system depend on how many sensors are used, where and how the sensors are mounted, and on the utilized algorithms. For example, the sensor coordinate systems should be sufficiently well-aligned with a meaningful coordinate system of the body part of interest, to which the sensor is attached, or methods for non-restrictive sensor-to-segment calibration or automatic anatomical calibration should be applied (Seel et al., 2014b).

For clinical gait data analysis, further mathematical tools are required to extract spatiotemporal gait parameters and often anatomical models are utilized for extracting kinematic parameters. Commonly in a two-stage approach, first gait events and phases are detected and, secondly, spatial parameters are determined. Various approaches exist on how and to what detail gait phases are detected from IMU recordings. Reliable gait detection can be achieved by exploiting the angular rates from the gyroscopes (Bertoli et al., 2018) or by combining them with the accelerometer measurements using peak detection algorithms (Mariani et al., 2013). Automated methods deploy adaptive thresholds based on the subject's walking style (Bejarano et al., 2014; Seel et al., 2014a). Spatial parameters are obtained by either signal integration, kinematic gait models, or ML techniques (Yang and Li, 2012; Caldas et al., 2017). Major gait parameters, for example, stride length, walking speed, can be derived with the most commonly used setup of two inertial sensors that are placed on the feet/shoes (e.g., Schlachetzki et al., 2017) or on the shank. Especially when postural control and balance parameters shall be extracted, a third sensor is added either on the chest, pelvis or lumbar spine and the acceleration is used to calculate COM and sway parameters (Mancini et al., 2012b; Curtze et al., 2015; Hsieh and Sosnoff, 2021). Recently, it has been shown that several gait events can be obtained from a single IMU at the pelvis even in individuals with neurological conditions (Pham et al., 2017). Tracking of the lower body or full body motion tracking is facilitated by further sensors (e.g., Schepers et al., 2018; Teufl et al., 2019).

Available commercial systems for gait and balance analysis applied in neurological patients are, for example, *Xsens MVN* (Xsens Technologies B.V., Enschede, Netherlands) for full-body motion tracking with up to 17 sensors, *Mobility Lab* (APDM, Inc., Portland, OR, USA) with six IMUs and data analysis software for different test scenarios (Dewey et al., 2014; Mancini and Horak, 2016; Morris et al., 2019), or *RehaGait* (HASOMED, Magdeburg, Germany) with up to seven inertial sensors and gait data analysis software (Donath et al., 2016). The sensors and systems diverge in their software, namely algorithms for sensor fusion and parameter estimation, as well as in their communication and housing. The housing and its dimensions vary depending on the battery capacities and on-sensor storage (Diaz et al., 2020). Furthermore, different data collection modes are available, such as real-time streaming or post-recording data download, and their transmission to a computer or smart device. The provided sampling rates correlate with the number of utilized sensors and show a large range (22–320 Hz), although this parameter has a high impact on the accuracy (Caldas et al., 2017). Besides, the pricing for IMU-based gait analysis systems varies strongly with individual wireless inertial sensor being available at affordable prices. However, the more detailed the gait analysis software has been evaluated, the more expensive it is. This is one reason for the trend toward own investigations and open-source gait analysis software (e.g., Gurchiek et al., 2019). Therefore, before deciding on a sensor system, the complete application scenario and budget should be outlined and recent developments need to be taken into account.

3.1.2. Applications

Inertial sensors in PD. Inertial sensor technology applied in PD was able to reproduce the findings of distinct spatiotemporal gait characteristics including short steps, shuffling gait, and postural instability, specific for different disease stages and levels of motor impairment (Schlachetzki et al., 2017); cf. Section 2.3. A typical application is the instrumentalization of established clinical tests with IMUs with the goal of making the assessment rater-independent and gaining additional information (Palmerini et al., 2013). For example, Dewey et al. (2014) used the *Mobility Lab* system in an instrumented TUG and instrumented sway assessment in 135 PD subjects and 66 age-matched controls. For both tests, they identified multiple variables (e.g., stride length, turn duration, total sway area) that correlate with PD severity measures and differentiate PD subjects from controls. Instrumented gait

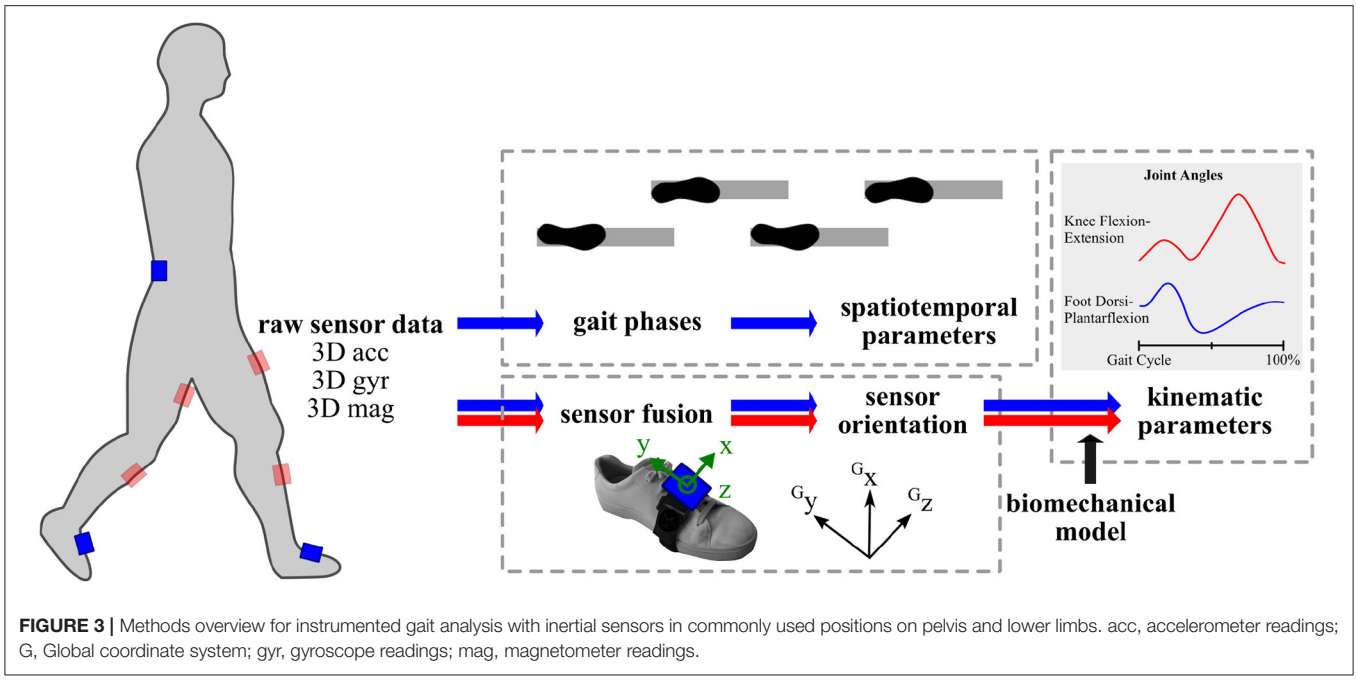

FIGURE 3 | Methods overview for instrumented gait analysis with inertial sensors in commonly used positions on pelvis and lower limbs. acc, accelerometer readings; G, Global coordinate system; gyr, gyroscope readings; mag, magnetometer readings.

analysis with IMUs offers the possibility to examine the differential effects of established and novel PD treatments on gait. A selection of exemplary studies is presented in **Table 2**.

For instance, Curtze et al. (2015) studied the effect of levodopa treatment on gait in a large cohort of patients and found that pace-related gait measures responded well to levodopa treatment, while balance parameters did not improve in the ON- compared to the OFF-state. Iijima et al. (2017) used 24 h single-accelerometer measurements from the trunk in order to track improvements in the gait fluctuations of PD patients after the addition/increase in dose of selegiline, showing a higher sensitivity than clinical scores. Recently, Cebi et al. (2020) used gait kinematics derived from IMU sensors placed at the hip and ankles to examine the therapeutic outcome of deep brain stimulation of the Nucleus subthalamicus (STN-DBS) on gait disorders in PD. Time to complete a 7 m walking task and number of steps were reduced and gait kinematics improved (stride length, ROM) 8 weeks after STN-DBS surgery in the DBS-ON compared to the DBS-OFF condition. In addition, freezers with a pre-surgical levodopa response of gait kinematics responded better to STN-DBS, indicating that the assessment with IMUss might be useful to predict the outcome of such treatments in specific patient subgroups.

Another popular application of IMUs in PD is as a tool to recognize and quantify FoG, a symptom which is rarely observed during clinical consultations since it occurs episodically. Freezing of gait usually appears in everyday life situations, i.e., during turning or walking through narrow doorways, and is associated with an increased risk of falls (Gray and Hildebrand, 2000; Bloem et al., 2004). Various sensor-based methods have been developed to objectively measure FoG in terms of number of episodes and episode duration (Moore et al., 2008; Rodrguez-Martn et al., 2017; Silva de Lima et al., 2017; Suppa et al., 2017; Pardoel et al., 2019). Sensor-based FoG detection opens up the possibility of monitoring FoG in the home environment of patients, which could facilitate the diagnosis and treatment of FoG (Suppa et al., 2017; Mancini et al., 2021).

Furthermore, IMUs are integrated in novel therapeutic cueing devices, which aim to monitor and treat gait disorders in PD. Cueing was shown to be effective in improving gait function in PD and a multitude of cueing paradigms exists (Muthukrishnan et al., 2019). **Table 2** includes examples of cueing devices using IMUs to either administer gait-synchronized cues or to analyze the gait pattern in response to treatment. For example, the gait training tool *CuPiD-system* consists of wearable IMUs, a smartphone, and headphones to deliver intelligent auditory feedback on gait (Casamassima et al., 2014; Ferrari et al., 2016). Patients using the device showed improvements in maintaining cadence during prolonged walking, improved balance, and quality of life (Ginis et al., 2016, 2017). The *GaitAssist* system applies adaptive, rhythmic auditory cues and was used in the home environment of PD patients, who showed a trend toward reduced FoG episodes after several days of gait training with the system (Mazilu et al., 2015). Other cueing systems administer gait-synchronized sensory stimulation, which process IMU data online to analyze the gait while walking: Mancini and colleagues examined the effect of vibrotactile cueing at the wrist (*VibroGait*) and found reduced FoG, improved turning and trunk stability, increased first step duration, but reductions in gait speed and stride length (Harrington et al., 2016; Mancini et al., 2018; Fino and Mancini, 2020; Schlenstedt et al., 2020). Sijobert et al. (2016) developed a smart cueing device applying sensory, electrical stimulation at the lower leg via skin electrodes and found that

TABLE 2 | Exemplary clinical studies utilizing IMUs for gait assessment in PD.

Publication	Study population	IMU position(s)	Clinical intervention	Outcome
IMUs for therapeutic outcome				
Curtze et al. (2015)	$n = 104$ PD patients, $n = 64$ age-matched controls	Ankles, wrists, lumbar spine, sternum	Levodopa treatment (ON- vs. OFF-state)	Improved pace-related gait measures in ON-state: increased stride velocity and stride length, improved lower leg ROM and arm swing; impaired balance measures in ON-state: increased postural sway
Iijima et al. (2017)	$n = 14$ PD patients	Waist	Selegiline Treatment (before vs. after the addition/increase in dose)	Increased amplitudes and range of gait accelerations after dosage addition/increase in 40–63% of the patients; diminished fluctuations in gait throughout the day (86%)
Cebi et al. (2020)	$n = 13$ PD+FoG, $n = 5$ PD-FoG	Ankles, lumbar spine	DBS-STN (DBS-ON vs. DBS-OFF)	Reduced time to complete walking task, increased stride length, improved lower leg ROM; reduced freezing events (freezer subgroup)
IMUs for cueing				
Mazilu et al. (2015)	$n = 9$ PD patients	Feet, ankles, thighs, lumbar spine, wrists	Adaptive auditory cueing (metronome beats)	Trend toward reduced number of FoG episodes
Sijobert et al. (2016)	$n = 13$ PD patients	Foot	Gait-synchronized sensory electrical stimulation	Reduction of FoG events and reduced time to complete a walking task
Ginis et al. (2016)	$n = 40$ PD patients	Feet, ankles	Adaptive auditory feedback, personalized gait advice (active control)	Improved single / dual task gait speed (both groups), improved balance and quality of life (adaptive auditory feedback)
Ginis et al. (2017)	$n = 28$ PD patients, $n = 13$ age-matched controls	Feet, ankles, lumbar spine, wrists	Adaptive auditory feedback, continuous auditory cueing, adaptive auditory cueing (metronome beats)	Reduced deviation of cadence (continuous and adaptive cueing), maintaining cadence but increased fatigue (adaptive feedback)
Mancini et al. (2018)	$n = 25$ PD+FoG, $n = 18$ PD-FoG	Feet, shins, lumbar spine, sternum	Gait-synchronized tactile feedback at wrist, rhythmic auditory cueing	Both modalities reduced FoG during turning, increased smoothness of turns, decreased turning speed
Fino and Mancini (2020)	$n = 43$ PD patients	Feet, ankles, lumbar spine, sternum, wrists	Gait-synchronized tactile feedback wrist, rhythmic auditory cueing	Improved trunk stability (tactile cueing), but reductions in gait speed and stride length and increased stride time
Schlenstedt et al. (2020)	$n = 36$ PD+FoG, $n = 18$ PD-FoG patients	Shins, lumbar spine	Gait-synchronized tactile feedback wrist	Increased first step duration, no effect on anticipatory postural adjustments

the time to complete a walking task and the number of FoG episodes decreased.

These studies show that sensor-based gait measurements (1) might help to objectively examine treatment effects on gait disorders, (2) might facilitate the monitoring of treatment outcomes over longer follow-up periods, (3) may be used to predict the outcome of treatments in specific patient subgroups, and (4) could become integral part of new therapeutic methods.

Inertial sensors in MS. Shah et al. (2020) postulated that daily life monitoring with IMUs might be more sensitive to impairments from neurological diseases than laboratory IMU-based gait measures but that the analyzed neurological diseases (PD and MS) might require different gait outcome measures. Trunk-, shank-, or foot-placed IMUs have been frequently applied to measure gait and, especially, balance dysfunction in MS patients, commonly in the form of the instrumented TUG test (Shanahan et al., 2018): Spain et al. (2014) utilized IMUs to differentiate between mild MS, moderate MS, and control groups based on the variability in gait velocity, trunk motion, and sway (range, area). Craig et al. (2017) showed the reproducibility

of the instrumented TUG results over two sessions and that stride velocity, cadence, and cycle time correlate significantly with disease severity and number of recent falls. IMU-based analysis has been found useful to detect even early changes in gait and balance in MS (Spain et al., 2012). Measurements with IMUs were able to reflect intra-individual changes in identified biomarkers associated with a change in clinical severity scores in a 12-month prospective study by Galea et al. (2017). Therefore, objective gait analysis with IMUs might increase the sensitivity of clinical and performance tests to monitor gait dysfunction in MS (Vienne-Jumeau et al., 2020). Moreover, spatiotemporal parameters from walking have been used to objectively measure MS disease specific characteristics, such as muscle fatigue, which could be helpful in monitoring and evaluating rehabilitation and treatment efficacy (Motta et al., 2016; Ibrahim et al., 2020). In the area of therapeutic aids and home-care, IMU-based fall detection is an emerging application for various gait disorders (Wang et al., 2020).

3.2. Smart Devices

3.2.1. Technology

Although smart devices, such as smartphones or smartwatches, use inertial sensors as a technique, they are presented separately in this section due to their high presence and popularity in everyday life that makes them particularly interesting for long-term monitoring in home environments. Smart devices can be used as single sensor units like previously described IMUs, for example, by wearing a smart device on the hip for a postural control assessment (Kosse et al., 2015). The data can then be transferred and processed in the same way as previously described for IMUs. Usually, measurement setups are limited to two measurement locations, for example, one smartphone and a paired smartwatch. However, most frequently only one device is utilized (e.g., Chomiak et al., 2019; Hsieh et al., 2019). Available sampling rates for smart-device-based IMUs depend on the hardware (e.g., for Apple products[3] (Cupertina, CA, USA), it is supposed to be at least 100 Hz), and can limit the range of applications. The reliability of smart device measurements for motion tracking is still being investigated (Vohralik et al., 2015).

In addition to regular IMUs, smart devices come with an integrated interface and specific software ("apps") facilitating a user-friendly operation of the data assessment. Different apps provide different data collection modes, such as real-time streaming, recording, and post-recording wireless data download. In literature, mostly customized apps were used to record the sensor data and calculate gait or balance parameters on- or offline (Franco et al., 2012; Kosse et al., 2015; Chomiak et al., 2019), or to upload the data to cloud servers for offline gait analysis (Manor et al., 2018). As an advantage to standalone IMUs, smart devices promote direct biofeedback in the form of visual, auditory, or haptic signals. Due to these features, smartphones are often combined with IMUs for gait monitoring and therapy systems (e.g., Ferrari et al., 2016; Palmerini et al., 2017).

[3]https://developer.apple.com/documentation/coremotion/getting_raw_accelerometer_events [accessed July 6, 2021].

3.2.2. Applications

Although the use of smart devices to assess gait and balance is under extensive investigation, most applications are still under development. Multiple studies explore smart devices for balance assessments measuring trunk movements and postural stability but so far mostly in neurologically intact participants (e.g., Alberts et al., 2015a,b; Kosse et al., 2015; Hsieh et al., 2019). Roeing et al. (2017) reviewed 13 studies and found that five evaluated the validity of their smartphone applications for balance and risk of falls assessment; the results demonstrated strong concurrent validity with standalone accelerometry, 3D motion capture, and force plate measurements. Three of these studies included a measure of reliability revealing high ICC values for mixed variables (Mellone et al., 2012; Cerrito et al., 2015; Kosse et al., 2015; Roeing et al., 2017). Standardized clinical assessments, such as sit-to-stand evaluation (Cerrito et al., 2015; Marques et al., 2021), the TUG (Mellone et al., 2012; Ponciano et al., 2020), and postural balance (Hsieh and Sosnoff, 2021), were instrumented using a single smart device. Also applications in rehabilitation in the form of biofeedback loops with potential use at home, e.g., as a smartphone-based audio-biofeedback in order to improve balance during bipedal standing (Franco et al., 2012), are being evaluated. However, special research interest is on utilizing smart devices for gait assessment as there lies a great potential for long-term monitoring in everyday activities. Fall detection with smart devices is already available on the market in the form of *Apple Watch Series 4–6* (Apple Inc, 2020). The accelerometer and gyroscope readings from the wrist are used in combination with a fall detection threshold yielding a high false-positive rate (Wang et al., 2020).

Most approaches aim at extracting gait parameters from the use of a single smart device (Ellis et al., 2015; Kosse et al., 2015; Manor et al., 2018). For example, Manor et al. (2018) created an app for systematic gait data recording and analysis that can be performed independently by the user either in the laboratory or at home with the smartphone placed in the trousers' front pocket. When comparing normal and dual-task trials in neurologically intact volunteers, average stride times derived from the app demonstrated high correlation with the simultaneously used instrumented mat in the laboratory. Lipsmeier et al. (2018) explored the potential of smartphones for assessing biomarkers in PD that might serve as outcome measures in clinical trials. The authors presented moderate to strong retest reliability and successful discrimination between PD and controls with increased sensitivity compared to traditional clinical scales (Buckley et al., 2019).

Despite regular gait assessment, smart devices were evaluated for continuous monitoring in PD for FoG detection and fall prevention. For example, Ellis et al. (2015) developed a mobile application with the smartphone at the front waist to track gait and its variability, an indicator for FoG in PD, presenting it as an alternative to conventional gait analysis technologies. Chomiak et al. (2019) utilized an *iPod Touch*, worn on the thigh, and ML to identify gait-cycle breakdown and freezing episodes of varying duration. Ahn et al. (2017) presented a system for FoG detection

and visual cueing based on smart glasses (Android): The subject's movements are tracked using the inertial sensor from the glasses, which projects visual patterns in the case of a recognized FoG event. Furthermore, numerous smartphone applications have been designed for the assessment and monitoring of multiple health parameters in patients with PD (Monje et al., 2019). The apps combine questionnaires, cognitive, voice, and motor tasks providing repeated measures of the patients motor state along with valid and clinically meaningful knowledge of symptom evolution (Bot et al., 2016; Lakshminarayana et al., 2017; Lipsmeier et al., 2018). Similar applications are available for monitoring MS patients [e.g., elevateMS by Pratap et al., 2020].

These diverse applications of smart devices in gait and balance assessments reveal their future potential to be utilized for objective evaluation of treatments over short and long follow-up periods, closed-loop applications, and telemedical consulting in real-life environments.

3.3. Instrumented Insoles

3.3.1. Technology

Instrumented insoles are insoles that have integrated force or pressure sensors to measure changes in pressure between the foot and the ground. Force sensors measure the applied force discriminating the component of each axis that is measured, whereas pressure sensors are non-discriminating and thereby measure the combined ground reaction force (de-la Herran et al., 2014). Most commonly used insole sensors are capacitive, resistive piezoelectric, and piezoresistive sensors (de-la Herran et al., 2014). The measurement principle is based on the detection of voltage changes caused by fluctuations in electrical capacity or electrical resistance in semiconductor materials due to stretching or compression (Chen and Yan, 2020). The choice of sensor depends on the desired range of pressure/force, sampling rate, and sensitivity (Diaz et al., 2020). Insoles typically incorporate arrays of sensors measuring a spatial pressure/force profile over the plantar foot surface (Shanahan et al., 2018). The profile varies during the gait cycle and depends on a person's body weight: In healthy gait, the maximum vertical force is applied and, thereby, the maximum pressure occurs when the whole body weight is on one leg/foot during the stance phase (Clarke, 1980). No force is applied during the swing phase. The profile's spatial resolution depends on the number of integrated sensors in the insole, its temporal resolution on the applied sampling rate, and its sensitivity on the utilized sensor and analog-to-digital converter.

Available systems are among others the *F-Scan* (Tekscan Inc., Boston, MA, USA) with 3.9 force-sensitive resistors per cm^2, the *Moticon SCIENCE* pressure insoles (Moticon, Munich, Germany) with 16 capacitive pressure sensors, or *WalkinSense* (Kinematix SA, Sheffield, UK) with eight force-sensing piezoresistors. The latter two and other newer insole types often incorporate additional sensors such as an IMU (Arafsha et al., 2018). Besides, the available systems differ in the type of power supply, data transmission and storage, in the user operation, and associated analysis software.

The validity of discrete pressure and force measurements with insoles is comparable to optical motion capture and they show a high reliability within and between trials (Shanahan et al., 2018). From the profiles, spatiotemporal gait parameters (e.g., stride time, gait phases) can be extracted. However, patients with neurological gait disorders tend to walk slowly, shuffle, and perform short and dragged steps making it challenging for automatic gait event detection based on heel strike or initial contact (Pirker and Katzenschlager, 2017; Diaz et al., 2020). For balance analysis, insoles are regularly used to measure the COP to evaluate postural stability (Ma et al., 2016).

3.3.2. Applications

So far, the clinical application of instrumented insoles in PD patients has mostly been limited to the differentiation between PD and controls. Extracted gait and balance parameters have been used successfully for discrimination between the groups (Mazumder et al., 2018; Chatzaki et al., 2021), in line with the findings from established laboratory gait assessments. Furthermore, instrumented insoles have been investigated for their ability to recognize and quantify FoG in PD (Popovic et al., 2010; Shalin et al., 2020; Pardoel et al., 2021). Pardoel et al. (2021) combined features derived from a pressure-sensing insole and IMUs on the leg to detect FoG in 11 PD patients. The authors reported that the combination of both modalities outperformed classification models that used data from a single sensor type. In a small data sample ($n = 5$), Shalin et al. (2020) demonstrated that foot pressure distributions from 60 × 21 sensor-arrays could be used for FoG prediction (0.5–3 s before FoG onset). Therefore, together with inertial sensors, instrumented insoles could be integrated into therapeutic cueing devices for treating gait disorders in PD (cf. section 3.1).

Few studies utilized insoles to examine gait function in MS patients so far (Shanahan et al., 2018). Viqueira Villarejo et al. (2014) reported an increased plantar pressure during the stance phase and variability in step timing in MS compared to controls. Galea et al. (2017) quantified MS-related gait and balance deterioration over 12 months using EMG and insoles and observed decreases in gait speed and balance scores, and an increase in double support time. Domínguez et al. (2020) validated gait velocity and other parameters from a new insole system with an incorporated IMU against a common instrumented walkway in 205 MS patients. The results revealed a high correlation between devices in velocity, ambulation time, cadence, and stride length. Note that spatial parameters, such as stride length and stride wide, can only be derived from the IMU data (Farid et al., 2021).

Although the use of insoles is unobtrusive and, therefore, has a high potential in monitoring daily activities (Diaz et al., 2020), the hesitant use in research and clinical application may have practical reasons. For reliable measurements, diverse sole sizes must be available to cover the variety in foot sizes. Systems with multiple soles and validated analysis software can initially require a five-digit amount. Due to the mechanical stress during walking, the soles' life is limited. People must wear shoes that allow the use of additional insoles. Furthermore, shoes must be taken off and put on again to set up the measurement, an additional obstacle for elderly patient groups such as PD. However, for long-term monitoring in the future, the ease of integration in patients' everyday life could be an advantage.

3.4. Summary and Discussion

Wearable sensor technology is currently being applied and explored in existing and newly developed clinical gait and balance assessments as well as for long-term monitoring of various activities in daily living. For multiple reasons, body-worn sensors are of great value for balance and gait assessments in neurological disorders: Their high level of portability theoretically facilitates unlimited use in laboratory research environments, clinical settings, and home environments. No line-of-sight restrictions apply as in vision-based technologies. The small, lightweight, and wireless devices do not restrict the subject's movement. In contrast to laboratory-based methods, wearable devices might come at low prices and facilitate easier setups. When provided with a graphical user interface and validated analysis software, usability can be as good that patients can record data on their own. The number of gait parameters that can be extracted from wearables has expanded dramatically over the last years and new, more robust algorithms are under permanent development.

However, all these potential advantages are not always met in the available systems. The gait estimation algorithms for IMUs and insoles are often still in exploration, not evaluated to a reliable extent in the desired target group. The optimal sensor layout is still debated and requires a trade-off between usability and accuracy. Furthermore, it is challenging to calculate paths and distances traveled (Buckley et al., 2019). Necessary sensor-to-segment alignment, the need for precise manual sensor attachment, and required calibration movements by many methods halt the advance of inertial sensor techniques into clinical trials. When utilizing magnetometer readings, measurement errors occur in magnetically-disturbed environments, such as typical clinic or home environments containing electronic devices and objects of ferromagnetic material (de Vries et al., 2009). With increasing algorithm complexity, required processing resources rise yielding high energy consumption and waiting times between subsequent recordings. Still, algorithm development is an active area of research tackling these issues (e.g., Marín et al., 2020; Laidig et al., 2021). Also, existing hardware issues, such as limited recording time by battery and storage capacity, and data loss during the wireless transfer from sensors to applications or cloud servers should be a trivial problem in the future. Patient user interfaces continue to improve (Shanahan et al., 2018).

In addition to their use in recording and analyzing gait and balance disorders, wearables can be applied in rehabilitation technologies or therapeutic aids, such as a cueing device to treat gait impairments in PD (cf. **Table 2**). Besides beneficial therapeutic effects, full-time body-worn sensors allow long-term monitoring and might contribute to the individualization of therapies as well as to telemedicine concepts. The objective tracking and quantification of a PD patient's motor activity over the day is valuable information for the precise adjustment of individual medication plans. Particularly in times of global pandemics, where the number of regular face-to-face visits is reduced (Roy et al., 2020), automatically extracted and shared parameters from wearables have the potential to support clinical decisions. Automatic evaluation methods of data from wearables in clinical gait and balance assessments (e.g., Karatsidis et al., 2017; Nguyen et al., 2019) but also in unrestricted activities of daily living (e.g., Roth et al., 2021) are constantly investigated. Machine learning techniques are the driving force behind this rapid growth of applications. Still, a remaining challenge lies in obtaining validated measures and standardized motor parameters that predict relevant clinical outcomes for each neurological disease (Monje et al., 2019; Shah et al., 2020). Further investigations are required before the analysis of locomotion in everyday activities becomes reliable and thereby clinically relevant (Graham et al., 2008; Lord et al., 2013).

4. NON-WEARABLE TECHNOLOGIES: VISION-BASED MOTION ANALYSIS

Marker-less optical motion capture systems have become popular with the launch of affordable in-depth cameras. Even though computer gaming and virtual reality serve as the main drivers for this rapid evolution of digital image processing, the practical application in the health sector has been discussed and performed frequently (Clark et al., 2012; Albert et al., 2020). Despite being an older technology, motion tracking with optical markers is generally handled as the gold standard with which newly developed technologies for gait analysis are compared. However, marker-based tracking requires an extensive, expensive, non-portable setup. Similar restrictions apply for instrumented mats, walkways, or treadmills, although they are portable on a large scale and often easier to handle. For the sake of completeness, we mention these approaches as references; overviews of gold standard methods can be found elsewhere (e.g., Shanahan et al., 2018; Celik et al., 2021).

Presently, vision-based non-wearable technologies with standard cameras or depth cameras are increasingly applied in human motion tracking. Image acquisition is most conveniently achieved via standard 2D cameras that output images as 2D pixel grids. Each pixel traditionally carries a red, green, and blue (RGB) value, with intensities ranging from 0 to 255. However, 2D cameras do not provide any spatial depth information on the tracked pose. This information has to be obtained either by performing additional post-capture processing with machine learning (ML) algorithms, by using multiple cameras, or by switching to another technology, such as depth cameras which provide 4D information on the tracked object. Pixels obtained with depth cameras are primarily coupled to the distance of the tracked object from the sensor and are typically paired together with a classical RGB value. Both, standard and depth cameras, are able to extract detailed information required for biomechanical analyses.

4.1. In-depth Camera Technology

There are several types of in-depth cameras that rely on different methods to infer depth, as illustrated in **Figure 4**. Structured light imaging uses patterned light to capture the 3D topography of a surface (Geng, 2011). Here, the scale and direction of a distorted pattern are used to assess the depth of an object. Furthermore, time-of-flight (ToF) technology measures the time it takes for infrared light to travel toward an object and reflect into the

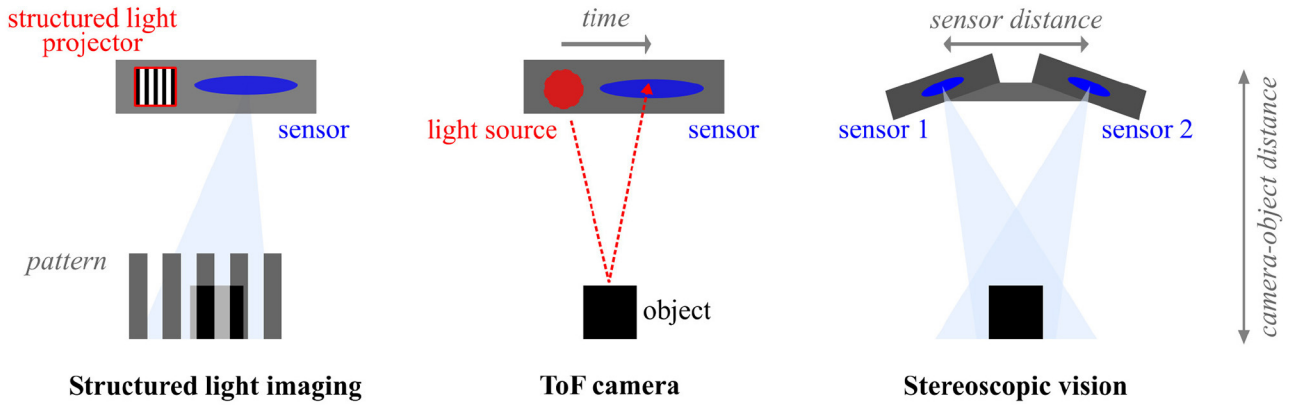

FIGURE 4 | Illustration of different camera technologies for in-depth measurements.

imaging sensor (Kolb et al., 2010). The corresponding phase shift in the signal is subsequently measured and converted into distance. Lastly, stereoscopic vision (also: stereotactic imaging) incorporates two or more stereo cameras to compare two or more simultaneously recorded images for the estimation of depth. Likewise to human eyes, the distance between the cameras is fixed and used to measure the closeness of an object on multiple juxtaposed images obtained by using any type of light.

Two well-known, affordable depth-sensing cameras that are frequently used in medical applications are *Kinect* (Microsoft, Redmond, WA, USA) and *RealSense* (Intel, Santa Clara, CA, USA), which are reviewed here as examples due to their manifold occurrence in literature on gait and balance. Other commercially available systems on the market are, e.g., *ZED* (StereoLabs, San Francisco, CA, USA) or *XtionPro* (ASUS, Taipeh Taiwan).

4.1.1. Microsoft Kinect

Microsoft's *Kinect* is a motion-sensing device originally developed for gaming purposes and is one of the earliest motion capture technologies of its kind to be used in medical research. Owing to *Kinect's* long history in pose estimation, it has been well-assessed in various research settings and utilized in tracking different movement patterns. Throughout the last decade, several versions of *Kinect* have been produced: The introductory model *Kinect 1* (2010) integrates a structured near-infrared light source with an accompanying sensor to capture the reflected light patterns, whereas *Kinect 2* (2013) and *Azure Kinect* (2019) use wide angle ToF cameras (Zhang, 2012).

Although *Kinect 1* is a well-established system, when compared to gold standard techniques, it provides only basic motion capture capabilities such as collecting temporal gait parameters, estimating single joint angles, or assessing postural control during reaching and balance tasks (Clark et al., 2012; Schmitz et al., 2014). In kinematic gait recordings, the system generally underestimates joint flexion and overestimates extension during walking in the sagittal plane. Here, stride timing measurements perform surprisingly well with the highest accuracy at low gait speeds, despite a high error in hip and knee displacement (Pfister et al., 2014). Clothing and different body shapes were discussed as possible reasons for measurement errors. Therefore, approaches that use additional multi-layer filtering, where the estimated pose is further refined through a synthetic library of posture variations, can alleviate some tracking inaccuracies, increase parameter precision, and allow for better recognition of occluded body parts (Shotton et al., 2011; Wei et al., 2012; Xu et al., 2013). Moreover, recording frameworks with multiple cameras were able to improve pose estimation accuracy and approximation of occluded segments at the costs of a higher setup effort (Gao et al., 2015).

Nonetheless, *Kinect 1* has been used in several clinically-oriented studies to measure lower body biomechanics for determining stride time, length, and speed in healthy individuals (Gabel et al., 2012; Auvinet et al., 2015). In the context of PD, scientists used wavelet-based digital signal processing to analyze gait parameters and quantitatively distinguish gait phases with an accuracy of up to 93% (Muñoz et al., 2018). Spatiotemporal parameters were distinguishable in stage II and III PD patients compared to a control group, reaching a maximum accuracy of 97.2% after classification with a neural network (NN) (Ťupa et al., 2015). Likewise, *Kinect 1* technology has been implemented in MS gait analysis to discern MS patients from neurologically intact controls by differences in the average walking speed and lateral body sway (Behrens et al., 2014), or ROM, stride length, and step width (Gholami et al., 2016).

The newer *Kinect 2* system uses continuous-wave ToF technology instead of structured light, enabling a more stable data feed with an increased accuracy within the measurement range of 4m (Gonzalez-Jorge et al., 2015). In clinical assessments, *Kinect 2* displayed an adequate performance when tracking joint center displacement (Napoli et al., 2017). The second generation demonstrates better accuracy in joint estimation and stays more robust to body rotation as well as occlusions during various movements like walking and jogging (Wang et al., 2015; Guess et al., 2017). Therefore, *Kinect 2* seems to outperform *Kinect 1* in locomotion tracking except for foot position tracking during standing, where a larger amount of noise is generated, possibly

due to ToF artifacts (Otte et al., 2016). *Kinect 2* reliably assessed spatiotemporal parameters during comfortable and fast-paced gait (Mentiplay et al., 2015). However, significant performance variations in different motion planes and incompatibility with certain functional movements still exist in *Kinect 2* when compared to marker-based systems, especially in the context of compound joint movement (Mentiplay et al., 2015). The validity of lower limb joint kinematics depends on the camera's capture angle for recording the walking subject. Moreover, in treadmill walking, accuracy levels appear to vary across gait parameters, with temporal parameters based on heel strike having fewer errors than those based on toe-off, and their accuracy fluctuates with changing walking speeds (Xu et al., 2015). Linear pelvic and trunk ROM can still be tracked with reasonable precision at 70 and 90% of maximal locomotion speed, providing a reliable reference point across all velocities (Macpherson et al., 2016). In attempts to use multiple *Kinect 2* cameras to achieve a higher tracking accuracy, several cameras have to be calibrated together via geometric trilateration. The distance between the subject and at least three recording cameras is measured through signal strength. When used to determine gait parameters, three *Kinect 2* sensors show a much higher spatiotemporal reliability compared to a single *Kinect 2* camera (Yang et al., 2016).

Kinect 2 has been applied in PD patients, where 92% of freezing episodes, 91% of tremor occurrences, and 99% of falling incidents could be detected with customized algorithms (Bigy et al., 2015). Moreover, *Kinect 2* measurements in combination with customized algorithms were able to consistently produce results similar to a marker-based system and output significant differences between PD and control groups for stride length, gait, and swing velocity (Eltoukhy et al., 2017; Sabo et al., 2020). In MS patients, moderate and fast walking speed measurements agree with results derived from marker-based systems, but once more, only if combined with customized software or auxiliary ML-based classifiers (Bethoux et al., 2018; Elkurdi et al., 2018). Indeed, it seems that additional ML algorithms or NNs can frequently increase the validity and reliability with depth cameras (Rocha et al., 2018).

Microsoft's *Azure* is the most recent *Kinect* upgrade that supports additional features and several depth-sensing modes. Although part of the same production line, it has been specifically designed for distinctive non-gaming purposes such as research and health care use. Compared to *Kinect 2*, *Azure* has a higher angular resolution, lower noise, and better tracking accuracy (Tölgyessy et al., 2021). When used as a dual system consisting of two cameras, *Azure* outputs precise knee angles and demonstrates an overall improved validity over *Kinect 2* (Ma et al., 2020b). During the estimation of sagittal hip and knee joint angles, a single *Azure* appears to have a superior depth resolution and shows better tracking performance when subjects walk at non-frontal camera viewing angles (Yeung et al., 2021). In treadmill walking, spatial gait parameters (e.g., step length and width) can be measured more reliably with *Azure*, though the accuracy of temporal parameters (e.g., stride duration) does not change significantly between the two models. Interestingly, *Kinect 2* seems to outperform *Azure* regarding upper body tracking. However, an overall increase in the quality of lower extremity parameters and the additional introduction of integrated deep learning-based body tracking algorithms create appeal for *Azure* to be used in gait rehabilitation (Albert et al., 2020). As far as the application of *Azure* in PD and MS studies is concerned, to our knowledge there has not been any material published yet.

4.1.2. Intel RealSense

Intel's *RealSense* cameras stem from several generations of stereo depth cameras with a production start in 2015. The system comprises a left-right depth stereo camera pair and an additional color camera. The stereo cameras use textured light to ensure unambiguous image matching, which in turn enables more accurate depth measurements. Accordingly, stereotactic systems including *RealSense* are less sensitive to noise compared to other in-depth camera types, which allows for a more flexible experimental setup (Keselman et al., 2017; Zabatani et al., 2019). In motion analysis, the system can be used to measure a definite amount of spatiotemporal variables, however, joints with multiple degrees of freedom exhibit inaccuracies yielding difficulties for the forthcoming gait data analysis (Mejia-Trujillo et al., 2019). In general, *RealSense* seems to perform better at slow to normal walking speeds located in small to medium-sized environments (Hausamann et al., 2021). Auxiliary tools can be used to extend the current three-part system to up to six cameras to improve body shape and joint position tracking (Boppana and Anderson, 2019). Intriguingly, despite having an older production age, both *Kinect 1* and *2* seem to rival *RealSense*'s signal quality and capture range during walking (Mejia-Trujillo et al., 2019). Moreover, temporal parameters seem to exhibit slightly better accuracy when recorded with *RealSense*, whereas spatial parameters retain similar values to *Kinect* measurements (Gutta et al., 2021). While a few gait studies with Intel's *RealSense* exist, up to the present moment no publications known to the authors have used the technology to assess gait and balance explicitly in either PD or MS patient groups. However, *RealSense* convincingly holds the potential to be used in clinical research, whether as a new method for motion tracking or as a *Kinect* substitute (Clark et al., 2019).

4.2. Standard Camera Technology

In daily clinical practice, video recordings are still predominantly recorded with conventional standard cameras. Clinicians may film their patients during outpatient or inpatient visits (e.g., in frequented hallways) or are presented with home videos for neurological evaluation (Sato et al., 2019). However, the material has so far only been used for subjective assessment and documentation, not exploiting its full potential. The use of standard camera material for motion analysis would require a less demanding setup, fewer recording constraints, and would offer more favorable pricing, and integrability into daily research, clinical and telemedical settings. The resulting demand for swift algorithms that accurately determine body part locations on video images drove the development of numerous approaches for pose estimation in standard imaging. In comparison to depth cameras that output distance information without requiring training and often include built-in post-processing software,

standard camera footage has to be analyzed offline by a separate learning pipeline for motion tracking. The software pipeline either determines pose coordinates in 2D or deduces depth, in case 3D coordinates are the desired output. In this section, we go over recent findings in pose estimation and discuss available toolboxes designed as ready-to-use software packages for a broader scientific audience that might be applied for gait analysis in neurological disorders.

4.2.1. 2D Pose Estimation

Most recent 2D pose estimation approaches rely heavily on contemporary advances in deep learning, a branch of ML that employs NNs with many layers. With an annotated image data set where objects have been manually labeled, a NN can be trained via supervised learning to classify and track those objects. Pose estimation algorithms frequently use convolutional neural networks (CNNs) as their architectural foundation with multiple layers (e.g., Toshev and Szegedy, 2014). The greatest advantage of CNNs is their ability to learn feature representations directly from the data set in use, which removes the need for additional training data, thus, ensuring a straightforward experimental flow. Their convolutional structure produces 2D probability maps for the location of each body part after they had been trained to recognize image features that belong to specific shapes (e.g., knee, foot) (Wei et al., 2016). This establishes a statistical relationship between the input images and output pose key-points, which can be used to track pose in yet unanalyzed data and make predictions on the spatiotemporal appearance of tracked key-points.

In video data, 2D pose tracking represents a unique set of challenges and numerous network designs have been created to optimize both for speed and reliability in their specific study context. Contrary to static image analysis, images that have been extracted from video frames are often subject to motion blur, frequent body occlusions, unconventional subject positions and further represent large data sets due to the sheer amount of frames in a single video (cf. **Figure 5**). The continuously increasing amount of new pose algorithms also evokes the demand for largely manually annotated data sets that thematically represent the defined area of research: sports, outdoors, medical research, and many others (Sigal et al., 2010; Ionescu et al., 2013; Andriluka et al., 2014). To withstand these challenges, attempts have been made to increase the quality of parameter supervision by, for example, cross-correlating features in adjacent video frames or integrating various mathematical approaches with NNs, and to reduce the amount of required pre-labeled data (Ouyang et al., 2014; Szegedy et al., 2015; Tompson et al., 2015; Feichtenhofer et al., 2017).

In gait analysis, established preliminary models use standard cameras ranging from simple mobile phone cameras to multiple cameras accompanied with additional sensors such as IMUs or floor sensors (Alharthi et al., 2019; Viswakumar et al., 2019; Vaith et al., 2020; Stenum et al., 2021). The validity, reliability, and processing time of these models vary according to the type and quality of camera footage, computational system architecture, type and amount of training data used as well as many other factors. Therefore, choosing a suitable pose estimation model is strongly influenced by the experimental setting and might depend on the number of tracked legs, frequency of body part occlusions, subjects' clothing, and room background color. Until these and other issues are resolved, 2D pose estimation will not be applied on a wide scale in the clinical field. However, first studies indicating possible applications of this technique in neurological disorders have been published: Li et al. (2018) combined the outcome of convolutional pose machines with ML-based classification for discriminating disease and symptom severity in PD patients in tasks such as toe-tapping and stamping. Hu et al. (2019) successfully established a novel graph CNN to classify freezing episodes from regular gait in the TUG test of 45 Parkinsonian patients, recorded in frontal view.

FIGURE 5 | An example of 2D motion tracking performed with DeepLabCut. Here, several joints are being tracked simultaneously to determine the exact limb position during straight walking.

4.2.2. Single-View 3D Pose Estimation

Occlusion of body parts has continuously presented a challenge to 2D human pose estimation for gait analysis, especially when both legs are tracked simultaneously, as desired, for example, for analyzing gait symmetry in PD. Thus, advances have been made toward setting the pose in a 3D coordinate framework instead of 2D by subsequently generating a 3D environment from images obtained by a single RGB camera. Complementary 3D pose libraries can be used to create 2D projections from virtual camera views. In such cases, 2D pose estimation is performed on input images and then depth is calculated using an additional pre-existing 3D library as a reference (Chen and Ramanan, 2017). However, the employment of 3D libraries requires even larger amounts of annotated data. To address this challenge, specialized CNNs have been implemented to output 2D key-points together with body silhouettes, which are later synchronized with a mathematically generated 3D body mesh model to estimate full 3D pose (Loper et al., 2015; Pavlakos et al., 2018). Moreover, some networks specialize in the detection of individual people from

group images and automatically crop out single subjects that are present on the input image, subsequently performing individual 2D pose tracking and later placing the obtained parameters into a virtual 3D environment (Moon et al., 2019). Recently, single-view 3D pose estimation has been integrated into the gait analysis of PD patients, where spatiotemporal parameters including step length, velocity, and cadence evaluated with a deep learning pose estimation algorithm seemed in good agreement with reference data obtained through pressure sensors (ICC > 0.9) (Shin et al., 2021).

4.2.3. Multi-View 3D Pose Estimation

The multi-view approach to 3D pose estimation is an alternative scheme that further reduces training set size and eliminates the need for large 3D libraries. One strategy is to train the network on images from multiple cameras before predicting the 3D pose from images obtained by a single camera (Rhodin et al., 2018). Specifically, a network is trained to predict the same 3D pose regardless of camera perspective and can perform 3D predictions solely based on 2D imagery. Other methods include algebraic and volumetric triangulation that are speculated to be more robust to occlusions or partial body visibility (Iskakov et al., 2019). Further strategies use so-called key-point coordinates instead of heatmaps (Pavllo et al., 2019) or employ a multi-stage architecture to reconstruct the 3D pose from 2D heatmap predictions at each CNN processing stage (Tome et al., 2018).

As multi-view 3D pose estimation approaches effectively deal with body part occlusions and simultaneously alleviate the need for large training libraries, they present a promising tool in gait tracking. Indeed, such models are able to qualitatively reproduce locomotion compared to marker-based motion capture, albeit still producing a small error rate in the final 3D pose (Nakano et al., 2020). Therefore, technical challenges of multi-view systems such as the setup of multiple cameras, triangulation, and more extensive processing make the experimental setting more demanding but at the same time offer an opportunity to improve the quality of gait parameters.

4.2.4. Software Toolboxes

While numerous algorithms have been created in the attempt to improve the performance of 2D and 3D pose estimation algorithms, we will now briefly summarize several that have been pre-packaged as software toolboxes and are being used by a wider, non-specialist scientific community to track human motion promoting new fields of application (**Table 3**).

One of the earliest of such packages is *DeeperCut*, a multi-person pose estimation method based on the integer linear programming approach *DeepCut* (Pishchulin et al., 2016). Here, deep residual neural networks (ResNets) have been adapted inside a convolutional architecture in form of a sliding window-based body part detection (He et al., 2016). ResNets build on constructs known from pyramidal cells in the cerebral cortex: They utilize skip connections, or shortcuts to jump over some network layers and map nonlinearities. Moreover, *DeeperCut* features image-conditioned pairwise terms or architecture components that indicate the presence of other body parts in the vicinity of a tracked point and group these body parts into a valid pose configuration (Insafutdinov et al., 2016). Published in 2018, *DeepLabCut* is a more recent tracking toolbox. Although a CNN architecture as well, *DeepLabCut* significantly differs from its predecessor *DeeperCut* by implementing pre-trained ResNets, which fine-tune the already existing node weights following the tracked body part. Therefore, *DeepLabCut* exhibits a faster performance and requires a smaller amount of pre-labeled images for training. After network processing, the user can readily access spatial coordinates and the existential probability of every tracked body part, stored in the form of x- and y-coordinates for each video time frame (Mathis and Warren, 2018; Mathis et al., 2018). **Figure 5** shows an example of 2D motion tracking with *DeepLabCut*. Additional reconstruction of 3D kinematics with *DeepLabCut* is possible by either establishing individual networks for each camera view or training a single network that generalizes across all views (Nath et al., 2019).

OpenPose is a real-time 2D pose estimation approach developed for motion processing of multiple individuals on a single image. An integral part are Part Affinity Fields (PAFs), a set of 2D vector fields that encode the orientation and location of limbs on the analyzed image. Moreover, PAFs are bottom-up representations of unstructured pairwise relationships between detected body parts that enable the reconstruction of the full-body pose while decreasing the total computational cost. As with any multi-person tracking algorithm, *OpenPose* faces obstacles like subjects present on the image at different positions or scales and body part occlusions (Cao et al., 2019). *OpenPose* has recently been implemented with multiple synchronized cameras to evaluate motor performance in a 3D pose framework. Compared to a marker-based system, the mean absolute error of points tracked during walking equaled less than 30 mm, excluding 10% of cases where *OpenPose* initially failed to recognize the correct body segment during 2D estimation (Nakano et al., 2020).

Several other prominent pose estimation toolboxes exist which have not yet been frequently featured in gait research: *Anipose* is an open-source toolkit designed to augment the existing 2D tracking methods for accurate pose tracking in a 3D setting. It deploys optimization on the calibration, triangulation, and filtering over multiple camera views that accompanies the processing by antecedent NN packages (Karashchuk et al., 2020). *DeepPoseKit* aims to resolve the limitations of over-parametrization by pre-trained ResNets and the lack of robustness in GPU-based approaches. The pipeline is based on alternative confidence map processing methods, multi-scale inference, and GPU-oriented convolutional layers (Graving et al., 2019). Lastly, *AlphaPose* is another open-source multi-pose estimator featuring a regional multi-person pose estimation (RPME) framework (Fang et al., 2017). During training, the RPME pipeline detects single humans on the image by establishing bounding boxes around each individual. Afterwards, single pose estimation is performed on each bounding box and the output is further refined (Xiu et al., 2018; Li et al., 2019).

In conclusion, several toolboxes have already been tested on human footage of walking and running. Among the software packages in **Table 3**, *OpenPose* has been most extensively evaluated both in 2D and 3D gait estimation. In 2D video

TABLE 3 | Overview of available software toolboxes for 2D and 3D pose estimation from 2D cameras.

Toolbox	Modality	Feature	Tracking	Gait analysis research
DeeperCut	2D	ResNets, pairwise terms	Multiple	-
DeepLabCut	2D/3D	Pre-trained ResNets	Single*	Cronin et al., 2019 Needham et al., 2021
OpenPose	2D/3D	Part Affinity Fields	Multiple	Xue et al., 2018 Gu et al., 2018 Viswakumar et al., 2019 D'Antonio et al., 2020, 2021 Zago et al., 2020 Needham et al., 2021 Stenum et al., 2021
Anipose	3D	Pre-trained ResNets	Single	-
DeepPoseKit	2D	Multi-scale inference	Single	-
AlphaPose	2D	Regional pose estimation	Multiple	Needham et al., 2021

**Designed for single person tracking, but can optionally perform multi-pose tracking.*

analysis, mean absolute errors of temporal parameters are smaller than differences arising from natural variations in the walking pattern making temporal changes detectable in healthy gait (Stenum et al., 2021). Step length estimation accuracy depends on the participant's position in the camera field of view, with central positions resulting in lower error rates. Unlike gait speed that reaches accuracy levels similar to the gold standard, errors in sagittal hip, knee, and ankle angles are in proximity of test-retest errors in the same plane. In an underwater running setup, the accuracy of predictions for 2D-joint marker positions extracted with *DeepLabCut* seems to match manual labels with a mean difference of fewer than three pixels (Cronin et al., 2019). Although not compared to a marker-based system, *DeepLabCut* seemed sensitive enough to differentiate between closely-spaced running cadences with a high test-retest reliability of the mean stride data. In 3D motion capture obtained with *OpenPose*, *DeepLabCut*, and *AlphaPose*, significant kinematic differences at hip and knee occurred in comparison to marker-based systems (Needham et al., 2021). Here, tracking accuracy of the ankle unexpectedly performed better than other joints, possibly owing to more precise manual annotation during training due to its apparent anatomical position. When compared to IMUs, *OpenPose* seems to exhibit tracking discrepancies in joint angles of up to 14 (Gu et al., 2018; D'Antonio et al., 2020, 2021). Despite these reports, Sato et al. (2019) employed a pipeline with *OpenPose* to analyze cadence in daily clinical movies recorded from the frontal angle in healthy controls (n = 117) and two PD patients with prominent FoG. The authors reported a discrimination performance for mild PD gait from controls of 0.75–0.96 (area under curve) and for comparing gait sequences before vs. after DBS treatment (n = 1) of 0.98. On the whole, as the demand for efficient and cost-effective technologies for gait analysis grows, deep learning architectures are still lacking in precision but continue to improve rapidly and are increasingly being implemented into clinical studies and home assessments (Xue et al., 2018; Viswakumar et al., 2019; Sibley et al., 2021).

4.3. Summary and Discussion

Non-wearable technologies are becoming an attractive tool for gait and balance analysis due to their advantages compared to wearables. Their availability, portability, easy setup, and complete non-intrusiveness shorten the preparation time significantly and may reduce the stress of the participant. These attributes yield comparatively low pricing, bringing non-wearable marker-less tools distinct advantages over customary gold standard technologies that are costly and difficult to deploy in environments of everyday activities. Conversely, vision-based motion tracking accuracy of non-wearable systems remains lower than that of marker-based systems. While discrepancies in temporal parameters stay at a small scale, spatial parameter differences including joint angles vary from system to system and are significantly influenced by the experimental environment. Indeed, the error rate of most systems depends on the recording conditions as well as movement complexity and speed, which limits data capture to greater constraints and reduces the number of feasible walking assessments. Moreover, depth camera technology remains sensitive to potential light interference from multiple sensors and operates only in certain volume ranges, reducing the amount of suitable settings (Colyer et al., 2018).

At present, the application of in-depth technology in neurological disorders to quantify gait and balance impairments is yet in exploration. Although the performance of the reviewed systems has been exploited in healthy gait, studies on validity and reliability in pathological gait patterns are still rare, especially for most recent developments (*Azure*). Existing studies showed that spatiotemporal and kinematic parameters from walking and standing can be extracted and used for differentiation between PD/MS individuals and neurologically intact controls (Behrens et al., 2014; Ťupa et al., 2015; Gholami et al., 2016; Eltoukhy et al., 2017; Sabo et al., 2020), as well as for falling, tremor, and freezing detection in PD (Bigy et al., 2015). Furthermore, combining the in-depth camera output with downstream ML methods seems promising for robust gait analysis in the clinical context (Ťupa

et al., 2015; Bethoux et al., 2018; Elkurdi et al., 2018; Rocha et al., 2018). However, this comes at the loss of simplicity, and requires expert knowledge in the application.

Intensive research is currently carried out in the area of pose estimation with standard cameras. Yet, the available methods appear too complex for human gait analysis to be applied outside research environments at the moment. Nonetheless, the rapid evolution of these techniques can be predicted due to the high availability of video material and the already distributed toolboxes under creative commons licenses. Once intensively trained networks on large, standardized data sets are available, the application in clinical and home environments will be possible on a larger scale. In conclusion, for current and planned studies on movement disorders, the careful recording of video material, ideally from two or more perspectives, should be an integral part as this could allow a detailed motion analysis in the near future.

Altogether, marker-less vision-based motion tracking offers an exciting new opportunity for capturing gait-related data in the clinical context. Even though the technology is not yet mature, it shows distinct advantages over gold standard methods and might help unfold a new niche of easily accessible, repeated, longitudinal data collection not only in clinical but patients' home environments. The steady transition toward simpler recording technologies also fits impeccably the contact restrictions in the ongoing COVID-19 pandemic pushing the need for remote video measurements and analysis in telemedicine (Sibley et al., 2021).

5. CONCLUSION AND FUTURE DIRECTIONS

This review examined established and emerging wearable and vision-based portable technologies for objective gait and balance analysis applicable for neurological disorders. The literature published on the topic is extensive reflecting the high demand for reliable, sensitive, easily accessible, easy to use, and mobile measurement systems. New developments aim to reduce monetary and personnel costs, improve accessibility, and allow short as well as long-term assessments in and outside the clinic. Meeting all these demands still poses a challenge, since the continuous detection and characterization of locomotion in various environments is a complex task. Nonetheless, a great number of gait and posture parameters can be captured with inertial sensors, instrumented insoles, smartphones, in-depth cameras, and also to some extent with standard camera technology. Due to the increased sensitivity of these objective parameters, early subtle gait dysfunction or disease progression become measurable (Horak et al., 2015). Therefore, instrumentalized gait and balance analysis will play a major role in prospective diagnosis, prevention, therapy, and monitoring of neurological disorders.

The decision on a suitable measurement and analysis tool for current studies and clinical examinations depends on balancing the requirements for validity, reliability, and usability. The first step is to define the key parameters that are to be measured with high accuracy and sensitivity with respect to the target group and their gait and movement characteristics. For example, step length was shown to be an important biomarker in PD and vision-based tracking methods might be more reliable than wearables in tracking this parameter (de-la Herran et al., 2014). Especially in joint angle tracking, the reviewed technologies still lack reliability compared to laboratory-based systems, which offer the greatest sensitivity and are reliable over a wide spectrum of measures. Secondly, the choice of a measurement instrument is heavily influenced by the given or desired measurement setup. The various technical solutions also offer different operating concepts and workflows. Parameters can be either extracted in real-time, thus being available for immediate biofeedback or adaptive therapies, or parameters are determined offline, often yielding a higher accuracy. The distinct usability aspects must be carefully weighed before deciding to integrate a system into clinical trials, workflows, or home applications.

Provided with the broad overview of literature in this review, we recommend a number of improvements for future research: (1) To overcome the existing inconsistencies in application, reporting, and interpretation of the extracted gait and balance measures, the utilized hardware and software, including the version number, should be reported. (2) When comparing the assessed parameters with values from the literature, one has to be very careful regarding the exact definition of the parameter calculation. At the moment, reported gait and balance parameters vary greatly between studies, making it difficult to compare treatment effects or to choose meaningful parameters for future investigations. Therefore, publications should provide the exact parameter definitions and methods in the supplements, when using self-implemented algorithms, or refer to applied definitions from literature (Benedetti et al., 2013; Siragy and Nantel, 2018). (3) For the same reasons, in any gait data analysis, gait velocity should be included in experiments as a final common expression of gait performance, plus a range of gait variables according to pre-defined criteria (Lord et al., 2013). (4) Due to rapid developments in pose estimation, the careful recording of video material, ideally from two or more perspectives, should be an integral part of any upcoming study as this material could allow a detailed motion analysis soon.

However, before the new systems are integrated into clinical routines, further research into the validity and reliability of each device is essential, preferably with comparative studies in large populations of neurologically intact controls and individuals with neurological disorders (Horak et al., 2015). This requirement contrasts with the advantage that wearable and marker-less vision-based systems are less expensive than gold-standard technologies: The more effort that has been put into the development and validation of a technology, the more expensive commercially available systems become. Despite the required improvements, we hold the opinion that portable systems for objective assessment of gait and balance characteristics are indispensable to support the neurological, face-to-face exam along with imaging and other biomarkers to facilitate individualized, adaptive treatments in the future. We

see that there is a vicious circle to be escaped where as long as the technologies for simple and reliable gait analysis are not yet mature, the search for disease-specific biomarkers will be held up yielding skepticism toward the usefulness of these techniques. One future direction is the integration of several and novel sensor modalities (Buckley et al., 2019; Espay et al., 2019; Morita et al., 2020). Multiple sensors can provide redundant information and their fusion might reduce uncertainty, which can increase reliability in case of a sensor failure. The different modalities can provide objective, real-world data about the clinical phenotypes of individual patients over flexible amounts of time, possibly boosting our knowledge of locomotion and disease pathologies in the concept of deep phenotyping (Dorsey et al., 2020). The creation of normative databases (big data approaches) will yield an increased understanding of pathologies, enhancing the evaluation of therapies, and improve patient care (Buckley et al., 2019; Monje et al., 2019). In the long term, the emerging techniques for gait and balance tracking might be used for continuous monitoring and predicting disability such as fall risks in real-world environments (Weiss et al., 2015) and can be integrated into new, personalized therapeutic interventions. In the context of tele-consultations, tele-therapy and -rehabilitation, wearable and vision-based technologies can be utilized to report and monitor movement conditions and compliance with treatments. In the development of these telemedical applications, a strong focus should be on usability such that target user groups suffering from motor as well as mild cognitive impairments can use the technologies safely and reliably.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CS-H, MS, and MJ drafted the work (Introduction: CS-H, Measures of Gait and Postural Control and Wearable Technologies: CS-H and MJ, Non-wearable Technologies: Vision-Based Motion Analysis: MS and CS-H, Conclusion and Future Directions CS-H). All authors contributed to the conception, design of this work, and revised it critically for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Combined Subthalamic and Nigral Stimulation Modulates Temporal Gait Coordination and Cortical Gait-Network Activity in Parkinson's Disease

Jonas R. Wagner[1], Miriam Schaper[2], Wolfgang Hamel[2], Manfred Westphal[2], Christian Gerloff[1], Andreas K. Engel[3], Christian K. E. Moll[3], Alessandro Gulberti[1,3†] and Monika Pötter-Nerger[1†]*

[1]Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3]Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Freezing of gait (FoG) is a disabling burden for Parkinson's disease (PD) patients with poor response to conventional therapies. Combined deep brain stimulation of the subthalamic nucleus and substantia nigra (STN+SN DBS) moved into focus as a potential therapeutic option to treat the parkinsonian gait disorder and refractory FoG. The mechanisms of action of DBS within the cortical-subcortical-basal ganglia network on gait, particularly at the cortical level, remain unclear.

Methods: Twelve patients with idiopathic PD and chronically-implanted DBS electrodes were assessed on their regular dopaminergic medication in a standardized stepping in place paradigm. Patients executed the task with DBS switched off (STIM OFF), conventional STN DBS and combined STN+SN DBS and were compared to healthy matched controls. Simultaneous high-density EEG and kinematic measurements were recorded during resting-state, effective stepping, and freezing episodes.

Results: Clinically, STN+SN DBS was superior to conventional STN DBS in improving temporal stepping variability of the more affected leg. During resting-state and effective stepping, the cortical activity of PD patients in STIM OFF was characterized by excessive over-synchronization in the theta (4–8 Hz), alpha (9–13 Hz), and high-beta (21–30 Hz) band compared to healthy controls. Both active DBS settings similarly decreased resting-state alpha power and reduced pathologically enhanced high-beta activity during resting-state and effective stepping compared to STIM OFF. Freezing episodes during STN DBS and STN+SN DBS showed spectrally and spatially distinct cortical activity patterns when compared to effective stepping. During STN DBS, FoG was associated with an increase in cortical alpha and low-beta activity over central cortical areas, while with STN+SN DBS, an increase in high-beta was prominent over more frontal areas.

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***Correspondence:**
Monika Pötter-Nerger
m.poetter-nerger@uke.de

†These authors have contributed equally to this work

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Conclusions: STN+SN DBS improved temporal aspects of parkinsonian gait impairment compared to conventional STN DBS and differentially affected cortical oscillatory patterns during regular locomotion and freezing suggesting a potential modulatory effect on dysfunctional cortical-subcortical communication in PD.

Keywords: freezing of gait (FOG), Parkinson's disease, deep brain stimulation, subthalamic nucleus, substantia nigra, electroencephalography, stepping in place, beta oscillations

INTRODUCTION

Freezing of gait (FoG) is a sudden and episodic inability to produce effective forward stepping movements and is most commonly experienced in Parkinson's disease (PD). FoG typically occurs during gait initiation, turning, and gait adjustments (Nutt et al., 2011). Different freezing phenotypes exist including high-frequency leg shuffling, trembling in place, and akinetic freezing (Schaafsma et al., 2003). Due to its unpredictable nature, FoG increases the risk of falls and hospitalization (Latt et al., 2009) and causes a substantial reduction in quality of life (Moore et al., 2007).

Normal gait function is enabled by effective communication within a large-scale functional system of cortical, subcortical, and spinal hubs (Snijders et al., 2016; Takakusaki, 2017). During steady-state walking, automatic gait control is achieved by downstream projections from the mesencephalic locomotor area (MLR) and pedunculopontine nucleus (PPN) to spinal central pattern generators producing and modulating basic bipedal locomotor pattern (Takakusaki et al., 2008). Movement initiation and anticipatory adjustments of ongoing motion in response to changing environment are achieved by cortical gait control. Descending tracts from distributed cortical areas, including supplementary motor area (SMA), primary motor cortex, and somatosensory cortex, project *via* the basal ganglia (BG) loop to adjust the activity of MLR/PPN by GABA-ergic inhibitory output of the substantia nigra pars reticulata (SNr; Sherman et al., 2015; Lewis and Shine, 2016; Weiss et al., 2020).

Evidence accumulates that the underlying pathophysiology of freezing arises from a complex disbalance within a distributed locomotor network (Nieuwboer and Giladi, 2013; Weiss et al., 2020). Recently, it has been proposed that a "circuitopathy" of the supra-spinal locomotor network including the sensorimotor cortex, BG, and midbrain locomotor centers is a key feature in the common neural pathway of FoG in PD (Lewis and Shine, 2016; Pozzi et al., 2019). Dopaminergic depletion of substantia nigra pars compacta leads to an overinhibitory activity of the SNr resulting in an excessive suppression of the MLR (Sherman et al., 2015). In parallel, overactive nigral output strongly inhibits thalamocortical projections which interrupt cortical gait control (Snijders et al., 2016).

Several neurophysiological studies have highlighted the role of over-synchronized oscillatory activity within the cortico-BG network in the pathophysiology of motor and non-motor impairments in PD (see review Oswal et al., 2013). Recently, Pozzi et al. (2019) revealed a sudden and transient breakdown in functional connectivity between motor cortex and STN for the time of motor block in PD patients in the theta-alpha band within the more affected hemisphere which was already present during the transition from walking to FoG. Of interest, directionality analysis revealed that the pathologically increased synchronization within the cortico-subcortical network during resting-state is mostly driven by abnormal cortical activity (Litvak et al., 2011; Sharott et al., 2018; Cagnan et al., 2019) further emphasizing the important role of sensorimotor cortex failure in the underlying mechanism of freezing.

Deep brain stimulation of the STN (STN DBS) may improve certain spatial aspect of parkinsonian gait disturbance especially in early years after DBS implantation but usually fails to modulate temporal gait characteristics (Pötter-Nerger and Volkmann, 2013). In particular, STN DBS reduces dopamine-responsive OFF freezing (Fasano et al., 2012) but has limited therapeutic effect on dopamine refractory FoG. Clinical response to STN DBS has shown to be correlated to its modulatory effects on functional connectivity within the sensorimotor cortex (Weiss et al., 2015).

In view of apparently untreatable gait impairments under STN DBS, multi-site DBS such as the co-stimulation of the STN and of the substantia nigra (STN+SN DBS) moved into focus. From a pathophysiological perspective, additional SNr stimulation is supposed to suppress pathological nigral activity and thereby may reduce excessive inhibition of the brainstem locomotor centers through overactive GABA-ergic SNr-PPN-projections (Snijders et al., 2016). In clinical practice, simultaneous high-frequency STN and SN stimulations are realized by co-activating the most caudal contact of the STN DBS electrode when located in the SN area. Recent intraoperative microelectrode recordings of the SNr during test stimulation seem to confirm the DBS-induced neural inactivation of SNr neurons (Milosevic et al., 2018). Nevertheless, the modulatory effect of STN+SN DBS on cortical-subcortical network level has not been investigated yet. So far, there are few case series (Weiss et al., 2011; Brosius et al., 2015) and one double-blinded cross-over study on STN+SN DBS (Weiss et al., 2013) suggesting an improvement of FoG by additional nigral stimulation. Currently, randomized multi-center data of STN+SN DBS are being analyzed (clinical trial registration number NCT02588144). Of interest, high-frequency SN stimulation showed the beneficial effect on bilateral temporal gait coordination (Scholten et al., 2017) which plays an important role in the temporal evolution of FoG (Plotnik et al., 2005; Chee et al., 2009).

Simultaneous EEG and kinematic measurements in PD patients during active DBS offer the opportunity to investigate the cortico-subcortical network by measuring activity changes in the cortical locomotor network in response to DBS-induced

modulation of important subcortical locomotor hubs as the STN and the SN. The goal of this study was first to analyze the effect of STN+SN DBS compared to STN DBS on temporal gait characteristics in PD patients and second, to characterize cortical activity changes induced by additional SN stimulation during resting-state, effective lower limb stepping, and freezing episodes. We hypothesized that additional high-frequency stimulation of the SN leads to a disinhibition of both mesencephalic locomotor area and thalamo-cortical projections. This DBS-induced modulation of the cortical-BG-mesencephalic locomotor network might result in an improvement of gait function and might be quantifiable by changes in oscillatory activity over cortical areas.

MATERIAL AND METHODS

This study was conducted in agreement with the Code of Ethics of the World Medical Association (World Medical Association Declaration of Helsinki, 2013) and was approved by the local ethics committee (reference: PV5281). All participants gave their written informed consent before taking part in the study.

Subjects

A total of 12 patients with idiopathic PD (11 male, age: 66.5 ± 7.6 years, disease duration: 14.8 ± 4.7 years, Montreal Cognitive Assessment (MoCA) score: 26.9 ± 1.9) with chronically-implanted DBS electrodes, (time with DBS: 4.0 ± 3.8 years), were assessed and compared to 12 age-matched healthy controls (all male, age: 61.3 ± 7.5 years, MoCA score: 27.3 ± 1.4). PD patients were considered suitable candidates for the experimental protocol when the conditions were met that: (i) bilateral STN DBS electrodes were implanted for at least 6 months, and their lowermost contacts were localized within the dorsal substantia nigra; (ii) patients were able to stand and walk for at least 1 min without external assistance; (iii) did not present any competing neurological diseases or other gait-affecting musculoskeletal impairments by the time of testing; and (iv) the dopaminergic medication remained unchanged in the preceding 4 weeks. Preoperatively, all PD patients were screened and selected for DBS surgery in accordance with the common guidelines of DBS surgery (Defer et al., 1999). All patients were tested on their regular dopaminergic medication. As the PD patients selected for the study suffered from levodopa-resistant FoG, we expected no relevant medication-induced changes in stepping performance or cortical activity during a motor task. **Table 1** provides further details of the clinical characteristics.

Surgery and Electrode Localization

All DBS systems were implanted at the Department of Neurosurgery at the University Medical Center Hamburg-Eppendorf, Germany. A detailed description of the surgical and lead placement procedure has been reported elsewhere (Sharott et al., 2014; Hidding et al., 2017; Dietrich et al., 2020). In brief, individual target coordinates for the dorsal STN were determined using preoperative magnetic resonance images fused with stereotactic computed tomography scans. In all patients, final electrode placement was adjusted according to intraoperative microelectrode recordings. The subthalamic and nigral region was mapped with sharp tungsten electrodes (Alpha Omega Inc., Nazareth, Israel) in up to five parallel tracks. Neurons of the sensorimotor STN were identified by tonic irregular oscillatory bursting activity in the range between 10 and 30 Hz and cell response to active and passive limb movements. A clear decrease of background noise and the emerging of high-frequency regular spiking activity signaled the entrance of the micro-tips into the SNr. Postoperatively, the reconstruction of the active DBS lead contacts (model 3389; Medtronic®, Minneapolis, MN, USA; electrode model 3389, Medtronic®, Minneapoli, MN, USA, in 10 cases, and electrode model 2202 and model 2201, Boston Scientific®, Valencia, CA, USA, in two cases) was performed by co-registration of the preoperative T1 MRI scans and post-operative CT scans using iPlan (iPlan stereotaxy; Brainlab, Feldkirchen, Germany). Further details concerning the localization of active electrode contacts are reported elsewhere (Hamel et al., 2003; Hidding et al., 2017, 2019).

Experimental Protocol

Patients were evaluated in three DBS stimulation conditions in a pseudorandomized order with at least 45 min waiting period between conditions to prevent potential carry-over effects of the previous DBS setting: (i) with DBS switched off (STIM OFF); (ii) with DBS switched on with omnidirectional activation of the standard therapeutic contact located in the STN (STN DBS); and (iii) with DBS switched on with omnidirectional activation of two contacts for each lead: the standard therapeutic contact located in the STN, and one supplemental contact putatively located in the SN (STN+SN DBS). STN DBS and STN+SN DBS were standardized with a pulse width of 60 μs and a pulse frequency of 125 Hz and 130 Hz for Medtronic® and Boston Scientific®, respectively. Active contacts and amplitudes were kept unchanged (i.e., the everyday therapeutic stimulation settings) to ensure the best individual STN stimulation. The combined STN+SN stimulation was provided by an additional activation of the lowermost contact using the "interleaving pulse" mode as suggested previously (Weiss et al., 2013) while active contacts and amplitudes of STN stimulation were held constant. Amplitudes for the "nigral" contacts were set according to a threshold testing for side effects prior to this study (Hidding et al., 2017). All stimulation settings were applied bilaterally. Details of DBS settings are provided in **Table 2**. We chose high-frequency DBS in both nuclei since this setting was most often used for the combined STN-SN stimulation mode in preceding studies. Patients and investigators were blinded to the counterbalanced sequence of stimulation conditions. To evaluate the clinical effectiveness of the different DBS stimulation settings, the motor sub-score of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) was assessed by the same experienced investigator throughout the entire study. First, a 1 min seated resting-state task with eyes open was performed. Second, a Stepping in Place (SIP) task was used to simulate gait and provoke freezing episodes. SIP was used as it shared the same basic features of gait such as rhythmic alternating bilateral leg movements but could be performed under the restricted space condition

TABLE 1 | Clinical and demographic characteristics of PD patients and healthy matched control persons.

	PD patients			Healthy controls (*n* = 12)
	All (*n* = 12)	**Freezers (*n* = 7)**	**Non-freezers (*n* = 5)**	
Age [years]	66.5 ± 7.6	68.6 ± 3.1	63.6 ± 3.0	61.3 ± 7.5
MoCA	26.9 ± 1.9	26.6 ± 0.8	27.4 ± 0.7	27.3 ± 1.4
Disease duration [years]	14.8 ± 4.7	15.7 ± 2.1	13.6 ± 3.4	*n.a.*
Postoperative time [months]	48.2 ± 46.0	48.6 ± 22.4	47.6 ± 23.6	*n.a.*
Hoehn and Yahr	2.4 ± 0.8	2.7 ± 0.4	2.00 ± 0.0	*n.a.*
MDS-UPDRS III				
STIM OFF	42.9 ± 10.9	45.1 ± 12.9	39.8 ± 9.4	*n.a.*
STN DBS	28.5 ± 10.5	31.7 ± 12.5	24.0 ± 7.4	
STN+SN DBS	29.3 ± 11.7	33.0 ± 13.1	24.0 ± 9.5	
Stepping variability				
STIM OFF	14.2 ± 7.4	17.7 ± 7.9	9.2 ± 1.7	8.1 ± 1.8
STN DBS	14.5 ± 6.8	17.4 ± 5.8	10.4 ± 6.4	
STN+SN DBS	13.0 ± 6.3	16.8 ± 5.6	7.7 ± 1.2	
Stepping asymmetry				
STIM OFF	14.1 ± 13.5	21.2 ± 13.6	4.1 ± 3.6	7.9 ± 5.1
STN DBS	12.0 ± 9.7	15.5 ± 8.3	7.0 ± 10.0	
STN+SN DBS	14.0 ± 11.6	19.1 ± 7.9	7.8 ± 5.1	
Mean FoG duration [s]				
STIM OFF	*n.a.*	4.1 ± 3.4	*n.a.*	*n.a.*
STN DBS		2.2 ± 2.6		
STN+SN DBS		6.8 ± 8.4		
Number of FoG episodes				
STIM OFF	*n.a.*	1.9 ± 1.7	*n.a.*	*n.a.*
STN DBS		1.0 ± 1.8		
STN+SN DBS		1.6 ± 1.8		

In "Disease duration (years)", the disease duration is calculated from the date of diagnosis to the date of baseline measurement. Abbreviations: FoG, Freezing of gait; MoCA, Montreal Cognitive Assessment score; MDS-UPDRS-III, motor-subscore (part III) of the Unified Parkinson's Disease Rating Scale of the Movement Disorder Society; n.a., not applicable.

during EEG recordings. Previous studies have demonstrated that forward walking and SIP showed similar altered temporal gait characteristics in PD (Syrkin-Nikolau et al., 2017) and that SIP effectively elicited FoG in PD freezers (Nantel et al., 2011; Fraix et al., 2013; Chomiak et al., 2015) which strongly correlated with patients' self-report of freezing (Nantel et al., 2011). SIP was performed during: (1) continuous, regular stepping; and (2) stepping requiring sudden gait adjustments to increase susceptibility to FoG. More specifically, in task 1 the participants were instructed to execute alternating stepping movements in the upright position with their left and right leg at a self-paced, comfortable speed for 35 s. In task 2, stepping movements had to be adjusted in response to 10 auditory "start" and "stop" signals at various, randomized latencies with SIP intervals of 3–10 s. For each DBS condition, recordings lasted for about 5 min.

Data Acquisition

Stepping kinematics of lower limbs were recorded using two tri-axial accelerometers (MMA7260QT, Freescale Semiconductor Inc., Tempe, AZ, USA) attached to the outer foot ankles. Cortical activity was recorded using a 64-channel EEG system, with active ring electrodes mounted in accordance with the 10–10 system and referenced to the nose tip, including two additional EOG electrodes (EASYCAP GmbH, Herrsching, Germany). The electrodes had integrated impedance converters fitted directly into the electrode in order to minimize noise from the surrounding area as well as from movement artifacts. EEG and accelerometer signals were simultaneously recorded using BrainAmp amplifiers with analog bandpass filters set at 0.016–250 Hz and at 0.016–1,000 Hz, respectively, and a sampling rate of 2,500 Hz (BrainProducts, Munich, Germany). The frequency cutoff value of the high-pass was chosen to reduce artifacts from cable movements and channel drifts while minimizing data distortion. Cutoff frequencies for low-pass filtering were set to 250 Hz and 1,000 Hz for EEG and accelerometers respectively to ensure the retaining of the full range of physiological frequency spectra for further offline analysis.

Behavioral Analysis

Heel strikes during SIP were automatically detected by a customized MATLAB script and checked by visual inspection. FoG episodes were identified based on the characteristic shift of frequency spectra of vertical leg acceleration towards higher frequency components compared to effective stepping (**Figure 1**; Moore et al., 2008). To this end, vertical accelerometer axes were bandpass filtered from 0.5 to 8 Hz and resampled at 100 Hz. Time-frequency transformation between 0.5 and 8 Hz was calculated using a Hanning-taper with a fixed time window of 4 s resulting in a frequency resolution of 0.5 Hz. For each point in time (10 ms), a freezing index (FI) was computed as the ratio between the square of the area under the power spectra in the "freezing" band (3.5 to 8 Hz) and the "locomotor" band (0.5–3 Hz). An individual freezing threshold was defined as a continuous period of time (≥3 s) in which FI was greater than the mean + 1 SD of the peak FI during standing before stepping initiation (Pozzi et al., 2019). This procedure has shown to be a reliable marker for objective freezing detection

TABLE 2 | Stimulation parameters for STN and STN+SN DBS.

		STN stimulation				Additional SN stimulation				Common settings			X/Y/Z coordinates
		Left electrode		Right electrode		Left electrode		Right electrode		Freq *[Hz]*	Pulse width *[μs]*		[mm]
ID	DBS syst	*Contacts*	*Amplitude*	*Contacts*	*Amplitude*	*Contacts*	*Amplitude*	*Contacts*	*Amplitude*		*left*	*right*	
PD01	ME	2	3.2 V	10	3.0 V	0	1.5 V	8	1.7 V	125	60	60	L: 11.2 / 1.9 / 5.6 R: 8.3 / 5.5 / 4.0
PD02	ME	2	3.7 V	9	2.8 V	0	2.0 V	8	2.0 V	125	60	60	L: 10.9 / 2.2 / 4.7 R: 1.05 / 3.8 / 4.7
PD03	ME	1	3.3 V	9	3.1 V	0	1.5 V	8	1.5 V	125	60	60	L: 10.9 / 1.4 / 7.7 R: 11.1 / 2.7 / 6.7
PD04	ME	2	3.2 V	10	1.5 V	0	1.5 V	8	1.5 V	125	60	60	L: 11.9 / 2.2 / 5.2 R: 10.2 / 4.0 / 5.6
PD05	ME	2	1.6 V	10	2.4 V	0	1.0 V	8	1.0 V	125	60	60	L. 11.2 / 2.7 / 6.7 R: 8.2 / 1.6 / 4.4
PD06	ME	1	3.5 V	9	3.3 V	0	1.0 V	8	1.0 V	125	60	60	L: 11.3 / 2.2 / 6.2 R: 12.2 / 0.2 / 5.2
PD07	BS	5 / 6 / 7	2.7 mA	13 / 14 / 15	3.2 mA	1	3.5 mA	9	3.7 mA	130	60	60	L: 10.9 / 2.5 / 5.7 R: 10.4 / 0.4 / 5.2
PD08	BS	2 / 3	3.2 mA	10 / 11	4.0 mA	1	4.2 mA	9	5.0 mA	130	60	60	L: 8.81 / 3.4 / 7.4 R: 7.04 / 4.3 / 6.4
PD09	ME	1	1.7 V	10	3.0 V	0	1.0 V	8	1.0 V	125	60	60	L: 11.0 / 2.5 / 5.9 R: 10.1 / 1.3 / 5.0
PD10	ME	3	1.6 V	11	2.9 V	0	1.0 V	8	1.0 V	125	60	60	L: 9.5 / 2.8 / 6.4 R: 11.2 / 1.4 / 7.2
PD11	ME	3	3.5 V	10	3.3 V	0	0.7 V	8	0.7 V	125	60	60	L: 9.2 / 2.8 / 7.7 R: 10.2 / 2.4 / 6.0
PD12	ME	1	2.4 V	9	2.3 V	0	1.0 V	8	1.0 V	125	60	60	L: 10.7 / 5.3 / 6.9 R: 7.7 / 3.1 / 6.8

STN+SN DBS was realized by additional activation of lowermost electrode contacts (Medtronic: contacts 0 and 8, Boston Scientific: contacts 1 and 9), while all other stimulation parameters used in STN DBS were held unchanged. Values reported are active contacts, amplitude (V = volts or mA = milliampere), pulse width (μs = microseconds) and stimulation frequency (Hz), for the left and right electrode. The neurostimulator case was always set as positive (anode) and the active contacts as negative (cathodes, contact number). For the left Medtronic (ME) electrode, contact 0 was the most ventral and contact 3 was the most dorsal. For the right ME electrode, contact 8 was the most ventral and contact 11 was the most dorsal. For the left Boston Scientific (BS) electrode, contact 1 was the most ventral and contact 8 was the most dorsal. For the right BS electrode, contact 9 was the most ventral and contact 16 was the most dorsal. Electrode coordinates are given in relation to the AC-PC line (mm) lateral to the midline (X), posterior to the mid-commissural point (Y) and inferior to the inter-commissural plane (Z).

(Morris et al., 2012). All selected freezing episodes were verified by visual inspection of the data. Patients were labeled as "freezers" if they experienced freezing episodes in at least one DBS stimulation condition and labeled as "non-freezers" if they did not show FoG in any DBS setting. Effective stepping was defined as consecutive alternating heel strikes outside of FoG episodes. For each patient, the longest period of uninterrupted effective SIP was visually determined during the first block of 35 s of continuous SIP excluding the first 2 s after stepping initiation. Based on these predefined stepping episodes, temporal stepping parameters were explored. We focused on effects on stepping variability and symmetry, as FoG severity seems to correlate with gait asymmetry (Plotnik et al., 2005), and a previous study suggested a selective effect of nigral stimulation on temporal bilateral gait coordination (Scholten et al., 2017). First, subject's mean step-to-step time for each foot was extracted from effective SIP episodes. Then, stepping variability (*var*) was analyzed as the *z*-transformed step-to-step time (*SPT*) coefficient of variability as

$$var = SD(SPT)/mean(SPT) \times 100$$

where higher value is associated with a higher degree of stepping variability. Stepping asymmetry (*asym*) was calculated as suggested in Plotnik et al. (2005).

$$asym = \left|\ln(SSDT/LSDT)\right|$$

where *SSPT* and *LSPT* correspond to the leg with the shorter and longer mean stride time, respectively. An asymmetry index closer to 0 represents a more symmetric gait.

Electrophysiological Analysis

EEG signals were pre-processed using the open-source EEGLAB toolbox (Version, 2020.0; Delorme and Makeig, 2004). To eliminate high frequency DBS artifacts, EEG data were low-pass filtered using a zero-phase Kaiser-windowed FIR filter at 100 Hz (pass-band 0–90 Hz, transition width 10 Hz, attenuation −60 dB). After down-sampling to 1,000 Hz, high-pass filtering at 0.75 Hz (zero-phase Kaiser-windowed FIR filter, stop-band 0–0.5 Hz, transition width 0.5 Hz, attenuation −60 dB) was performed to minimize slow drifts. Flat, noisy or uncorrelated channels were identified using the "clean_rawdata" EEGLAB plug-in, and replaced using spherical spline interpolation. On average, 58 out of 64 EEG channels per subject remained for further analysis (STIM OFF: 57 ± 4, STN DBS 58 ± 2, STN + SN DBS 58 ± 2). Artifact Subspace Reconstruction (ASR) was used to detect short-lasting artifacts in the data that most probably originated from muscular activity (Mullen et al., 2015). This principal component analysis (PCA) based method rejected non-stationary high-amplitude components and reconstructed channel data within a 0.5 s sliding window from remaining components. Rejection criterion was set to 15 SD of the mean amplitude of a clean portion of the same data. This threshold was in line with the one proposed in the literature (Chang et al., 2018) and visual inspection of the data before and after ASR ensured that clean portions of data were fully retained. EEG data were then re-referenced to a common average reference. Next, independent component analysis (ICA) was applied to decompose EEG signals. We used the adaptive mixture ICA method (AMICA) introduced by Palmer et al. (2008) which calculates temporal and spatial characteristics of independent components using a flexible sum of extended Gaussian models. AMICA was shown to outpower other common ICA methods in terms of component separation and dipole fitting (Delorme et al., 2012) and was successfully applied in a series of EEG analyses investigating human walking (Wagner et al., 2012, 2016, 2019). The number of independent components were reduced to the number of remaining eigenvalues of EEG data. Stereotypical artifacts including eye movements, blinks, ECG, DBS and muscular artifacts were removed based on their temporal characteristic and scalp projection. On average, 11 components per subject were rejected (STIM OFF: 11 ± 5, STN DBS 11 ± 5, STN+SN DBS 11 ± 6). Finally, a surface Laplacian transformation using the spherical spline method (lambda = 10^{-5}, spline order = 4, spline iterations = 50, Perrin et al., 1989) was applied to further reduce movement artifacts and volume conduction. Cortical activity was analyzed using power-frequency spectra of absolute power. To compare episodes of effective SIP with different length among participants, EEG data were segmented in consistent non-overlapping epochs of 1 s length on subject level. For each epoch, power spectra were calculated using the open-source Fieldtrip toolbox (Version 20170607, Oostenveld et al., 2011). The embedded multitapers technique was used to increase statistic sensitivity and to compensate for small trial numbers. Spectral power analyses were performed between 4 and 45 Hz with a frequency resolution of 1 Hz and a frequency smoothing of ±2 Hz resulting in three Slepian sequence tapers being used. The absolute power spectra were transformed for normalization using natural logarithm and averaged within main frequency bands: theta (4–8 Hz), alpha (9–13 Hz), low-beta (14–20 Hz), high-beta (21–30 Hz), and gamma (31–45 Hz).

Statistical Analysis

Statistical analyses were performed in SPSS Statistics 26 (IBM Coorp., New York, USA) and using the statistical methods as implemented in the FieldTrip toolbox for MATLAB® (Maris and Oostenveld, 2007). All residuals were checked for normal distribution using Shapiro-Wilk tests. Biographic characteristics of PD freezers and non-freezers were compared using independent samples Mann-Whitney-U tests. To evaluate changes in UPDRS-III symptom scores between DBS settings a non-parametric Friedman test was conducted followed by Wilcoxon sign-rank tests for *post hoc* pairwise comparison.

Mean freezing duration and number of freezing episodes were compared between DBS conditions using repeated-measures ANOVAs with the three-level within-subject factor "stimulation". To analyze the effect of stimulation setting on each temporal gait parameter in comparison to healthy controls, three separate independent samples *t*-tests (STIM OFF, STN DBS, and STN + SN DBS vs. controls) were performed. To compare the effect of the DBS conditions on gait parameters, repeated-measures ANOVAs were performed with the 3-level within-subject factor "stimulation" (STIM OFF, STN DBS, STN+SN

DBS) and the between-subject factor "freezing" ("freezers" vs. "non-freezers"). Planned *post-hoc* paired samples *t*-tests were used for pairwise comparisons between DBS settings.

We tested the effect of the three DBS conditions on cortical oscillatory activity with respect to the different motor states in PD patients. We analyzed patients' spectral power distributions in resting-state and continuous SIP (STIM OFF, STN DBS, and STN+SN DBS) in comparison to healthy controls (HCs) and between each other. We then compared relative power changes between SIP and resting-state conditions separately for healthy controls and each DBS condition. To do so, we used the non-parametric cluster-based permutation statistics as provided by the FieldTrip toolbox (Maris and Oostenveld, 2007). This approach was chosen due to the exploratory nature of this study, as it ensured a comprehensive analysis of the data without *a priori* assumptions and at the same time controlled for multiple comparisons. For each frequency band and channel, a distribution of the chosen test statistic was built. Two or more neighboring channels falling below a *p*-value of 0.05 were clustered on basis of spatial and spectral similarities. The sum of test statistic values within each cluster was then computed. To correct for multiple comparisons the maximum cluster-level test statistic was calculated using 2,000 random permutations across participants. Clusters below an alpha level of $\alpha = 0.025$ (each side) were considered significant. For comparison of cortical activity between HCs and PD patients during resting-sate and SIP t-value distribution were built using independent samples *t*-tests. Analysis of power modulation between resting-state and SIP was conducted using paired samples *t*-tests separately for controls and DBS settings. To assess differences in cortical activity between STIM OFF, STN DBS, and STN+SN DBS cluster-based permutation tests were performed using the embedded dependent ANOVA F-statistics with the within-subject factor "stimulation" (STIM OFF vs. STN DBS vs. STN+SN DBS).

To compare stimulation effects on cortical power during freezing episodes between STIM OFF, STN DBS, and STN+SN DBS power spectra were analyzed by conducting Linear Mixed Effects Models (LMMs) in order to compensate for different numbers of freezers in each DBS setting. To this end, we first calculated mean averaged power spectra at a central-midline region of EEG. This ROI included the averaged signal of "Cz" electrode and its six neighboring electrodes corresponding to "FCz" and approximately to the "C1", "C2", "CP1", "CP2", "CPz" position of the international 10–10 system (see pictogram in panel A of **Figure 3**). The central ROI was strategically positioned to sample activity from cortical areas with particular relevance to locomotion including the supplementary motor area, premotor cortex, and primary motor cortex (Nutt et al., 2011; Takakusaki, 2013, 2017; Snijders et al., 2016). All covariance structures for repeated measures and random effects embedded in SPSS were compared. We chose those covariance structures that provided the best model fit using likelihood ratio tests. If the model fit of covariance structures did not differ significantly, we compared the goodness of fit between models using the Akaike information criterion (AIC) and selected the model with the best relative fit to data. Random slopes were tested for each model using the same procedure. Restricted maximum likelihood was used for parameter estimation. Estimated marginal means were used for pairwise comparisons between DBS settings.

RESULTS

Clinical Characteristics and Freezing Severity

An overview of DBS effects on clinical and temporal gait characteristics is provided in **Table 1**. General motor performance as indexed by the MDS-UPDRS III was significantly improved by DBS ($\chi^2(2) = 18.43$, $p < 0.001$). STN DBS reduced the MDS-UPDRS III score by >30% compared to the baseline condition with DBS switched off (STIM OFF vs. STN DBS $Z = -3.07$, $p < 0.001$) indicating sufficient therapeutic effect and correct DBS lead position within the STN. The STN+SN DBS condition also significantly improved MDS-UPDRS III scores compared to baseline (STIM OFF vs. STN+SN DBS $Z = -3.07$, $p < 0.001$). There was no significant difference in MDS-UPDRS III scores between STN DBS and STN+SN DBS ($Z = -0.49$, $p = 0.327$). Based on biomechanical analyses, seven PD patients were identified as freezers as they showed at least one freezing episode in one of the DBS conditions during SIP. Five PD patients were identified as non-freezers as they performed the SIP tasks without any freezing episode. PD freezers and non-freezers did not reveal any significant group differences in terms of age, disease duration, time with DBS, MoCA score or Hoehn and Yahr disease stage (all *p*-values > than 0.1). In summary, six PD patients experienced 13 FoG episodes during STIM OFF with a total FoG duration of 82.3 s, whereas during standard STN DBS only three of 12 patients showed freezing behavior with a total number of seven freezing episodes and with a cumulative freezing duration of 50.5 s length. During combined STN+SN DBS five patients experienced a total of 11 FoG episodes with a duration of 70.5 s. Due to high interindividual variance in therapeutic response there was no significant main effect for stimulation on both FoG frequency ($F_{(2,12)} = 0.923$, $p = 0.424$) and FoG duration ($F_{(2,10)} = 0.964$, $p = 0.414$).

Temporal Gait Characteristics

We tested whether temporal gait characteristics were affected by different DBS settings. Comparing HCs and PD patients during STIM OFF condition, PD patients showed a significant lower step-to-step time ($t_{(22)} = -4.27$, $p < 0.001$) reflecting parkinsonian gait with small shuffling steps. Furthermore, PD patients were characterized by a temporal gait dysregulation with significant higher temporal variability during effective SIP ($t_{(22)} = 2.66$, $p = 0.014$) and a slightly, non-significant increase in stepping asymmetry ($t_{(22)} = 1.94$, $p = 0.076$) compared to HCs. Subgroup-analysis revealed that PD freezers in STIM OFF showed a significant higher degree of stepping variability ($t_{(22)} = 2.66$, $p = 0.014$) and stepping asymmetry ($t_{(7.02)} = 2.50$, $p = 0.041$) compared to HCs. In contrast, non-freezers and HCs did not differ significantly with regard to temporal stepping parameters. Repeated-measures ANOVA revealed a clear between-subject effect showing significantly higher step-to-

step time variability in freezers compared to non-freezers during effective SIP, independent of DBS condition ($F_{(1,10)} = 34.07$, $p < 0.001$, $\eta^2 = 0.77$) emphasizing temporal gait parameters as suitable surrogate markers for freezing severity. STN DBS failed to improve both stepping variability and stepping asymmetry with respect to STIM OFF. However, combined STN+SN DBS led to a reduction in stepping variability compared to standard therapeutic STN DBS, which was statistically significant for patients' more affected leg ($t_{(11)} = 2.47$, $p = 0.031$) suggesting a modulatory effect of STN+SN DBS on temporal gait integration in PD patients (**Figure 2**).

Cortical Activity in STIM OFF During Resting-State and Effective Stepping

High-density EEG recordings revealed that cortical oscillatory activity of PD patients and controls differed in the topographical distributions and absolute power levels, particularly at the central ROI between resting-state (**Figures 3A,B**), effective SIP (**Figures 3C,D**), and FoG episodes (**Figures 3E,F**). Cluster-based permutation test at rest revealed a significant power increase in low-frequency bands in untreated PD patients compared to HCs. In PD patients in STIM OFF, theta activity ($t = 99.01$, $p = 0.008$) at bilateral cluster of fronto-parietal electrodes and alpha activity ($t = 11.98$, $p = 0.048$) at right frontal cluster were significantly increased compared to controls. High-beta power in a cluster of midline-central channels was increased with p-value close to the alpha level ($t = 8.64$, $p = 0.072$; **Figure 4A**). During SIP, the cluster-based permutation tests still revealed elevated theta power at disseminated cortical clusters in PD patients with DBS switched off in comparison to control persons (STIM OFF vs. HC: $t = 102.27$, $p < 0.001$), elevated alpha power over bilateral frontoparietal sensors ($t = 68.94$, $p = 0.006$), increased high-beta power over left-lateralized clusters ($t = 73.34$, $p = 0.003$) and raised gamma activity ($t = 57.80$, $p = 0.004$) in PD patients in STIM OFF compared to controls (**Figure 4B**). Absolute theta power and beta power were not significantly modulated by continuous SIP compared to resting-state in PD patients in STIM OFF (**Figure 5A**). In HCs, alpha power was significantly desynchronized during SIP compared to resting over a right central-parietal cluster ($t = -26.83$, $p = 0.011$), but not in PD patients in STIM OFF condition. Gamma frequency power significantly increased during SIP compared to resting-state in both groups, HC and untreated PD, over a wide-spreading cluster of frontoparietal electrodes (HC: $t = 58.48$, $p = 0.002$, STIM OFF: $t = 190, 48$, $p < 0.001$; **Figure 5A**).

Summarizing, compared to healthy controls PD patients in the STIM OFF condition revealed increased, cortical absolute power in theta, alpha, and high beta frequencies in resting-state and effective stepping, and a reduced movement-related alpha desynchronization during SIP.

Cortical Activity in Active DBS During Resting-State and Effective Stepping

In a second step, we focused on the effects of STN DBS and STN+SN DBS on cortical oscillatory power during resting-state and SIP. In the resting-state condition, cluster-based permutation tests revealed a significant increase in theta activity in PD patients in both active DBS conditions compared to healthy controls (STN DBS vs. HC: $t = 91.26$, $p = 0.005$; STN+SN DBS vs. HC: $t = 62.14$, $p = 0.012$). In contrast, resting-state alpha power and high-beta power were no longer increased in PD during STN DBS and STN+SN DBS conditions compared to controls indicating a modulatory effect on alpha and high-beta activity by both DBS settings (**Figure 4A**). In line with the results on resting-state, cortical activity during stepping in place was characterized by a significant and excessive increase in theta power independent of DBS settings over disseminated cortical clusters compared to HCs (STN DBS vs. HC: $t = 88.20$, $p < 0.001$; STN+SN DBS vs. HC: $t = 134.53$, $p < 0.001$; **Figure 4B**). Theta power was not significantly modulated during regular SIP compared to resting-state in PD patients with active DBS (**Figure 5A**). Alpha frequency power during SIP was still significantly increased in PD patients with active DBS compared to HCs (**Figure 4B**), this effect was most pronounced over bilateral central-parietal areas (STN DBS vs. HC, left cluster: $t = 15.17$, $p = 0.031$, right cluster $t = 14.87$, $p = 0.032$; STN+SN DBS vs. HC: $t = 73.05$, $p = 0.003$). However, alpha power was significantly desynchronized during SIP compared to resting-state in both active DBS conditions indicating a re-established movement-related cortical alpha modulation (STN DBS: $t = -51.52$, $p = 0.004$; STN+SN DBS: $t = -11.95$, $p = 0.044$; **Figure 5A**). During regular SIP, high-beta power was reduced toward the level of HCs during both, STN DBS and STN+SN DBS (**Figure 4B**). Low- and high-beta power at central sites were significantly desynchronized by SIP compared to resting-state in STN DBS condition (low-beta: $t = -39.16$, $p = 0.004$; high-beta: $t = -18.56$, $p = 0.020$; **Figure 5A**). Gamma frequency power significantly increased during SIP compared to resting-state in PD with STN DBS over a wide-spreading cluster of channels. STN+SN DBS was instead showing a more focal gamma power increase over a central-parietal cluster (STN DBS: $t = 199.33$, $p < 0.001$, STN+SN DBS: $t = 132.04$, $p < 0.001$; **Figure 5A**).

Summarizing the effect of DBS on cortical oscillatory power changes, we observed that both STN DBS and STN+SN DBS modulated cortical activity, resulting in a normalization of pathologically increased resting-state alpha and high-beta power. During SIP, both DBS settings successfully reduced exaggerated high-beta activity and restored the physiological, movement-related alpha desynchronization.

Cortical Activity During Gait Freezing

In a third step, we assessed cortical activity changes during FoG episodes and the impact of the DBS conditions. We analyzed differences in cortical activity between regular SIP and FoG episodes within the PD "freezers" group using the cluster-based permutation test. In the STIM OFF condition, cortical activity did not differ significantly in any frequency band between regular SIP and FoG (OFF-FoG). However, FoG episodes that occurred during STN DBS (ON-FoG) were characterized by a significant increase in parietal alpha power ($t = 13.56$, $p < 0.001$) and central low-beta power ($t = 19.24$, $p < 0.001$) compared to regular SIP (**Figure 5B**). These effects were most obvious in midline-postcentral and midline-central areas, respectively. In

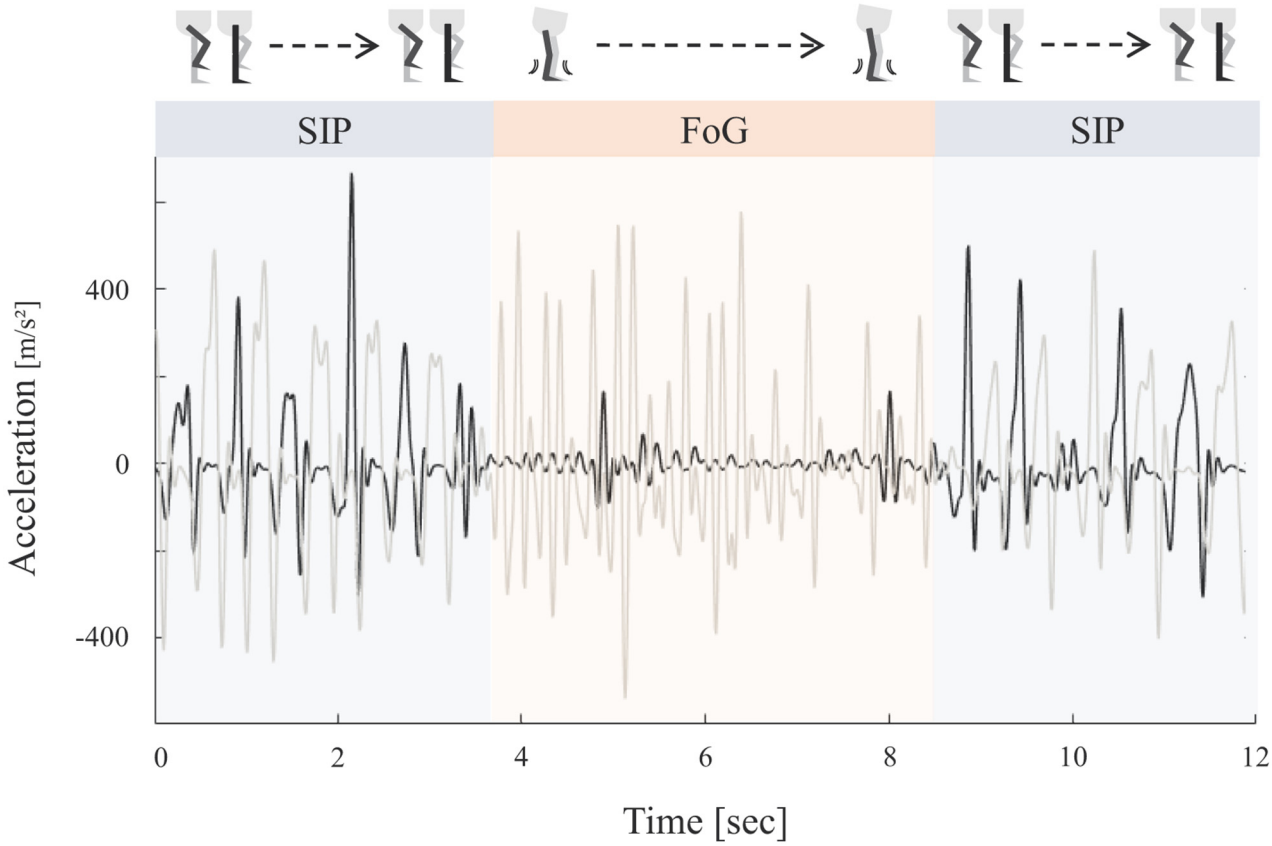

FIGURE 1 | Schematic representation of the stepping in place (SIP) task and corresponding accelerometer curves. Example of vertical accelerometer signals of both legs (black = right leg, gray = left leg) during continuous SIP interrupted by a freezing episode. Effective stepping was characterized by alternating heel strikes. Freezing episodes were defined by high frequency low amplitude oscillations reflecting leg trembling during freezing of gait (FoG).

contrast, ON-freezing during STN+SN DBS was characterized by a significant increase in high-beta power over a cluster of frontal sensors as during regular SIP ($t = 11.64$, $p = 0.034$; **Figure 5B**). To investigate differences in absolute cortical power between STIM OFF, STN DBS, and STN+SN DBS, we conducted LMMs for power differences over the predefined ROI located over central EEG signals that showed significant beta modulation during stepping in place in STN-DBS condition. For each frequency band, a random intercept fixed slope model with a scaled identity matrix as a repeated covariance type was used. Estimated marginal means of random intercept fixed slope LMM did not show significant group-level effects for any frequency band (all $p > 0.1$).

Summarizing, STN DBS, and STN+SN DBS induced spectrally and topographically different cortical activation patterns during FoG with re-emergence of parietal alpha and central low-beta activity with STN DBS and in contrast frontal high-beta activity during STN SN DBS.

DISCUSSION

In this study, we used a sensor-based analysis of a SIP task with simultaneous high-density EEG recordings in healthy controls and PD patients to evaluate the effects of conventional STN DBS and STN+SN DBS on temporal stepping characteristics and activity modulation of cortical nodes of the gait-network. At a behavioral level, STN+SN DBS was superior to STN DBS by modulation of temporal gait characteristics as a reduction of step time variability of the more affected leg. At the EEG level, we demonstrated that STN+SN DBS modulated cortical activity within the gait-network of PD patients. Both, STN DBS and STN+SN DBS normalized pathologically exaggerated alpha activity in PD patients compared to STIM OFF at rest. The excessive cortical high-beta activity was also successfully reduced to a similar extent by both active DBS setting. During FoG, STN DBS and STN+SN DBS revealed spectrally and topographically different cortical activity patterns with re-emergence of low-beta increase over the sensorimotor cortex with STN DBS and relative high-beta increase over frontal cortical areas with STN+SN DBS during motor blocks.

Limitations and Methodological Considerations

There are certain limitations of the study. We used a gait-like movement, SIP, which is lacking the propulsive movement

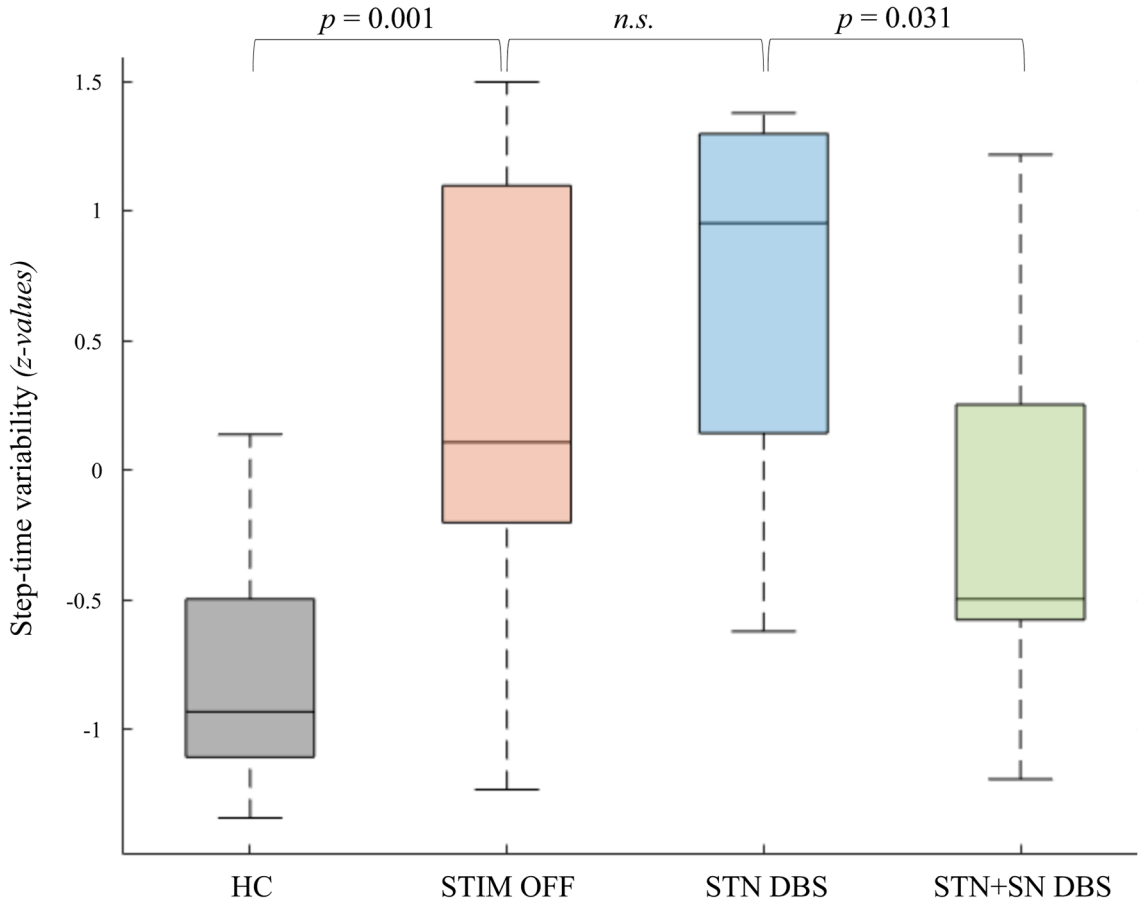

FIGURE 2 | Deep brain stimulation (DBS) effects on step-time variability of the more affected leg. The coefficients of variability of step-to-step time in healthy controls and Parkinson's disease (PD) patients in the three DBS conditions are displayed as boxplots. The values reported in the boxplots are median, interquartile range (IQR), whiskers (highest/lowest values of the data-set within 1.5 times of the IQR). Values reported above are significant *p*-values of planned *post-hoc t*-tests.

of real gait. We used SIP due to spatial constraints when recording simultaneously 64 channel EEG, but also since SIP was demonstrated to detect FoG in PD and since SIP correlated with subjectively perceived FoG severity as measured by FoG-Q (Nantel et al., 2011). SIP is therefore quite useful in the assessment of gait-like movements. Second, we assessed the PD patients with regular medication intake (MED ON), which might induce "ceiling effects" or residual fluctuations of the current motor state depending on the tablet wearing off. We chose the MED ON condition for three reasons. On the one hand, we aimed to assess the "real-world" condition, which might be easier to transfer into a clinical routine. On the other hand, we chose this MED ON condition to compensate for differences in symptom severity particularly FoG due to different disease severity leading to a more comparable baseline. Third, we were particularly interested in "ON-Freezing" which constitutes a particular clinical problem. Potential, residual medication-dependent fluctuations were clinically controlled and the DBS conditions were randomized to avoid order effects within the fluctuation state. Besides, the interpretation of EEG results needs to account for L-DOPA induced changes in cortical activity apart from DBS effects (Toledo et al., 2014).

Behavioral Effects of DBS on Gait

Previous studies revealed heterogeneous effects of conventional STN DBS on gait. In the early stages of the disease, STN DBS can improve levodopa-responsive gait impairment (Pötter-Nerger and Volkmann, 2013). However, as the disease progresses, it is observed that axial symptoms become dopa-resistant and STN DBS might become less effective in terms of gait improvement (Krack et al., 2003; Rodriguez-Oroz et al., 2005; Schupbach et al., 2005). There are even reports of STN DBS induced FoG postoperatively (van Nuenen et al., 2008; Fleury et al., 2016). In objective gait analyses, levodopa-responsive parkinsonian gait impairments are improved by STN DBS with better spatial gait characteristics as stride length and velocity (Xie et al., 2001; Krystkowiak et al., 2003). However, temporal gait parameters such as step time, symmetry, and rhythmicity are not ameliorated by STN DBS (Faist et al., 2001). This is critical, as temporal gait dysregulation is one hallmark in the pathogenesis of FoG (Nutt et al., 2011). Of interest, a recent study suggested a

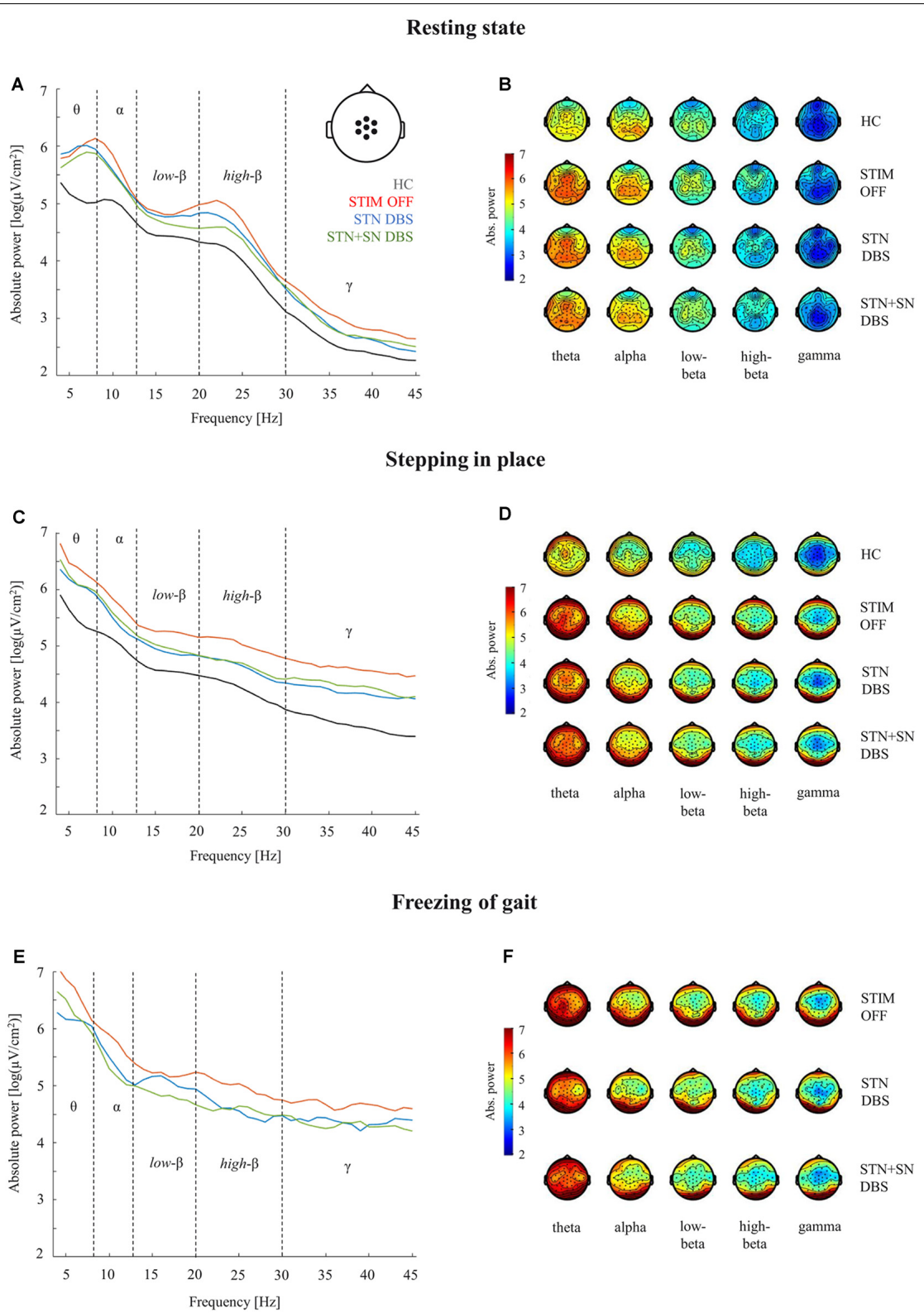

FIGURE 3 | Cortical activity during resting-state, stepping in place, and during freezing of gait episodes. Analyses of absolute power in healthy control persons and PD patients for the three DBS conditions were performed in five frequency bands (theta 4–8 Hz, alpha 9–13 Hz, low-beta 14–20 Hz, high-beta 21–30 Hz, gamma 31–45 Hz). Panels **(A,C,E)**: comparison of absolute power spectra in the central ROI (pictogram in panel **A**). Panels **(B,D,F)**: topographies of absolute EEG power for healthy control persons **(B,D)** and for PD patients **(B,D,F)** during the three considered motor conditions.

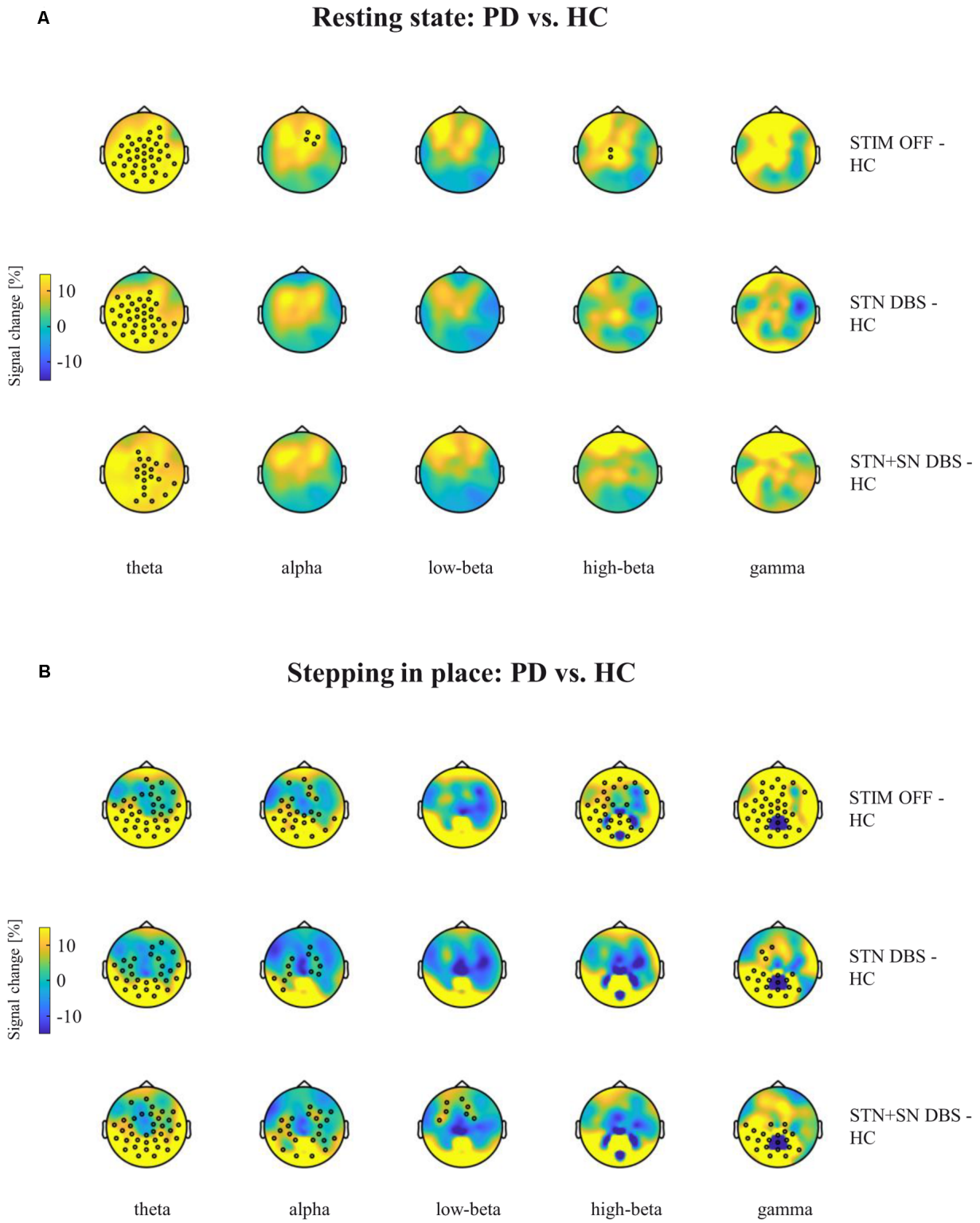

FIGURE 4 | Cortical activity differences between PD patients and healthy controls (HCs) during resting-state and stepping in place. Topographic percentual power signal change between HCs and PD patients in the three DBS settings (rows) is displayed for **(A)** the resting-state condition and for **(B)** the stepping in place condition separately for the five frequency bands (columns). Black circles represent significant clusters of EEG sensors showing significant signal changes between motor conditions based on cluster-based permutation tests. In panel **(A)** the high-beta power cluster of midline-central channels was increased with *p*-value closed to the alpha level ($p = 0.072$).

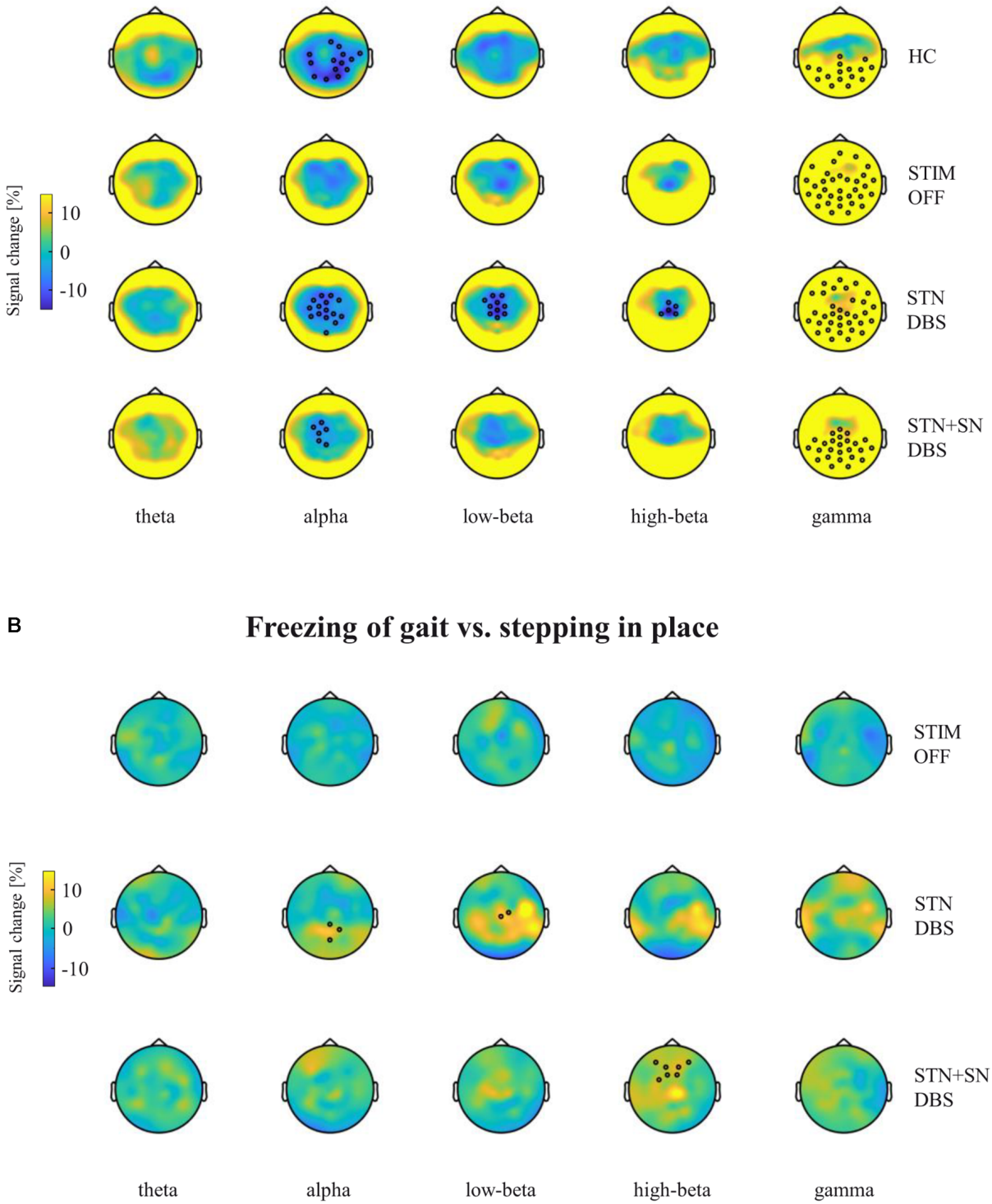

FIGURE 5 | Cortical activity modulation in response to different motor conditions. Topographic percentual power signal change is displayed for **(A)** stepping in place vs. resting-state and for **(B)** freezing episodes vs. unaffected stepping in place. The comparisons are represented for healthy control persons and for PD patients in the STIM OFF, STN DBS, and STN+SN DBS conditions (rows) separated into five frequency bands (columns). Black circles represent significant clusters of EEG sensors showing significant signal changes between motor conditions based on cluster-based permutation tests.

beneficial effect of nigral neurostimulation on temporal gait regularization in PD (Scholten et al., 2017). There are different hypotheses on STN DBS-induced gait impairment. A recent study using normative connectomes based on MR images of PD patients after DBS implantation revealed deterioration of FoG postoperatively if the ansa lenticularis of capsula interna fibers were unintentionally stimulated by DBS (Strelow et al., 2021).

In the present study, we investigated the effect of subthalamic and nigral stimulation on temporal gait characteristics in a cohort of PD patients in advanced disease stages suffering from ON-medication/ON-stimulation gait freezing according to the self-evaluation provided with the FoG questionnaire. We demonstrated that combined STN+SN DBS significantly reduced step-time variability of the more affected leg compared to STN DBS alone in line with recent findings of nigral-specific effects on temporal gait characteristics (Scholten et al., 2017).

What Are the Mechanisms of Action of STN+SN DBS?

One of the main goals of that study was to assess mechanisms of action of STN+SN DBS in the mediation of beneficial effects on gait and FoG. Originally, the new stimulation algorithm of STN+SN DBS was introduced in view of untreatable, residual gait symptoms and FoG under STN DBS (Weiss et al., 2013). The pathophysiological hypothesis for the use of STN+SN DBS in PD gait disorders was to intensify the release of the pathological inhibition of the BG-brainstem route. The SN is of particular interest since animal data suggest dense reciprocal interconnections between the SNr and mesencephalic locomotor region such as the PPN (Breit et al., 2001, 2005) projecting to spinal central pattern generators (Pahapill and Lozano, 2000). This subcortical BG route is assumed to be involved in automatic gait behavior including rhythmicity, posture preparations, and adjustments during locomotion (Takakusaki, 2013; Snijders et al., 2016; Marquez et al., 2020). However, automatic gait behavior is controlled by a multilevel network with cortical motor control centers involved in the initiation and adjustment of locomotion in environmental conditions as turning, stopping, or maneuvering obstacles (Marquez et al., 2020). The motor cortex is assumed to initiate gait by the descending command to release automatic rhythmic stepping patterns. The supplementary motor cortex is supposed to disconnect from BG resulting in the loss of internal cueing of automatic predefined motor stepping patterns and loss of automatic updating of motor programs (Marquez et al., 2020). In light of this fundamental role of the motor cortex in gait control, it was therefore of interest, whether STN+SN DBS mediates its beneficial gait effects not only by subcortical pathways but through cortical areas *via* BG thalamo-cortical projections.

Absolute Power Increase in PD Patients in Comparison to HCs

An increase of absolute power across a broad range of frequencies was observed in PD patients, especially during the STIM OFF condition, when compared to HCs (**Figures 3A,C**). This general enhancement of absolute power in PD patients is in accordance with previous studies, which attributed this phenomenon to a pathophysiological chain reaction initiated by the effects of dopamine denervation in BG-thalamo-cortical loops (Tanaka et al., 2000; Moazami-Goudarzi et al., 2008; Gulberti et al., 2015). In particular, the slowing of EEG activity in comparison to HCs is a consistent finding in PD patients (Soikkeli et al., 1991; Stoffers et al., 2007), and an increased theta power has been associated with clinical measures of disease progression (Soikkeli et al., 1991; Bosboom et al., 2006; Stoffers et al., 2007; Serizawa et al., 2008) and cognitive decline (Neufeld et al., 1988, 1994; Tanaka et al., 2000; Sinanović et al., 2005; Olde Dubbelink et al., 2013; Guner et al., 2017). In the context of the so-called thalamo-cortical dysrhythmia framework, the pathological increase of low-frequency oscillatory bursting activity in thalamo-cortical circuits, leads to the pathological emergence of aberrant low- and high-frequency oscillations at the cortical level (Llinás et al., 2005; Moazami-Goudarzi et al., 2008). The DBS-induced inhibition of aberrant BG output to the thalamus may in turn reduce abnormal thalamo-cortical rhythmicity and normalize high beta oscillatory activities at the cortical level (Llinás et al., 2005), and thus it may also facilitate stepping movements (see **Figures 3C,D** and **Figure 4B**).

Oscillatory Cortical Activity in PD Motor Control and Regular Stepping

To integrate the findings of specific cortical oscillatory power changes by STN+SN DBS compared to conventional STN DBS in the mediation of clinically beneficial effects, one needs to consider the current framework of spatially and spectrally segregated oscillatory activity changes within cortico-BG circuits in the pathophysiology of motor and non-motor parkinsonian symptoms (Oswal et al., 2013).

In PD at rest, excessive beta activity dominates within the cortico-subthalamic network involving motor and premotor areas (Hammond et al., 2007). There are further oscillatory activity changes in PD in other frequency bands within the subcortico-cortical loops as widespread alpha band (Litvak et al., 2011), gamma-band (Jenkinson et al., 2013), or theta band changes (Oswal et al., 2013). Within these subcortico-cortical networks, it was demonstrated, that cortical beta or lower band oscillations were the most likely driver or "master" and subthalamic oscillatory activity was the "slave" driven by the cortical control (Litvak et al., 2011). In contrast, gamma band activity was proposed to be driven "bottom-up" subcortically and driving higher cortical centers (Jenkinson et al., 2013).

In detail, the beta band activity is probably the best-investigated frequency band and is assumed to represent a hallmark of dopamine depletion in the bradykinetic parkinsonian pathophysiological state (Little et al., 2012). Spontaneous subthalamic fluctuations of beta activity were shown to correlate with the clinical state as bradykinesia (Kühn et al., 2009; Little et al., 2012). Non-invasive magneto-encephalography highlighted the exaggeration of beta band activity over motor cortical areas at rest in PD correlating with motor impairment (Stoffers et al., 2008; Pollok et al., 2012). Between cortical and subcortical sites, beta activity is

pathologically synchronized within the BG loop in PD (Williams et al., 2002; Hirschmann et al., 2011; Litvak et al., 2011). Prior to self- and externally paced movements, oscillations in the beta band are suppressed in the subthalamic nucleus and globus pallidum (Levy et al., 2002; Kuhn et al., 2004), as well as in the sensorimotor cortex (Pfurtscheller, 1981; Crone et al., 1998; Oswal et al., 2013). It was therefore proposed that in PD, bradykinesia might be due to the inability of the BG to release the cortical information flow during movement (Brown and Marsden, 1998) resulting in a blockade of information transfer through BG-cortical projections.

In this experiment, we could transfer those findings from general motor control onto SIP as a specific, gait-like movement. At rest, we observed pathologically enhanced high-beta activity at central channels in PD patients compared to HCs associated with a deterioration of flexible movement initiation. With movement-onset during SIP, cortical beta activity was desynchronized in healthy controls, but not in PD patients in STIM OFF reflecting the inability to release new motor commands through cortical areas.

Since beta oscillations play a predominant role in the pathophysiology of PD, it is of interest whether subcortico-cortical beta oscillations are modulated by therapeutical DBS. The effect of conventional STN DBS on beta oscillations within the BG-cortical loop has been intensively assessed. STN DBS suppresses the pathologically increased beta oscillations in the STN (Kuhn et al., 2008; Eusebio et al., 2011), GPI (Brown et al., 2004) and reduces the coherence in the beta band between the motor cortex and the STN (Kuhn et al., 2008). Thus, STN DBS exerts its effects locally at the site of stimulation within the STN and over functionally connected elements of the cortex-BG network. These STN DBS induced changes in beta oscillations and beta coherence were negatively correlated with movement amplitude (Kuhn et al., 2008).

Here we assessed whether there is therapeutic modulation of beta power at the cortical sites with STN DBS and STN+SN DBS within a stepping movement. At rest and during regular SIP, the pathologically enhanced cortical beta activity was reduced during STN DBS and STN+SN DBS compared to STIM OFF indicating that both DBS modes improve the resolution of beta-associated communication blocks and efficient release of motor programs to the motor cortex during regular SIP. Still, STN DBS and STN+SN differed topographically in their control of beta activity indicating possible different channels in the mediation of beneficial effects.

Alpha activity has regained interest in the understanding of PD pathophysiology. On the one hand, there is a diffused increase of cortical background alpha activity and even slower frequency bands in PD (Stoffers et al., 2007; Stam, 2010). Alpha activity is particularly present in a network between the STN, temporo-parietal and brainstem areas (Hirschmann et al., 2011; Litvak et al., 2011). At rest, coherent alpha oscillations were observed in the STN and at various locations in the ipsilateral temporal lobe (Hirschmann et al., 2011). Alpha activity has been proposed to be involved in orienting attention at a cortical level (Klimesch, 2012). It was proposed that alpha-band oscillations are involved in suppression and selection of actions which are closely linked to the fundamental functions of attention to enable controlled knowledge access and provide time, space, and context orientation (Klimesch, 2012).

We found the alpha activity to be modulated by task-condition and DBS. In HCs and PD patients treated with STN DBS or STN+SN DBS, alpha oscillatory power was reduced during SIP compared to rest, still, alpha activity levels in patients were generally higher compared to controls. During STN DBS and STN+SN DBS, stepping-induced alpha power reduction was more intense compared to STIM OFF in central clusters. This might indicate enhanced attentional resources in both DBS conditions which might be beneficial in the maintenance of stepping quality and prevention of FoG (Yarnall et al., 2011; Tessitore et al., 2012).

Particular attention has been paid to gamma band activity as a key element of higher brain function, participating in arousal, perception, executive function, memory (Garcia-Rill et al., 2019), and vigor of the motor task (Joundi et al., 2012; Jenkinson et al., 2013). Gamma band activity is an inconsistent, broad-band feature at rest, but most obvious during voluntary movement (Androulidakis et al., 2007; Jenkinson et al., 2013), that is recordable as synchronized activity throughout different sites of the BG loop (Alegre et al., 2005) including cortical areas (Lalo et al., 2008; Litvak et al., 2012). There is evidence of coherent gamma activity between STN and mesial and lateral cortex with symmetrical bidirectional coupling after dopaminergic therapy (Lalo et al., 2008). Activity in the gamma range seems to be primarily physiological as it can be recorded in healthy animals (Berke, 2009) or humans without PD (Ball et al., 2008; Cheyne et al., 2008). In PD, gamma activity is decreased without medication (Mazzoni et al., 2007) and increased following levodopa administration (Brown et al., 2001; Alegre et al., 2005). The extent of gamma power increase correlated with motor improvement (Kuhn et al., 2006). The gamma band was therefore proposed to be a "pro-kinetic" oscillatory activity. Gamma band activity was proposed to be mediated by "bottom-up" brain processing to communicate sensory events to higher centers to promote perception and arousal (Garcia-Rill et al., 2019). One important brainstem nucleus involved in the mediation of gamma activity seems to be the PPN with its ascending, widespread projections through intralaminar, parafascicular, and center median thalamic nuclei (Scarnati et al., 1987; Capozzo et al., 2003) to the cerebral cortex and BG structures (Steriade and Glenn, 1982; Otake and Nakamura, 1998). We found an increase in gamma oscillatory power in HCs and PD patients during SIP compared to rest emphasizing the prokinetic feature of gamma band activity. These gamma band changes differed between STN DBS and STN+SN DBS conditions with a more widespread topographically pattern of gamma modulation during STN DBS and a more focal gamma increase over central and parietal clusters during STN+SN DBS underlining potential differences in mechanisms

of action of these two stimulation modes. Since the PPN is assumed to play a major role within the mediation of gamma oscillatory activity to higher cortical centers and given the strong interconnections of PPN and SNr, one could assume that these direct SNr-PPN projections might be particularly modulated by STN+SN DBS resulting in specific cortical gamma oscillatory patterns.

Cortical Oscillatory Activity Changes During FoG in PD

In light of cortical oscillatory activity changes during regular stepping and its modulation by DBS, it is of particular interest how the cortical activity is modulated during FoG. Recently, cortical alpha and beta band oscillatory power were assessed in more detail in freezing PD patients. Summarizing the different results, there were two main findings. On the one hand, there were significant increases in beta power associated with FoG compared to regular walking. On the other hand, there was an increase of lower frequency as alpha activity in FoG and even in the transition phase to FoG.

In one study, EEG signals during effective walking, FoG, and transition to FoG were analyzed with mobile EEG (Shine et al., 2014). There was an increase in cortical beta activity when comparing freezing to regular walking in the frontal lead or freezing to the transition phase in the parietal lead. This was interpreted as impaired or blocked communication of frontally generated motor plans to the motor cortex, leading to gait impairment (Shine et al., 2014).

This effect could be replicated in another study with two PD groups of freezers and non-freezers during a lower-limb pedaling task (Singh et al., 2019). Freezing PD patients exhibited increased beta-band (13–30 Hz) power at mid-frontal electrode Cz during pedaling compared to the non-freezing group. This increment of cortical beta was shown to be accompanied by increased subthalamic high-beta activity in PD patients with freezing in OFF dopaminergic medication compared to non-freezers (Toledo et al., 2014). This increased beta activity was shown to be modulated by therapeutic intervention. After the application of L-Dopa, the high-beta power at cortical and subcortical sites in freezers was reduced, which was accompanied by clinical improvement with FoG event cessation (Toledo et al., 2014).

In congruence with these previous findings, we found a re-emergence of beta oscillatory activity at cortical sites during FoG compared to regular SIP in all DBS conditions. FoG might therefore represent a "breakdown" of the subcortico-cortical loop by exaggerated beta oscillatory activity stopping the release of motor programs for gait initiation and gait performance. The hypothesis on pathologically increased beta activity resulting in the abnormal persistence of the status-quo of the movement state (Engel and Fries, 2010) fits FoG phenomenology with the persistence of continued, inveterate movement arrest of the lower limbs. Clinically, FoG episodes were more frequent during STIM OFF than during both DBS active conditions, still, we found the re-emergence of beta activity in all DBS conditions with the same behavioral output of motor arrest during FoG. We propose the hypothesis, that STN DBS and STN+SN DBS might act on gait control and regular stepping by promoting a "beta-resilience" or "beta-buffer" by restauration of the movement-related beta desynchronization. This DBS-induced "beta-buffer" needs to be depleted before a threshold is passed resulting in FoG.

Interestingly, we observed different patterns of beta activity re-emergence in the two different DBS conditions. During STN DBS there was a reappearance of low-beta activity in central clusters, whereas during STN+SN DBS there was re-emergence of high-beta activity frontally. The role of low-beta and high-beta activity is not yet completely understood, still, it was proposed that low-beta and high-beta oscillations carry independent information about movements as observed during reach-to-grasp tasks (Vissani et al., 2021). It was proposed that low-beta oscillations convey information about the principal movement state and high-beta activity is more informative of the details of the different active movement phases (Vissani et al., 2021). It might be hypothesized, that STN DBS and STN+SN DBS might act differentially on cortical activity through different beta frequency band "channels".

Besides, previous studies on FoG emphasized changes in low frequency band activity. Alpha power and theta activity in the central and frontal leads were shown to be increased during FoG and even during the transition from normal walking to freezing (Shine et al., 2014). These findings of increased low frequency power, particularly theta activity, were interpreted as an increased cognitive load while conflict-processing directly before and during FoG since increment of low frequency oscillations has been associated with the performance of cognitive tasks (Basar et al., 2001), as the processing of conflict (Shine et al., 2013c) and cognitive interference (Lewis and Barker, 2009; Nigbur et al., 2011). This EEG finding of the relation of conflict-related signals indexed by increased low frequency changes in a network of fronto-parietal regions and FoG is in line with previous neuroimaging studies of FoG (Shine et al., 2013a,b). This finding could be also replicated for freezing of the upper limb in PD patients performing continuous tapping of the right index finger (Scholten et al., 2016). Freezing episodes of the upper limb were associated with increased cortical activity at 7–11 Hz. During the transition from regular tapping to "freezing" the cortical activity first increased over the left sensorimotor area followed by a spread to the left frontal and right parietal areas. In the STN DBS condition, we observed during FoG episodes a significant increase in alpha activity in the midline–parietal clusters. This finding is in line with the previous assumptions, that cortical conflict-processing reflected by cortical lower band activity enhances the risk for the occurrence of FoG and underlines the importance of cognitive-motor interference in the pathogenesis of FoG.

In summary, we found a superior behavioral effect of STN+SN DBS compared to conventional STN DBS on temporal SIP characteristics, which were accompanied by distinct cortical oscillatory patterns of low- and high-beta bands during SIP and FoG.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Ärztekammer Hamburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The work presented here was carried out in collaboration between all authors. (1) Research project: A. Conception: JW, AG, and MP-N designed methods and assessments. B. Organization: JW, MS, WH, MW, CG, AE, CM, AG, and MP-N. C. Execution: JW, MS, WH, CM, AG, and MP-N. (2) Statistical analysis: A. Design: JW, AG, and MP-N. B. Execution: JW analyzed the data. C. Review and critique: JW, AG, and MP-N discussed analyses, interpretation and presentation. (3) Manuscript: A. Writing of the first draft: JW, AG, and MP-N. B. Review and critique: JW, MS, WH, MW, CG, AE, CM, AG, and MP-N. All authors contributed to the article and approved the submitted version.

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A Fully-Immersive Virtual Reality Setup to Study Gait Modulation

Chiara Palmisano[1], Peter Kullmann[2], Ibrahem Hanafi[1], Marta Verrecchia[1], Marc Erich Latoschik[2], Andrea Canessa[1,3], Martin Fischbach[2] and Ioannis Ugo Isaias[1,4]*

[1]*Department of Neurology, University Hospital of Würzburg and Julius Maximilian University of Würzburg, Würzburg, Germany,* [2]*Human-Computer Interaction, Julius Maximilian University of Würzburg, Würzburg, Germany,* [3]*Department of Informatics, Bioengineering, Robotics and System Engineering, University of Genoa, Genova, Italy,* [4]*Parkinson Institute Milan, ASST Pini-CTO, Milano, Italy*

Objective: Gait adaptation to environmental challenges is fundamental for independent and safe community ambulation. The possibility of precisely studying gait modulation using standardized protocols of gait analysis closely resembling everyday life scenarios is still an unmet need.

Methods: We have developed a fully-immersive virtual reality (VR) environment where subjects have to adjust their walking pattern to avoid collision with a virtual agent (VA) crossing their gait trajectory. We collected kinematic data of 12 healthy young subjects walking in real world (RW) and in the VR environment, both with (VR/A+) and without (VR/A-) the VA perturbation. The VR environment closely resembled the RW scenario of the gait laboratory. To ensure standardization of the obstacle presentation the starting time speed and trajectory of the VA were defined using the kinematics of the participant as detected online during each walking trial.

Results: We did not observe kinematic differences between walking in RW and VR/A-, suggesting that our VR environment *per se* might not induce significant changes in the locomotor pattern. When facing the VA all subjects consistently reduced stride length and velocity while increasing stride duration. Trunk inclination and mediolateral trajectory deviation also facilitated avoidance of the obstacle.

Conclusions: This proof-of-concept study shows that our VR/A+ paradigm effectively induced a timely gait modulation in a standardized immersive and realistic scenario. This protocol could be a powerful research tool to study gait modulation and its derangements in relation to aging and clinical conditions.

Keywords: gait modulation, virtual reality, obstacle avoidance, gait analysis, kinematics

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****Correspondence:***
Chiara Palmisano
Palmisano_C@ukw.de

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INTRODUCTION

Bipedal walking is a remarkable ability of humans that requires highly complex neural control to effectively adapt in response to environmental challenges (Jahn et al., 2008; Queralt et al., 2008; Takakusaki, 2013; Tard et al., 2015; Corporaal et al., 2018; Nordin et al., 2019; Pozzi et al., 2019). Impairment of gait adaptation is common in older adults, and among the first indications of gait derangements in neurological diseases. This significantly increases the risk of falls (Caetano et al., 2016), resulting in fractures (Stalenhoef et al., 2002; World Health Organization, 2007),

loss of independence (Tinetti et al., 1994; Stalenhoef et al., 2002; World Health Organization, 2007), poor quality of life, and high mortality (World Health Organization, 2007; Osoba et al., 2019).

Many studies have investigated overground gait adaptation in response to obstacles in healthy young and older adults (Sparrow and Tirosh, 2005; Weerdesteyn et al., 2018). However, precise measures of gait patterns in response to real world (RW) demands are scarce (Weerdesteyn et al., 2018), primarily due to the lack of setups in gait laboratories that can fully replicate everyday life environments (Sparrow and Tirosh, 2005).

Previous works used two main approaches to study gait modulation, with fixed (Vallis and McFadyen, 2005; Da Silva et al., 2011; Jansen et al., 2011; Yamada et al., 2011) or mobile obstacles (Gérin-Lajoie et al., 2005; Cinelli and Patla, 2007, 2008; Da Silva et al., 2011; Olivier et al., 2012, 2013; Basili et al., 2013; Huber et al., 2014; Knorr et al., 2016; Vassallo et al., 2017). Fixed obstacles have the advantage of easier standardization across trials and subjects, but they may induce anticipation and pre-planning (Yamada et al., 2011) and do not allow adequate study of the gait modulation that occurs in an outdoor environment, where moving obstacles are prevalent (Sparrow and Tirosh, 2005). With respect to fixed obstacles, moving obstacles cause larger changes in the gait pattern (Gérin-Lajoie et al., 2005), requiring higher mental processing costs (Cutting et al., 1995; Gérin-Lajoie et al., 2005) and being more challenging for people at high risk of falling (Osoba et al., 2020). Gait pattern changes include both gait trajectory (Gérin-Lajoie et al., 2005; Cinelli and Patla, 2007; Basili et al., 2013; Olivier et al., 2013; Vassallo et al., 2017) and velocity (Cinelli and Patla, 2008; Basili et al., 2013; Olivier et al., 2013; Huber et al., 2014; Knorr et al., 2016). In the presence of sufficient space, directional adjustments are preferred (Huber et al., 2014), but braking strategies (i.e., speed modulation) can also be present with obstacle crossing angles of 45° and 90° (Huber et al., 2014). Time constraints, including different obstacle velocities, can also affect gait adaptation. In fact, the (medio-lateral) safety margins for collision avoidance (Cinelli and Patla, 2007, 2008) and the step length (Da Silva et al., 2011) depend on the speed of the obstacle. These results highlight the importance of standardizing obstacle presentation to evoke similar kinematic responses across trials and subjects.

Some previous studies have used a person trained to walk with specific trajectories and speeds as the moving obstacle (Olivier et al., 2012, 2013; Basili et al., 2013; Huber et al., 2014; Knorr et al., 2016). This has the advantage of closely replicating an everyday situation but increases the variability in obstacle presentation, which could not be standardized in these studies. Other studies used robots (Vassallo et al., 2017), mannequins (Gérin-Lajoie et al., 2005; Cinelli and Patla, 2007, 2008), or remote-controlled objects (Da Silva et al., 2011) to improve the accuracy of obstacle presentation, but with some limitations. In particular, the movement of the obstacles was not dynamically adjusted to the behavior (trajectory or velocity) of the subject but fixed and arbitrarily chosen (Cinelli and Patla, 2007, 2008; Vassallo et al., 2017), based on normative data (Da Silva et al., 2011) or on the velocity of the subject during unperturbed walking (Gérin-Lajoie et al., 2005). In addition, in all but one study (Vassallo et al., 2017), the obstacle trajectory was fixed and did not adjust for the ongoing walking pattern of the subject.

Virtual reality (VR) holds great promise for overcoming many of these limitations. Experimental conditions in immersive VR are ecologically valid, realistic, highly controlled, and replicable in a safe environment (Bailenson et al., 2003). A VR setup allows accurate and real-time measurement of the position of the subject and the obstacle (Loomis et al., 1999; Bailenson et al., 2003) for standardization in its presentation. A VR setup can also be enriched with multiple cognitive and motor tasks (dual-task paradigm; Janeh et al., 2019) and perceptual loads (Martelli et al., 2019), requiring additional resources for planning and sensorimotor integration (Mirelman et al., 2011) that can aid a more comprehensive study of gait adaptation (Gérin-Lajoie et al., 2005; Konczak et al., 2009). Obstacle avoidance tasks in VR have shown great potential also for rehabilitation purposes in parkinsonian patients (Mirelman et al., 2011), post-stroke patients (Jaffe et al., 2004), and patients with cerebral palsy (Gagliardi et al., 2018). In most of these studies, however, the use of a treadmill limited the level of immersiveness, which can be resolved by implementing overground walking with a head-mounted display (HMD; Winter et al., 2021).

In recent years, several studies have been successful in developing VR paradigms capable of inducing gait modulation with virtual objects (Fajen et al., 2003; Fink et al., 2007; Gérin-Lajoie et al., 2008; Cirio et al., 2013; Argelaguet Sanz et al., 2015) or virtual persons (Argelaguet Sanz et al., 2015; Lynch et al., 2018; Olivier et al., 2018). Overall, these studies showed similar gait adaptation strategies in VR and RW, with the former characterized by higher obstacle clearance (Fink et al., 2007; Gérin-Lajoie et al., 2008; Argelaguet Sanz et al., 2015; Olivier et al., 2018) and slower velocity (Fink et al., 2007; Argelaguet Sanz et al., 2015). These differences may be due to uncertainties in obstacle localization, possibly caused by excessive attentional demands required by the VR environment (Gérin-Lajoie et al., 2008), absence of body rendering (Fink et al., 2007), and diminished field of view (Fink et al., 2007; Gérin-Lajoie et al., 2008). This latest hypothesis was, however, questioned by Jansen and coll., who showed kinematic gait changes during static obstacles avoidance only for a field of view as small as 40° × 25° (Jansen et al., 2011), and by Knapp and Loomis, who found no underestimation of distances in relation to a decreased field of view (Knapp and Loomis, 2004).

All these studies have shown the great potential of VR in the study of gait modulation, but they are not without limitations. First, most of them used CAVE-like systems (Cruz-Neira et al., 1992) with joystick navigation, due to limited walking space (Lynch et al., 2018; Olivier et al., 2018). These devices are very expensive and require trained personnel, thus reducing their use in clinical and rehabilitation facilities. Second, studies of gait modulation in VR focused primarily on validating experimental setups previously used in RW rather than developing new ones. Static obstacles were preferred over moving obstacles, with the aim of understanding the impact of different characteristics of virtual obstacles on walking behavior (Bailenson et al., 2003; Argelaguet Sanz et al., 2015) or different avoidance strategies between VR and RW (Fajen et al., 2003; Fink et al., 2007;

Gérin-Lajoie et al., 2008; Argelaguet Sanz et al., 2015). The few studies employing moving obstacles in VR (Lynch et al., 2018; Olivier et al., 2018) used joystick navigation and did not adjust the movement of the obstacle to the movement of the subject. The potential of VR in replicating everyday environments and standardizing the presentation of obstacles has yet to be fully exploited.

Ours is a proof-of-concept study that aimed to demonstrate the feasibility of using a fully-immersive VR environment to study overground gait adaptation and obstacle avoidance in a highly standardized manner. We tested this protocol on a small group of young healthy subjects and described biomechanical features of overground gait modulation for collision avoidance. We employed an HMD to ensure immersiveness and facilitate future clinical applications. A virtual agent (VA) was preferred over a virtual object to replicate one of the most common scenarios in daily life, which is walking while another pedestrian crosses the path (Basili et al., 2013; Olivier et al., 2013; Huber et al., 2014; Knorr et al., 2016). A full-bodied VA was shown to induce larger gait adaptation with respect to inanimate objects (Argelaguet Sanz et al., 2015; Lynch et al., 2018). For the first time, the movement of the object (i.e., the VA) was standardized based on the ongoing movement of the participant to ensure a constant perturbation across subjects and trials. The speed of the VA was defined so that participants were induced to modulate their gait to let the VA pass first. Indeed, when two pedestrians cross their paths, the one way contributes more to collision avoidance (both in terms of walking trajectory and speed changes) than the one passing first (Olivier et al., 2013; Knorr et al., 2016). This setup was designed for future studies on patients with Parkinson's disease, where specific gait disturbances such as gait freezing predominantly occur during gait pattern modulation (e.g., confrontation with obstacles; Pozzi et al., 2019).

We had two main working assumptions: the first was that a highly realistic and immersive virtual environment would not alter the gait pattern. For this part of the study, our results should be considered preliminary, and we defer validation of our setup to future works with more subjects. The second hypothesis was that the presence of the VA would induce significant gait modulation, both in terms of stride velocity, length, and duration, and in terms of stride width, lateral trunk displacement, and lateral deviation of the gait trajectory. This second goal, especially for future clinical research applications, should be considered more relevant and the main purpose of this work.

METHODS

Subjects

The absolute novelty of this study setup and the lack of preliminary results prevented us from performing an *a priori* power analysis to determine the sample size. For this proof-of-concept study, we studied a number of participants similar to previous studies of ground-based obstacle avoidance in VR (Bailenson et al., 2003; Fink et al., 2007; Gérin-Lajoie et al., 2008). We recruited 12 healthy young participants (seven males; age 23–40 years; **Table 1**). No participant suffered from any medical condition and was a professional athlete. All participants had a normal or corrected-to-normal vision. They had no previous experience with any VR device. The study was approved by the local Ethical Committee of the University of Würzburg (n. 103/20) and conformed to the declaration of Helsinki (World Medical Association, 2013). All subjects gave their written informed consent prior to participation.

Study Protocol

The study protocol consisted of four sessions, each comprising 20 walking trials on a 10 m walkway. Kinematics were recorded using an optoelectronic system with six cameras (sampling rate 100 Hz, SMART DX-400, BTS Bioengineering, Italy) and a set of 29 markers placed on anatomical landmarks (**Figure 1A**; Palmisano et al., 2019, 2020a,b; Farinelli et al., 2020). During the first session, the subjects walked back and forth on the walkway in the RW. In the second session, the subjects walked in the same fashion, but in the VR environment (VR/A-). The last two sessions were performed in the same VR environment, with the addition of a VA (VR/A+). A verbal "start" and "stop" signal defined the beginning and end of the session. Between sessions, subjects were allowed to rest. Before starting the recording, subjects performed three-five walking trials in VR to become acquainted with the environment. In all conditions, participants were asked to walk at their natural (preferred) speed. In VR/A+, participants were informed that the VA would cross their path once in each walking trial and instructed to adapt their gait to avoid collision with the VA without stepping off the walkway. Sessions were presented in the same order for all recruited subjects (i.e., RW, VR/A-, VR/A+). Synchronization of acquiring devices was achieved using a transistor-transistor-logic (TTL) signal recorded at the same time by the VR and the SMART systems.

Virtual Laboratory Environment

The VR environment was made with Unity (Unity Technologies, USA). It was displayed to the subjects *via* a wireless HMD (Vive Pro, HTC, USA) connected to a PC (Intel Core i9-10900X 10 cores, NVIDIA GEFORCE 11 GB RTX 2080, 32 GB RAM). A virtual laboratory environment was created using one-to-one mapping to closely resemble the real laboratory. We did not apply any translational gains (Williams et al., 2006) or even redirected walking techniques (Steinicke et al., 2008), as they showed a detrimental effect on the gait pattern and altered the behavior of the subject during walking (i.e., subjects had the tendency to look down toward the floor during walking;

TABLE 1 | Demographic data and anthropometric measurements.

Gender (males/total (%))	7/12 (58.3)
Age (years)	29.3 (5.3)
Body height (cm)	168.9 (8.2)
Foot length (cm)	24.4 (1.4)
Limb length (cm)	90.2 (4.5)
Weight (kg)	66.3 (10.6)
BMI (kg/m^2)	23.3 (3.9)

Values are shown as mean (standard deviation) unless otherwise indicated. Abbreviations: BMI, body mass index.

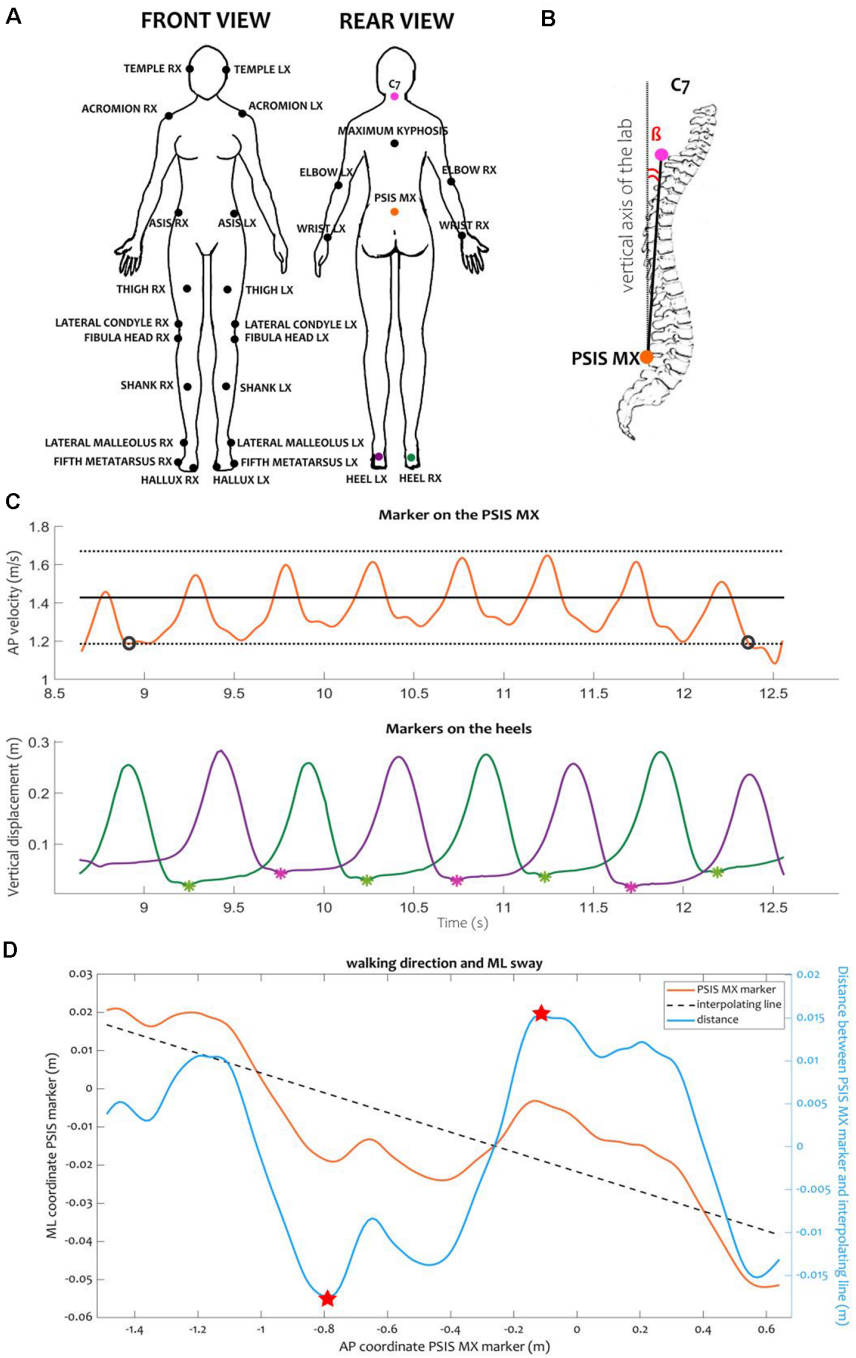

FIGURE 1 | Kinematic protocol and variables. **(A)** Position of the markers according to the LAMB protocol (Palmisano et al., 2019). Colored markers were used for the computation of kinematic events and variables. **(B)** Representation of the trunk inclination. Trunk inclination β was defined as the angle between the vertical axis of the laboratory and the vector connecting the markers placed on the middle point between the PSIS (PSIS_MX) and the C7 vertebra. **(C)** Example of computation of steady-state velocity and identification of heel contacts for one RW trial. We defined the steady-state velocity specific for each subject as the average (black solid line) ± the standard deviation (black dotted lines) of the AP velocity of the PSIS_MX marker computed in the central portion of the calibration volume. Only the interval during which the velocity was consistently inside this range (between the black circles) was considered for computing the gait cycle parameters. Inside the window at steady-state velocity, we identified the heel contacts as the local minima (asterisks) of the vertical tracks of the markers placed on the heels (green and purple lines for the right and left heels, respectively). **(D)** Example of ML sway and walking direction during a RW trial. We computed the ML sway as the range of the distance (light blue line) between the trajectory of the PSIS_MX marker in the transversal plane (orange line) and its interpolating line (black dashed line). The range was computed as the difference between the maximum and minimum values of the distance (indicated here as red stars). The direction of the walking trajectory was computed as the angular coefficient of the linear regression line interpolating the PSIS_MX trajectory in the transversal plane. Abbreviations: AP, anterior-posterior; C7, seventh cervical vertebra; ML, medio-lateral; PSIS, posterior-superior iliac spines.

Janeh et al., 2017). We positioned the virtual world so that the virtual walkway was aligned with the real one. In the virtual laboratory, two green tiles were visible at both ends of the walkway (**Figure 2A**). Participants had to repeatedly walk back and forth from one green tile to the other. At the beginning of each trial, the subject could see the VA standing 5 m in front and 1.5 m to the side (left and right alternately) of the green tile from which the subject was starting. The arrival of the subject on the green tile, before turning around, determined the repositioning of the VA for the next walking trial (**Figure 2A**). The VA was programmed to cross the walking path of the subject in a standardized fashion. Specifically, the VA started walking in a straight line towards the subject's pathway when the subject-to-agent distance was 3 m, with a constant speed equal to 1.5 times the speed of the subject at the instant of the VA start (**Figure 2B**). The trajectory of the VA was set to cross the walking pathway of the subject at 1 m distance from the subject, assuming that no gait adaptation took place. To quantify sickness elicited by our VR setup, we used the Simulator Sickness Questionnaire (SSQ; Kennedy et al., 1993).

Data Analysis

Kinematic data were extracted using *ad hoc* Matlab algorithms. For the RW and VR/A- sessions, we analyzed only the strides at steady-state velocity. A stride was defined as the interval between two subsequent heel contacts of the same foot, detected as local minima in the vertical displacement of the markers placed on the heels (**Figure 1C**). Steady-state velocity was defined as the mean ± standard deviation of the anterior-posterior velocity of the marker placed on the middle point between the posterior superior iliac spines [(PSIS_MX), approximating the center of mass (Yang and Pai, 2014)], computed in the central portion of the calibration volume (**Figure 1C**). For the VR/A+ trials, we identified a gait modulation phase as the time between the movement onset of the VA and the instant when the subjects regained their steady-state velocity, as identified in the VR/A- session. In the modulation phase, we identified three strides: first, second, and third modulator. For each stride (for RW and VR/A-) or modulator (for VR/A+), we measured the spatiotemporal parameters (i.e., stride length, width, duration, and velocity) and the trunk inclination as the angle between the vertical axis of the laboratory and the vector from the PSIS_MX marker to the marker on the seventh cervical vertebrae (C7; **Figure 1B**). For steady-state velocity walking (in RW and VR/A-) and for the gait modulation phase (in VR/A+), we measured the walking direction as the angular coefficient of the linear regression line interpolating the PSIS_MX trajectory in the transversal plane (**Figure 1D**). We also estimated the mediolateral sway as the range of the distance between the points of the PSIS_MX marker and the regression line in the transversal plane (**Figure 1D**).

Statistical Analysis

All variables were averaged for each subject across trials, and one value represented the subject in each condition. We used the Friedman and Wilcoxon matched-pairs tests to investigate differences between the RW, VR/A-, and VR/A+ conditions. A p-value of 0.05 corrected with the Bonferroni method was used as a threshold for statistical significance for both the Friedman and the *post-hoc* tests.

RESULTS

Demographic features and anthropometric measures are summarized in **Table 1**. None of the participants reported any discomfort or symptoms due to the VR during or after the study (SSQ total score <5).

No statistically significant differences were observed between the RW and VR/A- conditions for any parameter (**Table 2**).

We showed a clear gait pattern modulation during walking in the VR/A+ condition. Stride length and velocity decreased in all modulators, being lowest at the first modulator and increasing progressively from the first to the third modulator. The stride width selectively increased at the first modulator. All modulators had a longer duration than RW and VR/A- strides (**Table 2**, **Figure 3**). Trunk inclination increased during all modulators and peaked significantly at the third modulator (**Table 2**). The walking direction and mediolateral sway also increased during VA avoidance with respect to both control conditions (**Table 3**).

DISCUSSION

Our study showed that a fully-immersive VR environment is an effective setup to induce gait adaptation for obstacle avoidance. The consistent and replicable gait modulation induced by the VA in all participants indicates that this is a promising tool to study gait adaptation in a safe, highly-standardized, controlled, and lifelike environment.

The proposed VR environment did not induce changes *per se* in the basic kinematic features of gait. Still, we cannot rule out that the limited sample size may have prevented capturing significant differences, especially considering that previous studies described some alterations (e.g., stride length and velocity, cadence, heading angle) between walking in real and virtual environments (Hollman et al., 2006; Menegoni et al., 2009; Katsavelis et al., 2010; Janeh et al., 2017). Future studies are warranted to confirm these results in larger case series.

In all subjects, interaction with the VA induced significant changes in both gait trajectory (**Table 3**) and velocity, particularly the latter (**Table 2** and **Figure 3**). This was expected, based on the crossing angle of the VA (Huber et al., 2014) and the presence of the walkway (**Figure 2**), and supports previous observations on the role of speed adjustments in obstacle avoidance (Cinelli and Patla, 2008; Basili et al., 2013; Olivier et al., 2013; Huber et al., 2014; Knorr et al., 2016). By defining a limited space for gait modulation, we made speed changes alone insufficient to avoid a collision with the VA (Huber et al., 2014), thus requiring parallel adjustments in gait trajectory (Huber et al., 2014) and step length (Gérin-Lajoie et al., 2005). The recovery of stride length, only partially accompanied by

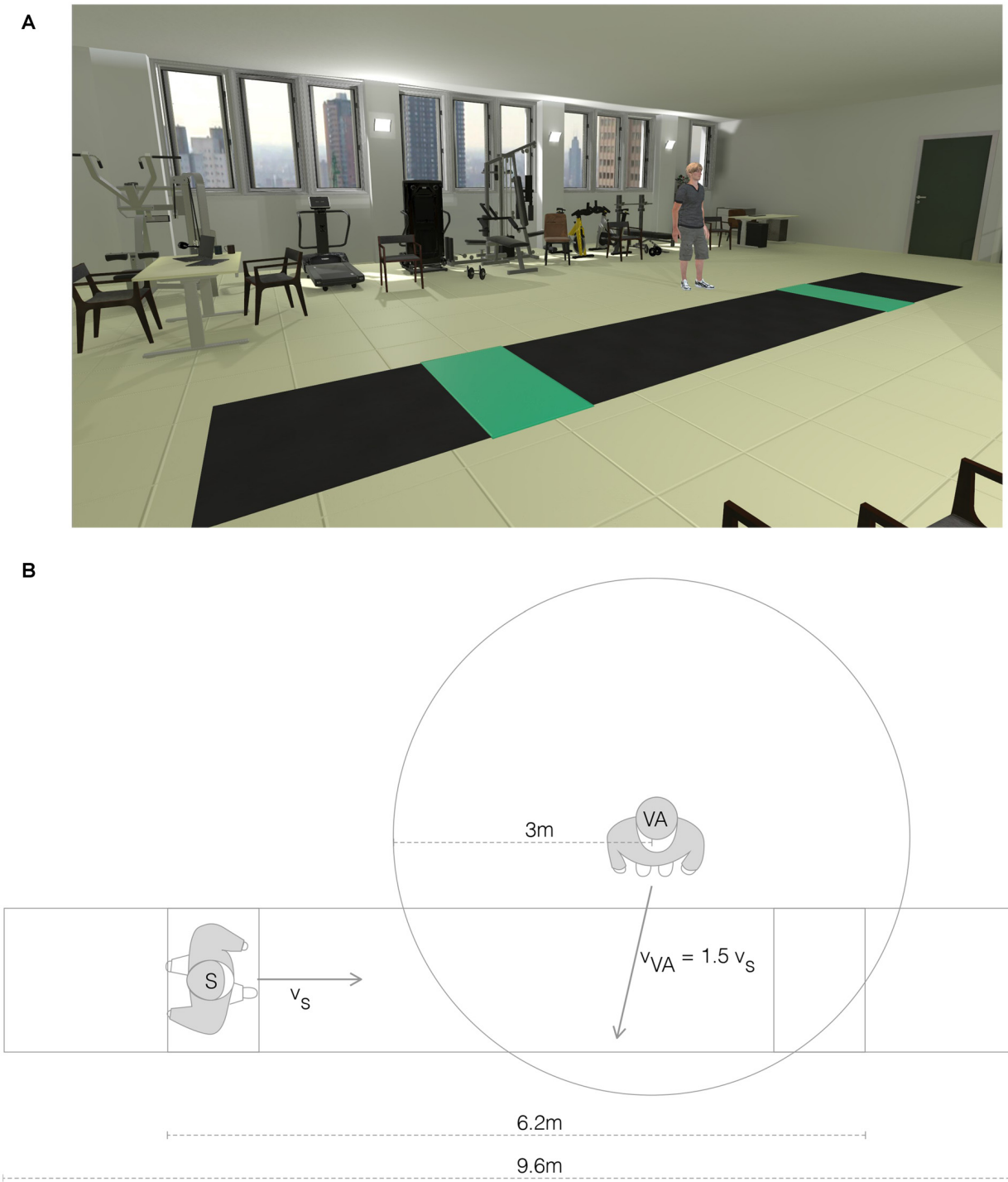

FIGURE 2 | Virtual reality environment. **(A)** View of the virtual reality (VR) environment with the virtual agent (VR/A+ condition). **(B)** Top view schema of the VR environment representing the relative positions of the subject (S) and the virtual agent (VA).

an increase in stride velocity, made the second modulator the longest in duration (**Figure 3**). Of note, changes between modulators were smooth, and values gradually restored to the unperturbed range during the second and third modulators (**Figure 3**).

Our VR paradigm also induced some additional mediolateral changes, which consisted of an increase in stride width and medio-lateral sway (**Tables 2** and **3**; Gérin-Lajoie et al., 2005; Cinelli and Patla, 2007, 2008; Huber et al., 2014). The increase in stride width may reflect a strategy to ensure balance for

TABLE 2 | Kinematic measures.

Condition	RW	VR/A-	VR/A+		
			M1	M2	M3
Stride length (cm)	132.4 (9.2)[a,b]	129.0 (11.2)[d,e]	96.1 (16.6)[a,d,g,h]	111.2 (13.0)[b, e, g, i]	124.0 (10.1)[h,i]
Stride width (cm)	8.2 (3.2)[a]	8.1 (2.3)[d]	10.3 (2.2)[a,d,h]	8.9 (2.9)	8.2 (2.2)[h]
Stride duration (s)	1.1 (0.1)[a,b,c]	1.1 (0.1)[d,e,f]	1.3 (0.2)[a,d]	1.3 (0.2)[b,e]	1.2 (0.1)[c, f]
Stride velocity (cm/s)	122.8 (13.2)[a, b, c]	117.5 (16.1)[d, e, f]	78.4 (15.7)[a,d,g,h]	88.1 (17.4)[b,e,g,i]	103.2 (13.4)[c,f,h,i]
Trunk inclination (°)	4.7 (1.6)[c]	4.2 (1.4)[e,f]	4.8 (1.9)[g]	5.6 (1.7)[e,g]	6.1 (1.7)[c,f]

Values are shown as mean (standard deviation). The letters "a, b, c, d, e, f, g, h, i" represent significant difference between conditions (Wilcoxon matched-pairs test for pairwise comparisons with Bonferroni correction for multiple comparisons). Abbreviations: RW, real world; VR/A-, virtual reality without virtual agent; VR/A+, virtual reality with virtual agent (i.e., perturbed gait); M1, first modulator; M2, second modulator; M3, third modulator.

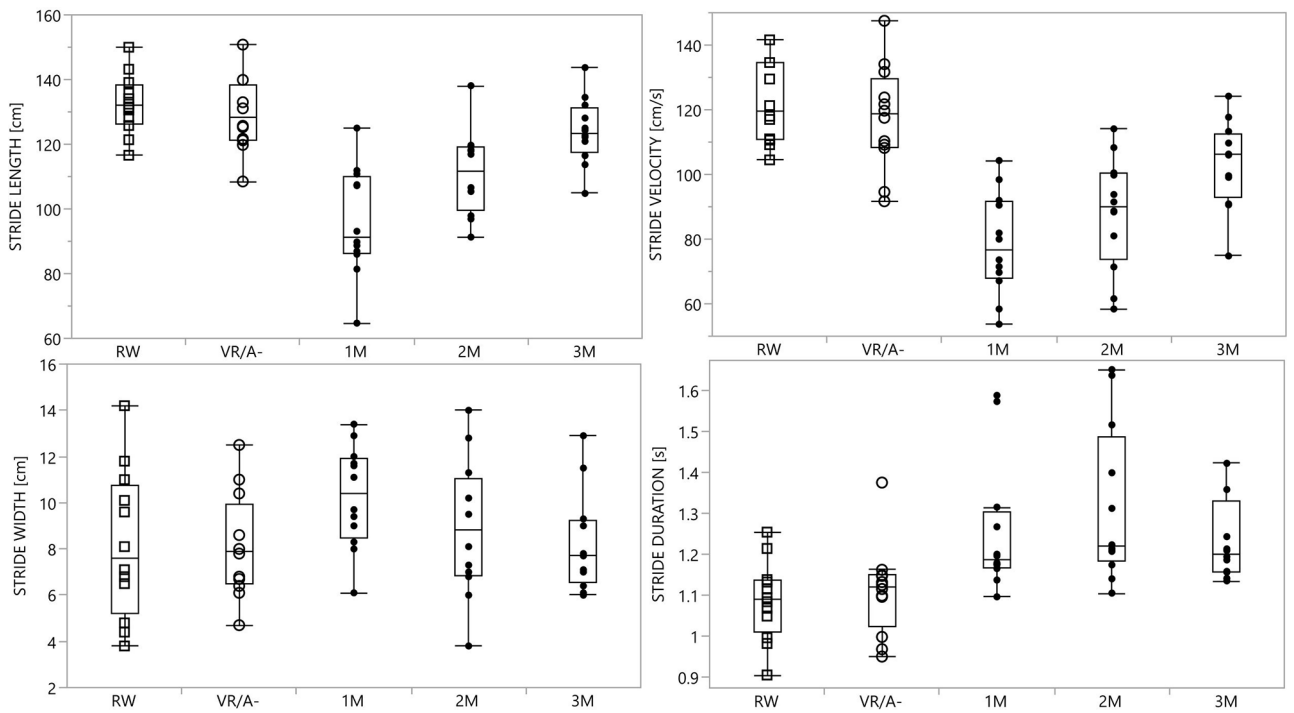

FIGURE 3 | Kinematic measurements of the stride. Graphical representation of kinematic measurements of the stride in all conditions; please see **Table 2** for kinematic values and statistics. Data are shown as the mean and standard error of the mean. Abbreviations: RW, real world; VR/A-, virtual reality environment without virtual agent; M1, first modulator; M2, second modulator; M3, third modulator.

TABLE 3 | Walking direction and mediolateral sway.

Measure	RW	VR/A-	VR/A+
Walking direction (°)	1.1 (0.3)[§]	1.4 (0.5)*	3.3 (1.0)*[§]
Mediolateral sway (cm)	5.4 (0.8)[§]	5.3 (1.0)*	7.9 (1.6)*[§]

*Values are shown as mean (standard deviation). *, § represent significant differences between conditions (Wilcoxon matched-pairs test for pairwise comparisons with Bonferroni correction for multiple comparisons). Abbreviations: RW, real world; VR/A-, virtual reality without virtual agent; VR/A+, virtual reality with virtual agent (i.e., perturbed gait).*

the avoidance of the VA, which perturbs postural stability as suggested by the increased medio-lateral sway in the VA/A+ condition (**Table 3**). Changes in stride width, however, were inconsistent across subjects and these findings should be further confirmed in larger cohorts.

Finally, we noticed an increase in trunk inclination during the second and especially third modulator. This could be an attempt to maintain sufficient personal space relative to the VA (Gérin-Lajoie et al., 2005, 2006, 2008; Argelaguet Sanz et al., 2015; Lynch et al., 2018; Olivier et al., 2018), particularly during strides in which the VA was close to the participant (i.e., the second and third modulators).

One limitation of our study is the choice not to randomize between conditions (i.e., RW, VR/A, and VR/A+). The main reasons for this are that switching repeatedly from RW to VR can induce discomfort (e.g., dizziness and nausea), and requires additional time to remove and reposition the HMD, reducing subject compliance and the number of overall trials. Randomization between the VR/A- and VR/A+ conditions would have resulted in wait-and-see behavior, with additional

gait changes given just by the expectation of whether the VA would begin moving. Instead, we wanted subjects to know that they needed to modulate their gait.

In conclusion, our VR setup was able to effectively induce timely gait modulation in a standardized, immersive, and realistic scenario that simulated a person crossing the path of the participant. Modulation involved both temporal and spatial adaptations of the gait cycle, as well as gait trajectory and trunk inclination. The use of this protocol in older subjects and patients with gait disorders could be useful to elucidate specific alterations in gait adaptation, and have diagnostic and therapeutic (physical therapy) value for future studies (Dockx et al., 2016; McCrum et al., 2017). In particular, we envision that the adaptive gait behavior induced by our VR paradigm may represent an ideal trigger for the occurrence of gait freezing episodes in patients with Parkinson's disease and other neurological disorders (Fasano et al., 2017; Pozzi et al., 2019). This assumption is based on our experience and previous studies describing the occurrence of gait freezing episodes, mainly during modulation of gait when facing an obstacle under conditions of temporal or spatial constraint (Nieuwboer et al., 2001; Hausdorff et al., 2003; Pozzi et al., 2019).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study involved human participants. It was approved by the local Ethical Committee of the University of Würzburg (no. 103/20) and conformed to the declaration of Helsinki. All subjects gave their written informed consent prior to participation.

AUTHOR CONTRIBUTIONS

CP: conceptualization, methodology, software, formal analysis, investigation, data curation, writing—original draft, and funding acquisition. PK: conceptualization, methodology, software, writing—original draft. IH: investigation, formal analysis, writing—original draft. MV: investigation, writing—review and editing. ML: conceptualization, methodology, writing—review and editing. AC: conceptualization and methodology. MF: conceptualization, methodology, resources, writing—review and editing, and supervision. IUI: conceptualization, methodology, formal analysis, investigation, resources, writing—review and editing, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Subthalamic Deep Brain Stimulation Lead Asymmetry Impacts the Parkinsonian Gait Disorder

*Frederik P. Schott[1], Alessandro Gulberti[1,2], Hans O. Pinnschmidt[3], Christian Gerloff[1], Christian K. E. Moll[2], Miriam Schaper[4], Johannes A. Koeppen[4], Wolfgang Hamel[4] and Monika Pötter-Nerger[1]**

[1] Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2] Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [3] Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4] Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

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***Correspondence:**
Monika Pötter-Nerger
m.poetter-nerger@uke.de

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Background: The preferable position of Deep Brain Stimulation (DBS) electrodes is proposed to be located in the dorsolateral subthalamic nucleus (STN) to improve general motor performance. The optimal DBS electrode localization for the post-operative improvement of balance and gait is unknown.

Methods: In this single-center, retrospective analyses, 66 Parkinson's disease (PD) patients (24 female, age 63 ± 7 years) were assessed pre- and post-operatively (8.45 ± 4.2 months after surgery) by using MDS-UPDRS, freezing of gait (FoG) score, Giladi's gait and falls questionnaire and Berg balance scale. The clinical outcome was related to the DBS electrode coordinates in x, y, z plane as revealed by image-based reconstruction (SureTune^{TM}). Binomial generalized linear mixed models with fixed-effect variables electrode asymmetry, parkinsonian subtype, medication, age class and clinical DBS induced changes were analyzed.

Results: Subthalamic nucleus-deep brain stimulation improved all motor, balance and FoG scores in MED OFF condition, however there were heterogeneous results in MED ON condition. DBS electrode reconstructed coordinates impacted the responsiveness of axial symptoms. FoG and balance responders showed slightly more medially located STN electrode coordinates and less medio-lateral asymmetry of the electrode reconstructed coordinates across hemispheres compared to non-responders.

Conclusion: Deep brain stimulation electrode reconstructed coordinates, particularly electrode asymmetry on the medio-lateral axis affected the post-operative responsiveness of balance and FoG symptoms in PD patients.

Keywords: deep brain stimulation, subthalamic nucleus, Parkinson's disease, balance, gait disorder, freezing of gait, electrode localization, lead asymmetry

INTRODUCTION

The parkinsonian (PD) gait disorder with freezing of gait (FoG) and balance disturbance is a common and incapacitating symptom with high impact on quality of life (Moore et al., 2007; Okuma, 2014). The treatment of the PD gait disorder remains quite challenging (Nonnekes et al., 2015). Beside dopaminergic medication, deep brain stimulation (DBS) of the subthalamic nucleus (STN) represents one therapeutical option, however the effects of STN-DBS on balance and gait are heterogeneous (Potter-Nerger and Volkmann, 2013). STN-DBS might have a positive impact on balance (Sato et al., 2019; Li et al., 2020) and FoG (Schlenstedt et al., 2017; Barbe et al., 2020), however despite stable improvements of global outcome scores after bilateral STN-DBS, there are also reports of post-operative worsening of gait (van Nuenen et al., 2008), increased risk of falls (Hausdorff et al., 2009) or persistent levodopa-resistant freezing of gait (Stolze et al., 2001). Long-term observations (>5 years) revealed a decrease of DBS effects on axial symptoms (Krack et al., 2003; Mei et al., 2020). Different factors might contribute to these heterogeneous gait effects of STN-DBS, as disease progression, age (Russmann et al., 2004) or the pre-operative levodopa-response (Bakker et al., 2004; Schlenstedt et al., 2017). One factor impacting gait outcome might be the exact lead localization of the STN electrode (Johnsen et al., 2010).

There are reports of differential effects on global motor outcome in terms of DBS electrode position (Johnsen, 2011). Systematic investigation of the different electrode contacts in the vertical axis in relation to anatomically and electrophysiologically defined STN boundaries revealed, that contacts located at the dorsolateral border of the STN had the best effect on contralateral appendicular motor symptoms (Hamel et al., 2003; Herzog et al., 2004). Further detailed analyses of axial MRI planes revealed that positioning of the lead in the anterolateral dorsal STN predicted the best general motor outcome (Wodarg et al., 2012). In terms of gait and balance improvement, the optimal electrode position within the STN and the relative position of DBS electrodes to each other across both hemispheres is less clear. One early study in a small PD cohort investigated the correlation of the position of the DBS electrode and outcome on objective measures of gait (Johnsen et al., 2010). Stimulation of contacts located in the dorsal half of the STN was more effective in improving step velocity and step length of the contralateral leg compared to ventral stimulation being in line with general motor symptom improvement (Johnsen et al., 2010).

The aim of the current, monocentric, retrospective analyses was to assess the effect of stereotactic DBS electrode localization within and across hemispheres on the post-operative outcome of the parkinsonian gait disorder and dissect these effects from other potential influencing factors as age, pre-operative symptom severity and levodopa-responsiveness of the parkinsonian gait disorder.

MATERIALS AND METHODS

Patient Characteristics

Sixty six patients (24 female, age 63 ± 7 years) suffering from advanced idiopathic PD (disease duration 10.41 ± 3.65 years; Hoehn and Yahr stage: 2.6 ± 0.81) were included into the retrospective analysis from clinical routine data. Inclusion criteria were 1. PD in Hoehn and Yahr 2–5, 2. Implantation of Medtronic, Boston Scientific or Abbott DBS systems, 3. Stable post-operative condition (>3 months, <1 year) 4. PD patients were not stimulated with a bipolar configuration.

Parkinsonian patients were screened and selected for DBS surgery in accordance to common guidelines of DBS surgery [CAPSIT protocol (Defer et al., 1999)]. Of all 66 patients, 17 patients were classified as tremor-dominant PD subtypes, 41 patients as akinetic-rigid subtypes and eight patients as equivalent subtypes.

Further clinical and demographic characteristics of PD patients are reported in **Supplementary Table**.

Implantation of the Permanent Deep Brain Stimulation Electrodes

Deep brain stimulation electrode placement was guided by intraoperative microelectrode recording (MER) and test stimulation. Up to five parallel tracks were used to map the subthalamic region with tungsten electrodes (NeuroProbe electrodes, Alpha Omega Inc., Nazareth, Israel). The subthalamic sensorimotor region was identified by cell responses to passive and active movements and a high prevalence of oscillating neuronal activities in the beta-frequency range (13–30 Hz). Permanent macroelectrodes were inserted in the best MER track with longest ventro-dorsal electrophysiological recording of STN activity and optimal clinical test stimulation effects.

Clinical Scores

Clinical assessments were performed pre-operatively after overnight withdrawal of medication (MED OFF) and after application of suprathreshold dosage of soluble dopaminergic medication (MED ON) to explore short-term dopaminergic effects. Post-operatively (8.45 ± 4.2 months after surgery), PD patients were assessed with DBS switched on (STIM ON) in MED OFF and MED ON. The following clinical scores were routinely applied:

1. The MDS-UPDRS part III score was used to assess general motor performance. The lateralized subitems (items 3.3–3.8, 3.15–3.18) were summarized. We calculated asymmetry scores from the lateralized items from the worst and best clinical side [(lateralized MDS-UPDRS worst side-lateralized MDS-UPDRS best side)/worst side] with asymmetry scores of 0 indicating perfect symmetry and 1 revealing most severe asymmetry.
2. The Ziegler's freezing of gait assessment course score (FoG score) (Ziegler et al., 2010) was used as short-interval rater-based scale to quantify festination and FoG.

3. The Giladi's gait and falls questionnaire (GFQ) (Giladi et al., 2009) was applied as a 16 items questionnaire reflecting the patient's subjective perspective on falls and FoG pattern.
4. The short version of the Berg balance scale (Chou et al., 2006) was assessed as a seven item rater-based balance score.

Localization of Electrodes and Active Contacts

Magnetic resonance imaging (MRI) scans (Siemens Skyra, 3 Tesla, 0.94–1.6 mm slice thickness, TR 2100, TE 2.5, FA 9.0) were obtained from all PD patients pre-operatively. MRIs were fused with post-operative CT scans (Siemens Somatom Definition AS, 1 mm slice thickness, RD 200, MA 154, KV 120, FOV 200 mm × 200 mm). The reconstruction of the stereotactic electrode position in the x, y, z plane was performed by using SureTune^{TM} software version 3.0.3.0 licensed by the Medtronic Company (**Figure 1**). The anterior (AC) and posterior commissure (PC) as well as the inter-hemispheric plane (IH) were defined in pre-operative, T1- weighted MRI (Hamel et al., 2003) and represented the axes of the three-dimensional coordinate system in which the electrodes coordinates were determined. The electrode reconstruction was performed by one main analyst and controlled by two experienced neurosurgeons of the local stereotactic neurosurgical department, who are doing routinely the DBS surgeries.

Magnetic resonance imaging (MRI) data were fused with pre- and post-operative CT scans in order to co-register the various images to the same reference. Individual contacts of DBS leads were displayed by the software after the DBS lead type had been specified (Boston Scientific, Abbott and Medtronic). The investigator performing reconstruction of DBS leads was blinded to clinical outcomes. The stereotactic x-, y-, and z-coordinates of the stimulated contacts were calculated. The stimulation parameters (amplitude, pulse width, pulse frequency) were used to calculate the volume of tissue activated (VTA).

Changes in the clinical scores between the pre- and post-operative state were correlated with the DBS localization on the medio-lateral (x-axis), anterior-posterior (y-axis), dorso-ventral line (z-axis) used by the neurosurgeons to define the target area of the STN referring to the midcommissural point. Electrode asymmetry of the two electrodes across hemispheres were analyzed by measuring the absolute distance to the midcommissural point in the right and left hemisphere respectively, and calculating the difference of x right-x left, this was repeated for the y and z reconstructed coordinates. A difference of 0 indicated optimal symmetry of the right and left electrode relative to the midcommissural point.

Statistics

In a first step, descriptive scores were reported as means and standard deviations of the mean (SD). Clinical scores pre- and post-operatively were compared by paired *t*-tests after testing for normal distribution. The VTA by DBS electrodes and levodopa equivalent daily dose (LEDD) were correlated with post-operative changes of the different motor scores by linear regression analysis and non-parametric Spearman tests.

In a second step, patients were subdivided into two groups depending on the responsiveness to the STN-DBS treatment. If the difference between the post-operative scores minus the pre-operative scores was negative in case of FoG score, Giladi's GFQ and MDS-UPDRS-III, and positive in case of the Berg balance scale, indicating a post-operative improvement of the scores, the patients were assigned to the responder group, otherwise to the non-responder group. The responsiveness to therapy was analyzed using a generalized linear mixed model approach with a logit-link function assuming binomially distributed data (SPSS

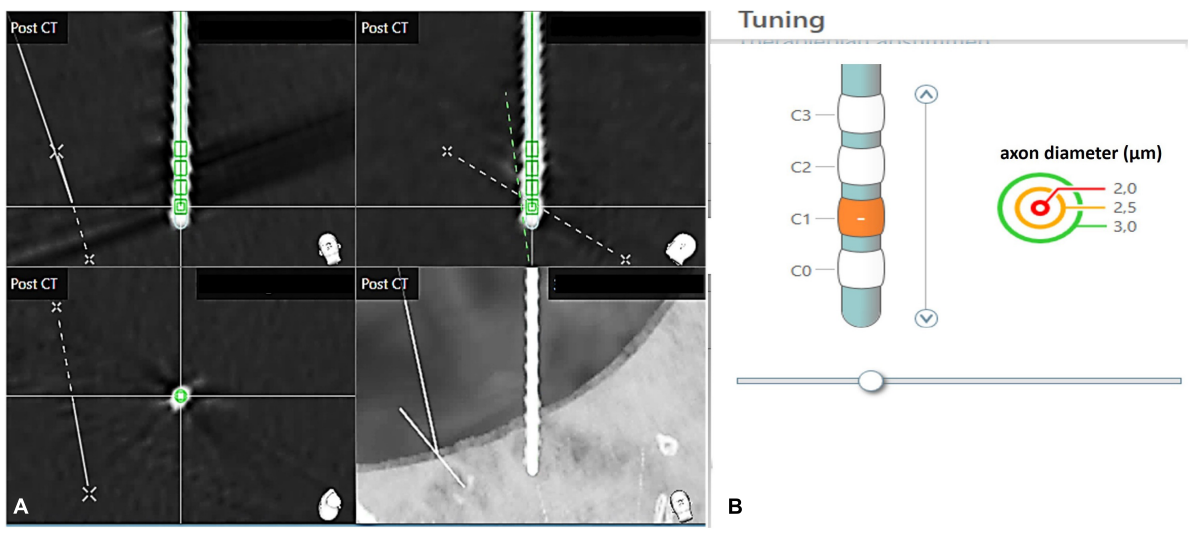

FIGURE 1 | Methodological approach of electrode localization within the SureTune^{TM} software. After definition of the AC-PC line in the axial and sagittal plane in the merged CT and MRI images, determination of spatial parameters of electrode localization was performed **(A)**. Definition of active contact and modeling of volume of tissue activated by using corresponding stimulation parameters **(B)**.

routine generalized linear mixed models; IBM SPSS Statistics for Mac, version 25.0.0.2, SPSS Inc., Chicago, IL, United States). Prior to analysis, all continuous variables with a positively skewed distribution were log for base 2 transformed to achieve normal distribution [log2x = ln(x)/ln(2)]; negatively skewed distributions were first reverse-score transformed before the log for base 2 transformation (Field, 2009). The asymmetry index of the x, y, z stereotactic coordinates (the absolute values of the difference between x, y, z right and x, y, z left, respectively), the parkinsonian subtype (TD, IP, PIGD), the medication (LEDD), the pre-operative MDS-UPDRS-III scores, age class (three classes: first age class ≤ 60; second age class $> 60 \leq 67$, third age class > 67) were considered as categorical fixed-effect variables, subjects assumed as random effects and the different axial subscores as dependent variables. The approximate degrees of freedom (df) were computed according to the Satterthwaite method. Starting from an initial model containing all fixed effects, non-significant independent variables were stepwise excluded following a hierarchical backward elimination procedure based on maximum likelihood estimation (Kleinbaum et al., 2010). The final models contained the significant effects of the remaining independent variables. The generalized linear mixed models-estimated marginal means and their 95% confidence intervals (CIs) were computed for all dependent variables. As *post-hoc* tests, in case of significant fixed-effect variables, as for example DBS-lead asymmetries, their values were correlated with the post-operative changes of the different scores by non-parametric Spearman tests. As this was an exploratory pilot study, no adjustments for multiple testing were done (Bender and Lange, 2001). Adjustments for multiple comparisons are reducing type I errors at the expense of increasing type II errors. Increasing the type II errors in our study could mean that truly detrimental effects following STN-DBS treatment could be deemed as non-significant: i.e., PD-patients could truly have a poorer gait-quality due to lead asymmetry, but we ignore these finding because of multiple comparison corrections for other factors as age, pre-operative symptom severity and levodopa-responsiveness (Rothman, 1990, 2014; Perneger, 1998; Field, 2009). This would be a more problematic issue as the type I error, where no real changes of the treated patients could have been spotted just by chance (Rothman, 1990). Therefore, we report here the uncorrected results, as suggested by a number of statisticians (Rothman, 1990, 2014; Saville, 1990; Savitz and Olshan, 1995; Perneger, 1998; Bender and Lange, 2001).

RESULTS

Post-operative Clinical Motor and Gait Performance

In accordance with previous studies, PD motor symptoms and LEDD were significantly reduced after STN-DBS surgery. The pre-operative LEDD (1170 ± 500 mg) decreased by 26% to 776 ± 415 mg ($p < 0.001$).

The pre-operative *MDS-UPDRS III* score was significantly impacted by DBS and medication ($F = 62.23$, $p < 0.001$). L-Dopa improved general motor symptoms pre-operatively (MED OFF 36.27 ± 14.24, MED ON 15.35 ± 9.94, $p < 0.001$) and post-operatively while active STN-DBS (STIM ON MED OFF 25.28 ± 11.92, STIM ON MED ON 17.63 ± 10.59; $p < 0.001$). STN-DBS improved general motor performance significantly by 30% compared to the pre-operative state without medication ($p < 0.001$), but not with medication. Symptom asymmetry as revealed by lateralized MDS-UPDRS items was significantly affected by L-Dopa pre-operatively (pre-op MED OFF: 0.36 ± 0.22, pre-op MED ON 0.49 ± 0.33; $p = 0.001$), but not by DBS post-operatively (post-OP MED OFF 0.36 ± 0.29). Pre-operatively, 42 PD patients (63.6%) were more severely affected on the left body side, 21 PD patients (31.8%) on the right body side, three PD patients (4.5%) revealed a symmetric motor symptom pattern, which was mostly in line with medical history of the reported subjectively perceived side of symptom onset by PD patients (87.9%). Post-operative general symptom asymmetry was not correlated with DBS lead reconstructed coordinate asymmetry in the x, y, or z-plane ($F = 1.28$, $p = 0.289$).

The *Berg balance* score was impacted by DBS and dopaminergic medication (GLM ANOVA $F = 17.18$, $p < 0.001$). There was a considerable confinement of balance pre-operatively in MED OFF (22.56 ± 4.48), which was improved during the pre-operative L-Dopa challenge (MED ON 25.95 ± 3.07, $p < 0.001$). Post-operatively, STN-DBS significantly improved balance about 6.9% to 24.36 ± 4.5 in STIM ON MED OFF ($p = 0.009$) indicating a significant improvement of balance in PD patients without medication. Further improvement of post-operative balance scores was observed with additional medication (STIM ON MED ON 25.95 ± 2.68, $p < 0.001$). However, comparison of pre- and post-operative scores in best MED ON revealed that DBS had no additional significant impact on balance performance.

Freezing of gait was significantly impacted pre- and post-operatively after STN-DBS as demonstrated by Giladi's GFQ and rater-based FoG score. All PD patients complained about subjectively perceived freezing as assessed by the Giladi's GFQ. The pre-operative Giladi's GFQ score was 21.21 ± 13.57 with a reduction to 14.62 ± 13.82 post-operatively ($p = 0.009$).

Freezing of gait in PD patients was impacted by DBS and medication ($F = 19.02$, $p < 0.001$). Rater-based FoG scoring revealed pre-operative freezing phenomena in 84% of the tested PD patients, which improved significantly after suprathreshold donation of L-Dopa (MED OFF 11.84 ± 11.18, MED ON 2.94 ± 5.72, $p < 0.001$). Within the whole cohort, the degree of L-Dopa responsiveness showed remarkable variability (mean improvement 70.94 ± 65.35%) with complete resolution of FoG in 26 PD patients and worsening in two patients after L-Dopa medication. DBS improved the rater-based FoG score in MED OFF post-operatively (8.64 ± 9.68, $p = 0.025$). Interestingly, in MED ON, a significant worsening of FoG from 2.37 ± 4.23 pre-operatively to 4.67 ± 7.7 post-operatively ($p = 0.042$) was observed.

We evaluated the impact of the pre-operative LEDD, the post-operative LEDD and the relative change of LEDD after DBS on the different motor scores as MDS-UPDRS, Berg balance scale, Giladi's GFQ and rater-based FoG score by linear regression

models. There were no significant interrelations throughout all correlative LEDD and motor measures.

Thus, STN-DBS improved all motor, balance and FoG scores in MED OFF condition post-operatively, however in MED ON there was no additional benefit of STN-DBS for motor or balance improvement and even slight worsening of FoG with STN-DBS.

The Effect of Deep Brain Stimulation Electrode Localization and Volume of Tissue Activated on Post-Operative Gait Performance

Electrode reconstructed coordinates were in the planned range with a slightly anterior position (right hemisphere: x = 12.08 ± 1.51, y = -0.5 ± 1.5, z = -1.83 ± 1.8; left hemisphere: x = 12.54 ± 1.07, y = -0.25 ± 1.57, z = -2.05 ± 1.67). The volume of tissue activated was comparable and not significantly different between left side (43.57 ± 19.45) and right side (39.82 ± 17.87, $p = 0.22$). When summing up the VTAs and correlating the sum score with the STN-DBS induced changes of the MDS-UPDRS, Berg balance score, Giladi's GFQ score and FoG score post-operatively, there were throughout non- significant correlations indicating that the stimulation volume alone is not predictive for the post-operative outcome (all p-values > 0.05).

Patients were subdivided into two cohorts depending on their responsiveness to STN-DBS in terms of FoG and balance tested in the MED OFF condition. PD patients improving with STN-DBS defined by the FoG score (35 responders, pre-operative score 16.14 ± 11.73 points, post-operative score 5.66 ± 6.19; 64% improvement) revealed slightly different electrode coordinates compared to non-responders (31 non-responders, pre-operative score 6.66 ± 7.95 points, post-operative score 13.00 ± 12.09, worsening -94.71%). The electrode reconstructed coordinates on the medio-lateral x-axis (right STN 12.11 ± 1.3, left STN 12.25 ± 0.96) was slightly more medial on the left hemisphere in FoG-responders compared to non-responders (right STN 12.04 ± 1.74, left STN 12.87 ± 1.11, $F = 5.8$, $p = 0.019$). There were no differences of other electrode coordinates (y, z-axis) nor of VTAs between the two groups.

Parkinson's disease patients improving with STN-DBS defined by the Berg balance score (42 responders, pre-operative score 21.64 ± 4.87 points, post-operative score 25.83 ± 2.0, 19% improvement) revealed no significantly different electrode reconstructed coordinates compared to non-responders (24 non-responders, pre-operative score 24.32 ± 2.97 points, post-operative score 21.35 ± 6.28; 12% worsening). Only the electrode coordinate on the medio-lateral x-axis tended to be slightly more medial in the left hemisphere (right STN 11.99 ± 1.45, left STN 12.37 ± 1.06) in Balance-responders compared to non-responders (right STN 12.23 ± 1.64, left STN 12.85 ± 1.05), however it did not reach a significant level ($F = 3.2$, $p = 0.080$). There were no differences between the other electrode coordinates (y, z-axis) nor between the VTAs of the two groups.

In summary, PD patients responding to STN-DBS in terms of FoG and balance had slightly more medially located STN electrodes.

The Effect of Spatial Electrode Asymmetry on Post-Operative Gait Performance

To assess the impact of spatial asymmetry of the bilateral DBS electrodes on post-operative axial symptom improvement, we used a binomial distribution in the generalized linear mixed models with the fixed factors electrode asymmetry in the medio-lateral (x), anterior-posterior (y), and dorso-ventral (z) axis as well as Parkinson subtype, medication, age and pre-operative severity of the particular scale, i.e., of the MDS-UPDRS part III, of the Giladi's GFQ score, of the FoG score and of the Berg balance score.

The post-operative change of general motor symptoms as assessed by the MDS-UPDRS was only associated with the pre-operative MDS-UPDRS score as revealed by generalized linear mixed models (**Table 1**). A high pre-operative MDS-UPDRS score was associated with a larger post-operative improvement ($p < 0.001$; **Table 1**). Neither the degree of electrode asymmetry, nor the Parkinson subtype, medication or age predicted the post-operative change.

The post-operative change of *balance* as assessed by the Berg balance score was significantly impacted by two factors, the pre-operative extent of balance disorder ($p < 0.001$; **Figure 2** and **Table 1**) and the relative electrode asymmetry on the x axis (**Table 1**). Electrode asymmetry on the anterior-posterior (y) and dorso-ventral (z) axis did not affect post-operative balance outcome, however electrode asymmetry on the medio-lateral (x) axis did ($p = 0.02$; **Table 1**). With higher spatial asymmetry

TABLE 1 | Fixed effects of the generalized linear mixed model for the scores of MDS-UPDRS part III, Berg balance, and freezing of gait (FoG), respectively.

Questionnaire or scale	Source	*F*	df1	df2	*p*-Values
MDS-UPDRS part III	Corrected model	21.740	1	130	<0.001
	Pre-op MDS-UPDRS score	21.740	1	130	<0.001
Berg balance	Corrected model	12.381	2	125	<0.001
	Delta x-coordinates	5.662	1	80	0.020
	Pre-op Berg balance score	24.000	1	125	<0.001
FoG	Corrected model	13.390	2	115	<0.001
	Delta x-coordinates	5.239	1	61	0.026
	Pre-op FoG score	25.065	1	125	<0.001

The reported values for the fixed effects are degrees of freedom (df1 and df2), F and p-values.

on the medio-lateral axis, there was higher probability to show no response or even a worsening of balance after STN-DBS treatment (**Table 1** and **Figure 3**).

The same factors were predictive for the post-operative outcome of FoG measured by the rater-based FoG score. Generalized linear mixed models revealed two predictive factors which affected the post-operative change of FoG, the pre-operative severity of FoG (**Figure 2**) and the relative electrode asymmetry on the x axis (**Table 1** and **Figure 3**). The higher the pre-operative FoG score, the larger was the relative post-operative change ($p < 0.001$; **Table 1**). Electrode asymmetry on the medio-lateral (x) axis impacted FoG improvement ($p = 0.026$; **Table 1**), the higher the spatial asymmetry on the medio-lateral axis, the smaller the post-operative FoG change (**Figure 3**). No predictive factors for the subjective Giladi's GFQ were found.

Summarizing these findings, we found two factors predicting the responsiveness to STN-DBS in terms of balance and FoG, the pre-operative symptom severity and the extent of medio-lateral asymmetry of the electrode localization across hemispheres.

DISCUSSION

In this retrospective, monocentric analysis, we found STN-DBS to improve all motor, balance and FoG scores in MED OFF condition, however heterogeneous results were showed in MED ON condition. Electrode reconstructed coordinates affected the responsiveness of balance and FoG symptoms in PD patients. PD patients responding to STN-DBS in terms of FoG and balance showed slightly more medially located STN electrodes and increased medio-lateral asymmetry of the electrode coordinates across hemispheres.

There are certain limitations of the study. These were monocentric, retrospective, statistically exploratory analyses of clinical routine data of a smaller cohort of PD patients, the findings should be confirmed by a prospective, multicenter study. The electrode coordinates in x, y, z planes on CT and MR fused images were analyzed, which might be associated with methodological constraints. Due to the closely spaced anatomy of subcortical nuclei and fiber tracts, image based reconstruction method represents a rough method missing exact subcortical alignment. The asymmetry of individual brain structures across hemispheres and the post-operative shift caused by the loss of cerebrospinal fluid might hamper comparative observations of electrode positions of right and left hemispheres. We did not relate the electrode coordinates to individual fiber tracts. Current advances in neuroimaging techniques as diffusion tractography and functional connectivity enable studying normative and individual connectomes involved in the mediation of STN-DBS beneficial effects (Horn et al., 2017; Fox, 2018), since therapeutic benefit of DBS may depend on modulation of remote brain regions connected to the stimulation site (Horn et al., 2019). Recently, MR based contact lead localization and DBS programing were even optimized by machine learning algorithms depending on the characteristic brain response pattern to DBS (Boutet et al., 2021). However, these advanced neuroimaging techniques are not available at all movement disorder centers using DBS, as they are not standard procedure at our center. We focused in this study on the stereotactic routine measures of clinical procedures, which are easily available in any center. We assessed a cohort of 66 PD patients and did not find an association of DBS electrode reconstructed coordinates in x, y, z plane and general motor symptoms as reflected by MDS-UPDRS, this might be due to the small size of patients.

Further limitations might represent variability of the L-Dopa responsiveness of the PD gait disorder, different degree of L-Dopa reduction post-operatively (LEDD) and the use of acute levodopa challenges pre- and post-operatively, which might not reflect the everyday life condition with regular medication and might not rule out effects of fatigue in the non-randomized MED OFF and MED ON condition. Still, in this cohort, we did not find any impact of the LEDD or the amount of post-operative LEDD reduction on relative motor score changes, indicating that DBS is the main driver for the observed motor and gait changes. Still,

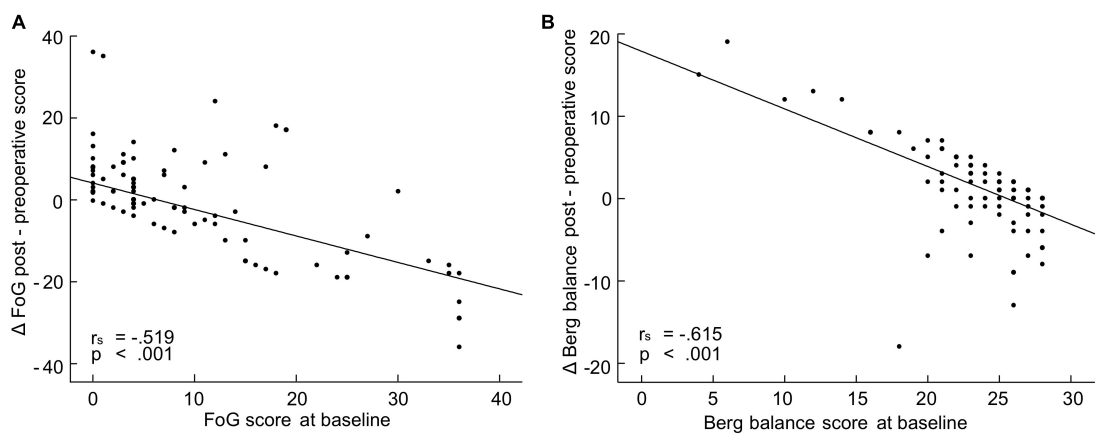

FIGURE 2 | Relation of freezing of gait (FoG) and balance improvement to pre-operative symptom severity. FoG **(A)** and Berg balance **(B)** scores as recorded before and after subthalamic nucleus (STN)-deep brain stimulation (DBS) surgery. The pre-operative scores were recorded in the MED OFF condition, the post-operative scores were recorded in STIM ON/MED OFF condition. Values inset of Spearman correlation and best fit lines are given.

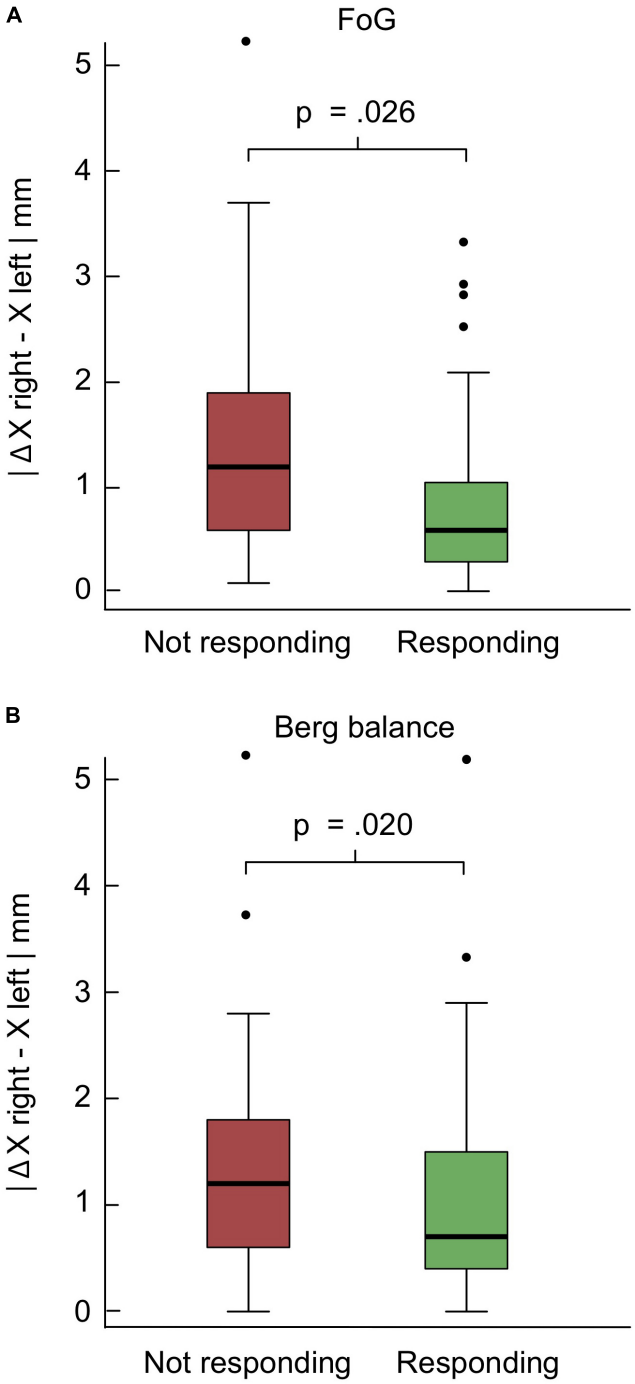

FIGURE 3 | Relation of post-operative freezing of gait (FoG) and balance outcome to deep brain stimulation (DBS) electrode reconstructed coordinates. Panels **(A,B)** show the box plots of the patients subdivided into two groups depending on the responsiveness to the subthalamic nucleus (STN)-DBS treatment. If the difference between the post-operative scores minus the pre-operative scores was negative in case of FoG and positive in case of the Berg balance, indicating a post-operative improvement of the scores, the patients were assigned to the responder group, otherwise to the non-responder group. *P*-values reported in panels **(A,B)** refer to the results of the general linear mixed models.

in previous studies, there is an overlapping effect of dopaminergic medication and STN-DBS on the different subdomains of balance and gait adjustment (Bejjani et al., 2000; Haslinger et al., 2005; Valalik et al., 2009), so that both treatment modalities seem to restore the dysfunctional parkinsonism network with partial overlap.

The STN is subdivided into different territories as the dorsal sensorimotor area, the associative ventro-lateral area and the medio-ventral limbic part (Benarroch, 2008). Whereas dorsolateral regions of the STN receive afferent input by primary motor areas, medial subterritories are innervated by supplemental motor areas. The STN contains a segregated somatotopic body map within the sensorimotor area as revealed by intraoperative subthalamic micro-electrode recordings (Romanelli et al., 2004a). Leg-related subthalamic cells were localized in the medial STN area and tended to be situated slightly more anterior relative to arm-related cells (Romanelli et al., 2004b). This topographical organization could explain the finding of a better balance and gait response profile of medial DBS electrode reconstructed coordinates where leg-related cells are located. Besides, medial STN areas receiving SMA inputs might play an important role in the pathophysiology of the gait disorder and FoG (Bartels et al., 2006; Snijders et al., 2011).

An interesting finding was the effect of DBS interhemispheric electrode asymmetry of the right and left hemisphere on balance and gait. Although individual, anatomical, hemispherical asymmetries of the STN must be considered, one could hypothesize that different DBS electrode coordinates within the STN are associated with different drive or efficacy of divers subthalamic efferent projections resulting in asymmetric motor performance of the right and left leg. Gait asymmetry of step length or stride time is closely associated with the freezing episodes and falls (Plotnik et al., 2005; Frazzitta et al., 2013). Reduction of gait asymmetry by dopaminergic medication (Plotnik et al., 2005) or by adjustment of DBS stimulation strengths, according to the best and worst body side, improves FoG (Fasano et al., 2011). Neuronal activity of the more affected hemisphere was shown to be associated with specific cortico-subthalamic synchronization in the low-frequency band during gait with an asymmetric decoupling and breakdown during FoG in the hemisphere with less striatal dopaminergic innervation (Pozzi et al., 2019). Therefore, DBS electrode symmetry for the bilateral adequate drive of the locomotor system might be one important factor in the post-operative improvement of balance and gait.

In conclusion, post-operative outcome of PD gait characteristics after DBS is dependent on the pre-operative symptom level and electrode reconstructed coordinates, as electrode asymmetry on the medio-lateral axis.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: monocentric clinical routine data. Requests to access these datasets should be directed to MP-N, m.poetter-nerger@uke.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik-Kommission der Ärztekammer Hamburg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WH and MP-N: conception of research project. FS, AG, CG, CM, MS, JK, WH, and MP-N: organization of research project. FS, AG, and MP-N: execution of research project and writing the first draft of manuscript. AG, HP, and MP-N: design, review, and critique of statistical analysis. FS, AG, HP, and MP-N: execution of statistical analysis. FS, AG, HP, CG, CM, MS, JK, WH, and MP-N: review and critique of the manuscript. All authors collaborated to carry out this work and have seen and approved the manuscript.

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Using Motor Imagery to Access Alternative Attentional Strategies When Navigating Environmental Boundaries to Prevent Freezing of Gait – A Perspective

Daniella How, Heiko Wagner and Michael Brach*

Department of Movement Science, Institute of Sport and Exercise Sciences, University of Münster, Münster, Germany

Freezing of gait can cause reduced independence and quality of life for many with Parkinson's disease. Episodes frequently occur at points of transition such as navigating a doorway. Therapeutic interventions, i.e., drugs and exercise, do not always successfully mitigate episodes. There are several different, but not exclusive causes for freezing of gait. People with freezing of gait are able to navigate dynamic situations like stairways by utilizing a different attentional strategy to over-ground walking, but may freeze when passing through a doorway. The question is, is it possible to employ a special attentional strategy to prevent freezing at this point? Motor imagery allows for learning motor skills in absolute safety and has been widely employed in a variety of populations, including other neuro-compromised groups. Motor imagery is not studied in a homologous manner in people with Parkinson's Disease, leading to conflicting results, but may have the potential to establish a different attentional strategy which allows a subject to mitigate freezing of gait episodes. This paper will identify and discuss the questions that still need to be answered in order to consider this approach i.e., can this population access motor imagery, can motor imagery alter the attentional strategy employed when moving through doorways, what is the best motor imagery approach for people with Parkinson's Disease and freezing of gait, and what dosage is most effective, while briefly outlining future research considerations.

Keywords: freezing of gait (FOG), motor imagery (MI), Parkinson's disease (PD), attentional strategies, telemedicine

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Moran Gilat,
KU Leuven, Belgium

****Correspondence:***
Daniella How
d.how@uni-muenster.de

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INTRODUCTION

Between one third and 63% of patients with Parkinson's Disease (PD) suffer from Freezing of Gait (FOG), which results in falls, decreased independence and reduced quality of life (QoL) (Rutz and Benninger, 2020; Silva-Batista et al., 2020). FOG is characterized by an abrupt, erratic gait interruption (Peterson et al., 2014; Pozzi et al., 2019) despite the person intending to move forward (Nutt et al., 2011). This can result in hesitation starting a movement, stopping during turns (Plotnik and Hausdorff, 2008) and trembling in place (Moore et al., 2008; Nonnekes et al., 2019). While medication with levodopa has been shown to be partially effective, FOG is still sporadically observed when patients are in the clinical "ON"-medication state (Schaafsma et al., 2003a). FOG episode (Lees, 1989; Pozzi et al., 2019; Silva-Batista et al., 2020) severity correlates with disease progression

(Paul et al., 2018). People with PD are considered to be in an ON-medication state when levodopa medication is effective in alleviating motor symptoms and in the OFF-medication state when there is not enough levodopa remaining in the brain to relieve motor symptoms sufficiently (Lees, 1989). Falls frequency is associated with FOG both in OFF-medication and ON-medication states but far greater in the OFF-medication state (Schaafsma et al., 2003b). Other non-invasive treatments which alleviate FOG severity include exercise rehabilitation programs (Cucca et al., 2016; Silva-Batista et al., 2020) but rehabilitation gains are not often retained (Lees, 1989; Gilat et al., 2021). If both rehabilitation and medication are not successfully alleviating FOG severity, then further treatment options should be explored.

Because FOG can occur during ON-medication states (Lewis and Barker, 2009), it may not be solely attributed to depleted dopamine (Schaafsma et al., 2003a; Lewis and Shine, 2016). Current theories as to the cause of FOG include:

(i) Poor conflict resolution between anticipatory postural adjustments (APAs) with stepping patterns between sensory motor area (SMA) and motor cortex (Schaafsma et al., 2003a). The person is stuck in a ready state;
(ii) Disconnection between basal ganglia (BG) and the SMA, causing interruption in internal cueing of learnt actions. This is further complicated by competition from the increased excitatory output of the subthalamic nucleus (STN) and other centers for motor, cognitive, and limbic cortical areas. BG fire synchronously and inhibition occurs in brain stem areas resulting in FOG. This theory is supported both by dopamine reducing FOG and by cueing which bypasses the caudate nucleus, thalamus and prefrontal cortex motor loop, allowing motor activity (Lewis and Barker, 2009);
(iii) Visuo-spatial judgment failures resulting from poor communication between the prefrontal cortex and the BG (Kostic et al., 2012);
(iv) Executive function as a result of poor communication between BG and the frontal lobe, especially evident in dual task scenarios where overload from competing demand interrupts communication (Shine et al., 2013a,b; Cucca et al., 2016; Marquez et al., 2020).

An earlier theory proposes a disruption of supraspinal controls to the central pattern generators (CPGs) (Plotnik and Hausdorff, 2008; Marquez et al., 2020). These causes may not be exclusive of each other.

Freezing of Gait is experienced by individuals with PD at environmental boundaries such as doorways, or crossing roads, when in tight spaces, and when facing an obstacle such as furniture or trip hazards such as uneven flooring (Ramos et al., 2020). However, people with PD report fewer FOG episodes when navigating obstacles such as stairways where specific attentional strategies are used, e.g., subjects may be able to focus on keeping each step even following the step treads (Rutz and Benninger, 2020) or when using a pedestrian cross walk following evenly spaced lines (Ramos et al., 2020). Could a person who experiences FOG learn and utilize a similar strategy to regulate their gait without freezing at an environmental obstacle or boundary?

In healthy individuals, motor control is not just regulated by CPGs and the brainstem but refined with cortical commands (Pozzi et al., 2019). The neuronal circuits that comprise CPGs which result in rhythmic movements such as walking are always active, but modulated by higher brain centers (Marder and Bucher, 2001; Behrendt et al., 2013, 2014). The cerebral cortex modulates rhythms that originate in spinal networks. In the PD brain, the depletion of dopamine may result in not enough to act as a neurotransmitter. Competition is created between complementary neural circuits, both inhibitory and excitatory (Lewis and Barker, 2009) which leads to FOG.

Rehabilitation exercises developed specifically to improve FOG symptoms show benefits (Gilat et al., 2021), but as those benefits are not retrained, would need to be continuously practiced to preserve the improvement. A safe, but effective adjunct therapy could be utilized to facilitate this practice independently, without the need for additional support by staff (Heremans et al., 2012). In this article the authors will propose why Motor Imagery (MI) could support standard rehabilitation practice to prevent FOG at environmental boundaries.

MOTOR IMAGERY AS A THERAPY FOR PARKINSON'S DISEASE PATIENTS TO SUPPORT MOTOR CONTROL

Motor imagery is the mental rehearsal of an action without its actual physical performance. It can be "performed" in the first person or "viewed" as a third person. MI can be visual in nature or kinesthetic (Saimpont et al., 2013). MI has been used successfully in healthy adults, especially in sports, for some time (Saimpont et al., 2013). One of the draw backs is it can be mentally demanding (Abbruzzese et al., 2015) but it can be performed seated as a visualization only without safety risks, and, once the skill is learnt, can be practiced independently without a therapist present (Heremans et al., 2012). This would not replace other rehabilitation practices but adjunct them (Slimani et al., 2016; Da Nascimento et al., 2019). MI is now being used in training for healthy older adults as an adjunct to physiotherapy. Studies are conflicting, but research currently supports the idea that MI can improve the outcomes of therapeutic interventions in older populations (Saimpont et al., 2013). It is believed to preserve or stimulate the forward planning neural pathways (Ashley Fox, 2013). MI shows the most benefit in healthy elderly adults when in the third person, supported by auditory cues and kinesthetic in nature (Saimpont et al., 2013). Importantly, the pathways used in MI are partially the same as those used in motor execution (Snijders et al., 2011), specifically the SMA, premotor cortex, primary motor cortex, posterior parietal regions (e.g., the inferior and superior parietal lobes), the BG and cerebellum (Moran and O'Shea, 2020).

Motor imagery alone can cause a significant improvement in muscle force, as well as increasing the motor-activity related cortical potential of healthy older adults (Jiang et al., 2016). Mouthon et al. (2015) showed that during MI, cortico-spinal

excitability is increased in healthy young adults during mental training of balance tasks, as evidenced by motor evoked potential facilitation. In healthy subjects, brain plasticity can be measured after MI, and motor performance is improved (Debarnot et al., 2014).

Traditional gait and balance therapy is usually delivered in an explicit teaching method. Explicit learning is a complex learning method requiring a high cognitive load, using working memory. As people age, and with the impact of disease, the ability to learn through explicit methods deteriorates. This is especially true in dual-task situations (Abbruzzese et al., 2015). People are expected to integrate and memorise instructions in traditional motor learning (Rutz and Benninger, 2020). This style of explicit learning is not retained in people with brain lesions in the motor pathways such as PD (Rutz and Benninger, 2020).

An important consideration for any clinician wishing to consider a patient for this therapy is their cognitive decline. People with PD may exhibit cognitive decline which varies with the stage and time of onset of the disease (Ding et al., 2015). Salient to gait rehabilitation are losses in executive function, short-term working memory and visual-spatial memory. Early cognitive impairment is difficult to diagnose. There is no clear pattern to the decline and the decline can only be assessed on an individual basis and is unique to each person (Ding et al., 2015). The gross progression of the pathology of PD will eventually include atrophy of several brain regions (Ding et al., 2015), some of which we can surmise could affect the person's ability to engage in MI and overall gait rehabilitation.

The advantage of MI is that it does not require learning (Snijders et al., 2011), it uses working memory efficiently, and allows for greater training endurance (Debarnot et al., 2014; Moran and O'Shea, 2020). Gait re-education and the creation of new attentional strategies through means such as MI should allow for greater retention of motor learning in people with PD (Mirelman et al., 2013). MI can be mentally fatiguing (Abbruzzese et al., 2015) and the authors suggest that using MI as an intervention (Podda et al., 2020) should be considered on a case-by-case basis, and that an appropriate dose is considered for that individual. It may not always be an appropriate intervention with this condition.

There are however, a number of questions that need to be carefully considered before pursuing MI as a possible treatment modality for FOG. These are:

CAN MOTOR IMAGERY SUPPLEMENT GAIT REHABILITATION THERAPY FOR PEOPLE WITH PARKINSON'S DISEASE AND FREEZING OF GAIT?

Can the General Parkinson's Disease Population Access Motor Imagery?

There is continued debate if people with PD can access MI, but studies have used inconsistent protocols with poor follow-up (Da Nascimento et al., 2019). The study of Abraham et al. (2018) showed promising results with improvements for the experimental group in motor symptoms, balance, physical activity and others. Their study was, however, poorly controlled. The MI group received an intensive in-person movement session whereas the control group received literature and an exercise video to perform at distance. They were asked to submit a video of exercise themselves, but the study does not describe how many completed the task. Another study indicated that MI was equally effective as relaxation (Tamir et al., 2007) therapy and that both improved gait in people with PD (Braun et al., 2011). They did not specifically address FOG. Tamir et al. (2007) compared conventional physical therapy with a combined motor imagery and conventional training approach and found that the latter was more effective, especially in reducing bradykinesia. The combined approach group showed "significantly faster performance of movement sequences than the control group." Further research is needed to either prove or disprove the success of MI with people with PD.

Can the Freezing of Gait Parkinson's Disease Population Access Motor Imagery?

Studies show that people with PD can access MI. The bradykinesia they demonstrate in gait is also apparent in their MI. People with FOG from PD visualize their MI more slowly than healthy controls and more slowly than people with PD without FOG (Cohen et al., 2011). When people with PD imagine their MI activity passing obstacles that cause them FOG, they experience an incongruency with time when compared with people with PD that do not have FOG imagining traversing the same obstacles (Cohen et al., 2011). Simply put, they are delayed in the imagined activity where they would be delayed in the same motor activity. This may be linked with the same deterioration in the motor circuits related to FOG. Overground walking has been observed to correlate with imagined walking times in PD for those with FOG and without (Peterson et al., 2014). Both these aforementioned observations have been under MRI scanning and not in a gait re-education program or with external cueing.

Can Motor Imagery Alter the Attentional Strategy Employed When Moving Through Doorways?

This is not yet known and requires the greatest research. Moran and O'Shea (Moran and O'Shea, 2020) discuss how MI can make the neural systems more efficient, possibly by changing how motor information is processed in the working memory, but admit that not enough is known about how the process works. The dorsolateral prefrontal cortex is active during MI which results in better working memory. Lewis and Shine (2016) also discuss that "global neuronal efficiency" should help alleviate FOG but that the underlying mechanisms to ensure such efficiency are not yet known. None of these studies answer if MI can improve gait learning in people with PD.

Cohen et al. (2011) established that people with PD and FOG demonstrate a mismatch between the motor execution and their motor imagery when approaching and walking through doorways. People with PD and FOG in this experiment slowed

more than people with PD but without FOG as they approached a doorway. However, when they imagined the same activity, they did not slow more than their experimental counterparts. They did not demonstrate a visual mismatch or an altered body schema when judging a door width. The suggested causes were an impairment in motor execution or a poor understanding of their gait impairment. If it is an impairment in motor execution, it suggests that training to improve APAs accessed when walking toward and through a doorway might improve the speed. It is not known if MI can improve APAs for people with FOG and further research is required in this subject area.

What Would Be the Best Approach of Motor Imagery in Rehabilitation Therapy?

In MI, older individuals show a stronger response to auditory cues (Hovington and Brouwer, 2010). Cueing for MI should support the kinesthetic or "visual" nature of the imagined scenario and can be in the first or third person (Abraham et al., 2018). External auditory cueing can be combined with kinesthetic MI to produce tailored rehabilitation programs for individuals (Cohen et al., 2011).

Any MI practice requires that the patient be assessed for a preference in their MI learning style. This can be assessed using a motor imagery questionnaire (Saimpont et al., 2013; Da Nascimento et al., 2019). Therapists need to be consistent with the practice and cueing style (Piccoli et al., 2018).

What Would Be the Duration, Frequency and Dose of a Suitable Motor Imagery Intervention?

A review of MI show incongruous durations and intervention times for MI studies in older populations. The findings show results in older research participants are possible in under a month with doses of less than 20 min long, 3 to 4 times per week (Schuster et al., 2011). The authors of this paper concede that a longer intervention duration may be required for individuals with FOG, as motor learning of all types worsens with PD (Olson et al., 2019).

One of the benefits of MI is the potential for the passive nature of the practice. It can safely be performed in sitting with no danger to the subject. This may allow the possibility of developing an online, patient specific therapeutic intervention. This might lower related costs to both therapist and patient (Heremans et al., 2012). During the Covid-19 pandemic, telemedicine has become an all-important way for patients to access therapy. Safety is always a consideration and limitation in what can be executed virtually (Middleton et al., 2020). It is not known if MI could be supervised virtually. This intervention is always an adjunct to standard physical therapies (Saimpont et al., 2013).

DISCUSSION AND CONCLUSION

Subjects with FOG experience a worsened QoL and risk falls through the sudden interruption of gait. Although much has been discovered about the underlying causes, no treatment to date has been completely successful in eliminating FOG. FOG often occurs at specific moments or places, such as environmental boundaries e.g., a person with FOG may get "stuck" at the threshold of a doorway. FOG rehabilitation exercises show benefits, but those benefits are not retained without ongoing intervention. What if the person with FOG could independently continue those exercises in absolute safety inside their own minds, thus continuing to benefit from improved mobility without a therapist present–MI?

Because studies of MI in FOG are not homologous in design, it is difficult to compare studies to have a clear understanding if MI in PD is an effective treatment to reduce FOG and how best to apply it. The drawbacks are that MI may cause fatigue and that it has been difficult to assess in PD subjects. For the therapist some treatment factors are unknown, such as an effective dose. An individual may not be able to fully benefit due to cognitive decline. It also requires practice on the part of the therapist to teach the technique consistently. The proposed benefits are that MI of an action uses many of the same neural pathways as the physical movement, has the potential to produce motor neuron plasticity, is an efficient way to learn and has shown substantial treatment benefits in other populations. It should not be disregarded without complete study and a larger body of comparable and well controlled research should be carried out to establish if MI can mitigate FOG at environmental boundaries.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DH had the idea for the article with support from MB and drafted the article with inputs from HW and MB. DH and HW performed the literature search. All authors critically revised the work.

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REVIEW
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Troubleshooting Gait Disturbances in Parkinson's Disease With Deep Brain Stimulation

Nicoló G. Pozzi[1], Chiara Palmisano[1], Martin M. Reich[1], Philip Capetian[1], Claudio Pacchetti[2], Jens Volkmann[1] and Ioannis U. Isaias[1,3]*

[1] Department of Neurology, University Hospital of Würzburg and Julius Maximilian University of Würzburg, Würzburg, Germany, [2] Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Pavia, Italy, [3] Parkinson Institute Milan, ASST Gaetano Pini-CTO, Milan, Italy

Deep brain stimulation (DBS) of the subthalamic nucleus or the globus pallidus is an established treatment for Parkinson's disease (PD) that yields a marked and lasting improvement of motor symptoms. Yet, DBS benefit on gait disturbances in PD is still debated and can be a source of dissatisfaction and poor quality of life. Gait disturbances in PD encompass a variety of clinical manifestations and rely on different pathophysiological bases. While gait disturbances arising years after DBS surgery can be related to disease progression, early impairment of gait may be secondary to treatable causes and benefits from DBS reprogramming. In this review, we tackle the issue of gait disturbances in PD patients with DBS by discussing their neurophysiological basis, providing a detailed clinical characterization, and proposing a pragmatic programming approach to support their management.

Keywords: Parkinson's disease, freezing of gait (FOG), deep brain stimulation (DBS), subthalamic nucleus (STN), globus pallidus pars interna (GPi), pedunculopontine nucleus (PPN)

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****Correspondence:***
Nicoló G. Pozzi
Pozzi_N2@ukw.de

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INTRODUCTION

In Parkinson's disease (PD) a progressive dopaminergic neuronal loss alters the functioning of the cortico-striatal-thalamic network and determines an increasing motor impairment (Albin et al., 1989; Isaias et al., 2006, 2011, 2012; Litvak et al., 2011; de Hemptinne et al., 2013; Cagnan et al., 2015). Along with disease progression, PD leads to increasing disability with worsening of quality of life (Rascol et al., 2011). One of the main determinants of poor quality of life in PD is gait impairment, mainly because it correlates with mobility reduction, falls and hospitalization (Muslimović et al., 2008).

The term gait impairment is unspecific and encompasses a variety of gait disturbances that range from shuffling gait to walking difficulties due to dyskinesias. PD can also present peculiar gait disturbances, such as freezing of gait (FOG) (Nutt et al., 2011a). This clinical variability reflects a complex and diverse pathophysiology that challenges an appropriate treatment, which remains limited at best (Muslimović et al., 2008). Dopaminergic replacement therapy may indeed yield only a partial benefit and eventually deteriorate some aspects of gait and balance in PD (Peterson and Horak, 2016), possibly because of the unselective impact of levodopa on the locomotor network (Curtze et al., 2015; Palmisano et al., 2020a).

Deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) or the globus pallidus pars interna (GPi-DBS) is an established treatment for PD that can provide a marked improvement of

quality of life in PD patients with motor fluctuations (The Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001; Deuschl et al., 2006; Follett et al., 2010; Schuepbach et al., 2013). Comparative studies showed a similar benefit for the two targets (Follett et al., 2010; Tagliati, 2012; Weaver et al., 2012; Williams et al., 2014; Ramirez-Zamora and Ostrem, 2018) with motor improvement lasting for more than 30 years for STN-DBS (Merola et al., 2011) and over 10 years for GPi-DBS (Mansouri et al., 2018). Despite this sustained improvement of motor symptoms, the effect of DBS on gait impairment remains debated.

Converging evidence showed a positive effect for STN-DBS and GPi-DBS on gait in the first year after surgery (Bakker et al., 2004), while long-term follow up studies reported a progressive worsening of gait for both targets (Pötter-Nerger and Volkmann, 2013). A meta-regression analysis of 12 studies (nine with STN-DBS and three with GPi-DBS) on postural instability and gait disorder (PIGD) in PD showed that PIGD worsens to the preoperative state already 2 years after STN-DBS in meds-on condition (i.e., with medication) (St George et al., 2010). In line with these data, up to 42% of PD patients with STN-DBS report a subjective worsening of gait performance 6 months after surgery, despite general motor improvement (van Nuenen et al., 2008).

While chronic progressive loss of efficacy might be due to disease progression and to concomitant worsening of postural control (Limousin and Foltynie, 2019), an early gait deterioration after DBS is likely related to suboptimal stimulation (Farris and Giroux, 2013; Pötter-Nerger and Volkmann, 2013; Limousin and Foltynie, 2019). In line with this hypothesis, a case series review of 50 PD patients with PIGD and unsatisfactory STN-DBS outcomes showed that suboptimal stimulation was responsible for up to 52% of cases and reprogramming of DBS parameters improved the clinical outcome in 75% of cases (Farris and Giroux, 2013). Still, DBS programming is an iterative and poorly standardized process that requires expertise and careful trial-and-error adjustments (Kühn and Volkmann, 2017).

In this review, we will tackle this issue and provide a pragmatic troubleshooting programming approach to manage early gait disturbances in PD patients with DBS. We will first describe the pathophysiological mechanism of gait impairment in PD, then provide a clinical characterization of gait disturbances and finally discuss the possible stimulation alternatives.

A comprehensive discussion of the long-term effects of DBS on PIGD is beyond the scope of this review and can be found elsewhere (Fasano et al., 2015; Limousin and Foltynie, 2019). Likewise, gait disturbances arising directly after DBS surgery are usually related to surgical causes and have already been reviewed elsewhere (Adams et al., 2011; Fleury et al., 2016; Sketchler and Shahed, 2019).

THE HUMAN SUPRASPINAL LOCOMOTOR NETWORK

In recent years, technological advances allowed to obtain important information about the physiology and pathophysiology of human gait, revealing the complex neural architecture of the locomotor network (Takakusaki et al., 2004; Takakusaki, 2017; Pozzi et al., 2019). This network comprises the primary motor cortex, the supplementary motor area (SMA), the basal ganglia, the thalamus, the mesencephalic locomotor region (MLR) with the pedunculopontine nucleus (PPN) and the cuneiform nucleus (CN), the cerebellum and the spinal network of central pattern generator (CPGs) (la Fougère et al., 2010; Tard et al., 2015; Snijders et al., 2016; Takakusaki, 2017).

The rhythmic activity of CPGs generates stepping movements, which are initiated and modulated by the supraspinal locomotor network (for review Nutt et al., 2011b).

The MLR is the core of locomotor adaptation as it is essential for the integration of sensorimotor and emotional stimuli that modifies the patterned activity of CPGs (Collomb-Clerc and Welter, 2015; Takakusaki, 2017). The main anatomical structures of the MLR are the CN and the PPN, which together regulate posture, muscular tone, and locomotion initiation (Takakusaki, 2008, 2017). A detailed discussion of the brainstem control of posture and gait is reported in Takakusaki (2008, 2017). In brief, the glutamatergic CN neurons exert a prokinetic effect possibly starting locomotion by releasing the CPGs, while the GABAergic PPN neurons inhibit the activity of the SNr that suppresses locomotor activities (Takakusaki, 2008, 2017). The PPN is innervated from the basal ganglia (in particular, the STN and the GPi), the thalamus (parafascicular and center-median nucleus) and the motor and premotor cortices (e.g., supplementary motor area, SMA) (Collomb-Clerc and Welter, 2015; Takakusaki, 2017), thus representing the cornerstone of MLR and key for sensorimotor integration (Mena-Segovia and Bolam, 2017). This role for the PNN in locomotor control has recently been supported by a study in five PD patients with GPi- and PPN-DBS that showed an increase in PPN neuronal activity during walking as compared to standing (Molina et al., 2020).

Within the basal ganglia, the striatum and its dopaminergic synapses are essential for motor learning and motor automaticity. Accordingly, the dopaminergic loss occurring in PD affects gait performances, especially when flexibility and adaptability in the gait pattern are required (Nutt et al., 1993, 2011b; Amboni et al., 2013; Fasano and Bloem, 2013; Santens, 2018).

The STN is ideally placed to regulate locomotion being directly connected with the SMA and projecting to the MLR structures (Nambu et al., 2002; Miocinovic et al., 2018). Accordingly, recent neurophysiological studies proved its role in locomotion control by assessing STN local field potentials (LFPs) in PD patients with advanced DBS devices (Rouse et al., 2011; Stanslaski et al., 2012). Time-frequency analysis of STN LFPs is altered in PD showing an *excessive* synchronization in the beta frequency band (13–35 Hz) and prolonged (>500 ms) beta-bursts (Oswal et al., 2013; Tinkhauser et al., 2017, 2018; Wang et al., 2018) in PD patients in meds-off (i.e., without medication) at rest. The neural activity of the STN during walking was mainly assessed as changes in beta synchronization as expressed by spectral power modulation. Fischer et al. (2018) showed a left-right alternating suppression of high-beta (20–30 Hz) spectral power in STN-LFPs of PD patients performing a visually guided stepping task while sitting and freely walking. Hell et al. (2018) reported suppression in high-beta power and bilateral oscillatory connectivity as well as a reduction in amplitude and duration of high-beta burst

during gait as compared to rest. However, these findings are not consistent with the results of other studies that did not find STN beta suppression in freely moving PD patients (Quinn et al., 2015; Arnulfo et al., 2018). Quinn et al. (2015) reported similar STN beta power during lying, sitting, standing, and forward walking in 14 PD patients. We also found no difference in beta power during walking compared to sitting and standing in seven PD patients with STN-DBS (Arnulfo et al., 2018), but reported an interhemispheric decoupling (Arnulfo et al., 2018) and a frequency-shift of STN beta oscillations during gait (Canessa et al., 2020).

Less evidence is available for the GPi. Recent works suggested a role for this nucleus in locomotion inhibition (Aristieta et al., 2021). One study in patients with isolated dystonia (without gait abnormalities) and GPi-DBS studied LFPs during treadmill-gait. The authors showed a selective suppression of beta power during gait as compared to rest (Singh et al., 2011). In PD, instead, no changes of GPi beta power were found in five patients during walking as compared to standing (Molina et al., 2020), so that other frequency bands might be related to gait in GPi neurons.

The cortical contribution to gait control has also received great interest recently. Molecular imaging studies unveiled a diffuse cortical activation during gait (Jacobs and Horak, 2007; Yogev-Seligmann et al., 2008; Collomb-Clerc and Welter, 2015; Tard et al., 2015; Peterson and Horak, 2016). In particular, the primary motor cortex is relevant for gait adaptation that requires precise forelimb positioning to avoid obstacles or to change direction (Drew et al., 2002; Beloozerova et al., 2003; Dunin-Barkowski et al., 2006). The SMA is involved in balance control during locomotion and plays a role in the timing of the anticipatory postural adjustments (APA) during gait initiation (Richard et al., 2017). The posterior parietal cortex is necessary to plan and execute gait pattern adaptations by modifying the internal model of body representation during locomotion (McVea and Pearson, 2009). Reactive and predictive sensorimotor adjustments during gait are assumed to be ruled by internal models located in the cerebellum (Blakemore and Sirigu, 2003; Morton and Bastian, 2016), which is intimately connected with the temporoparietal cortex and the frontal cortices (Collomb-Clerc and Welter, 2015; Santens, 2018).

Studies on motor cortex activity during gait showed suppression of spectral power in alpha and beta frequency bands as well as changes in cortical connectivity during gait (Wang and Choi, 2020). In particular, alpha and beta band power suppression along with theta power increase in the sensorimotor cortex were documented in demanding walking tasks (e.g., obstacle avoidance) and likely reflect a greater cortical planning (Bulea et al., 2015; Nordin et al., 2019). In PD, one study showed increased interhemispheric synchronization across many frequency bands during walking as compared to healthy controls, thus suggesting a more prominent cortical involvement in locomotor control in PD patients (Miron-Shahar et al., 2019).

Finally, some studies have focused on specific gait alterations, such as freezing of gait (FOG), a sudden and transient disruption of the gait pattern (Nieuwboer and Giladi, 2013). Tard et al. (2015) performed a [18F]-fluorodeoxyglucose brain positron-emission tomography in PD patients showing FOG and documented a cortical hypometabolism as well as a dysregulation of the GPi, STN, and the MLR. At cortical level, one study showed an increase in theta power during FOG (Shine et al., 2014). Studies on STN LFPs showed instead higher beta frequency amplitude (Toledo et al., 2014; Hell et al., 2018) and an increase in alpha frequency entropy (Syrkin-Nikolau et al., 2017) in PD patients with FOG. Beta burst duration was found to be prolonged in PD patients with FOG (Anidi et al., 2018). However, being FOG an episodic phenomenon, it is crucial to assess electrophysiological alterations during actual freezing episodes. We recorded STN- and cortical LFPs in five PD patients with STN-DBS and FOG and found no difference in beta power, beta burst duration or interhemispheric STN coupling between effective walking and freezing episodes, but showed a low-frequency cortical-STN decoupling at the transition from normal walking into gait freezing, which resolved with the recovery of an effective gait pattern. Of note, these changes were found only on the side with less dopaminergic innervation, thus supporting a role for striatal dopamine in FOG (Pozzi et al., 2019).

Taken together these results suggest that altered neuronal oscillations in the supraspinal locomotor network are associated with the occurrence of gait disturbances in PD. Neural oscillations reflect fluctuations of local neuronal ensembles and their synchronization provide a mean for dynamic brain coordination (Buzsáki and Wang, 2012). Alterations in neuronal oscillation dynamics (i.e., timely synchronization and desynchronization) in the locomotor network may thus hamper locomotor control and result in gait impairments. This knowledge provides a rationale for treating gait disorders with neuromodulation tools, such as DBS, that allows retuning the activity of neural ensembles, even if distant from the implantation site, by means of modulation of neural networks dynamics.

CLINICAL ASSESSMENT OF GAIT AND GAIT DISTURBANCES IN PARKINSON'S DISEASE

The complex pathophysiology of gait disturbances in PD translates into great clinical variability that can vary from shuffle bradykinetic gait to dyskinetic pseudo-ataxic gait and include peculiar gait alterations, like FOG (Nieuwboer and Giladi, 2013) or reckless gait (Fasano and Bloem, 2013).

To treat gait disturbances in PD with DBS is important to recognize their specific clinical features (Giladi et al., 2002, 2013). To this end, a careful clinical history is essential (Fasano and Bloem, 2013; Nonnekes et al., 2019b), first to distinguish between *continuous* and *episodic* gait disturbances, as well as their relation with dopaminergic medications intake (Giladi et al., 2013). The use of instrumental aids (e.g., orthosis) or any other compensatory strategy should always be evaluated and can be particularly informative in patients with FOG (Fasano and Bloem, 2013). The risk of falls should also always be investigated and can easily be done by screening for a previous fall, which is a reliable predictor of new falls (Grimbergen et al., 2004). Further, the implanted nucleus, time to surgery and the

active stimulation paradigm, as well as the permitted paradigms of stimulation by the implantable pulse generator (IPG), are essentials. Finally, in every patient with PD and STN-DBS with gait disturbances the lead location should critically be reviewed as even small misplacement might greatly impact the clinical outcome (Nickl et al., 2019).

The evaluation of gait cannot be separated from a complete neurological examination. It starts by assessing standing and postural abnormalities (broad base width, camptocormia, etc.) as well as the presence of dyskinesia or dystonia, which may differ in laying of standing position. Since DBS may also induce gait impairment, the clinical evaluation must be performed at least in stim-on and stim-off condition (i.e., with and without stimulation), although there is no consensus on the delay of the examination. Whenever possible, a prolonged suspension (up to 72 h) is recommended (Reich et al., 2016). Furthermore, we encourage to perform the clinical assessment in both meds-off and meds-on condition, especially in those PD patients still presenting motor fluctuations.

For clinical purposes, it may be useful to divide gait into four conditions: (1) gait initiation, (2) unperturbed steady-state walking, (3) turning, and (4) gait adaptation (Smulders et al., 2016; **Figure 1**). All these gait conditions can be described by specific biomechanical parameters (for review see Morris et al., 2001; Hof et al., 2005; Perry et al., 2010).

Gait initiation is the transition from quiet stance to steady-state walking. It is a highly challenging task for the balance control system and is of particular interest in the study of neural control of upright posture maintenance during whole-body movement (Delval et al., 2014). Gait initiation is characterized by APA, patterned muscular synergies (Farinelli et al., 2020) aiming to destabilize the antigravity postural set via misalignment between the center of pressure (CoP) and the center of mass (CoM) to generate a gravitational moment favoring CoM forward acceleration (Crenna and Frigo, 1991). The associated motor program seems to be centrally mediated (Palmisano et al., 2020b) with direct involvement of striatal dopamine (Petersen et al., 2012; Palmisano et al., 2020a). However, the contribution of the basal ganglia in gait initiation remains poorly known. This motor task also presents some methodological difficulties to be properly investigated in PD patients (Palmisano et al., 2020a,b). Subjects with PD usually have hypometric APA, with less weight shift than would be required to make an effective step (Burleigh-Jacobs et al., 1997; Jacobs et al., 2009). This translates clinically in a slower and shorter length of the first step as compared to healthy subjects (Rocchi et al., 2006; Jacobs et al., 2009), so that coordination of the movement pattern may not vary in PD (Rosin et al., 1997). The failure of APA is often associated with *start hesitation* (Giladi et al., 1992; Mancini et al., 2009), whereas multiple unsuccessful APA can occur with a subtype of FOG referred to as *trembling in place* (or *knee-trembling*) (Jacobs et al., 2009). Another pathological gait initiation pattern in PD, often associated with FOG, is *festination*, which is a rapid and progressive shortening of step length, accompanied by a compensatory increase in cadence (Nonnekes et al., 2019a).

Unperturbed steady-state walking refers to linear walking at preferred and constant speed on a flat surface. Even in the absence of biomechanical analysis, important spatiotemporal features of gait can be clinically evaluated, such as gait speed, cadence, steps variability, arm swing and limbs coordination. The step-length and -height for both feet separately can be also assessed. Unmedicated PD patients show bradykinetic gait with reduced step height and length (causing the typical *shuffling* gait), narrow base width, small step length variability with normal or increase cadence (Morris et al., 2001). PD patients can also show a progressive reduction of step length (i.e., sequence effect) as an expression of motor bradykinesia (Nutt et al., 2011a). The base width during walking is usually narrow in PD (Fasano and Bloem, 2013), while the step length variability may vary according to symptoms lateralization. This is usually more evident in the upper body, where bradykinesia is expressed by reduced arm swing and decreased range of motion of the trunk (Sterling et al., 2015). In case of great lateralization of the motor symptoms, a patient may present great stride-to-stride variability, an asymmetric reduction of arm swing, and poor range of motion of the trunk. Large gait variability is a dangerous alteration being associated with postural instability (Hausdorff et al., 1998; Hausdorff, 2005), which can lead to falls (Weiss et al., 2014). The presence of dyskinesia or dystonia might also alter the gait pattern with jerky movements of the limbs that may impair balance during walking. In this case, step length and gait velocity may be increased to reduce instability (Fasano and Bloem, 2013). The development of dyskinesia or dystonia during walking may be due to medication adjustments (e.g., levodopa-induced dyskinesia or meds-off dystonia) or be secondary to DBS itself (Krack et al., 1999; Baizabal-Carvallo and Jankovic, 2016).

Turning is one of the most frequent motor behaviors, taking place up to 100 times per hour (Mancini et al., 2016). Turing implies a modification of the gait pattern with asymmetrical steps and requires a dynamic adaptation of balance through coordinated movements of the trunk and limbs (Smulders et al., 2016). By asking the patient to turn it is possible to assess the mobility of the head, upper and lower part of the body, and the number of steps required. In PD, the physiological sequential movement of eyes-head-trunk-feet is lost in favor of an "en bloc" turning. This is characterized by a simultaneous onset of eyes, head, trunk, and leg movement (Crenna et al., 2007), which is slow and requires multiple steps (Smulders et al., 2016). Turning repetitively can elicit FOG (Reich et al., 2014), which appears most frequently at the end of a turn and affects the inner leg of the turn cycle (Spildooren et al., 2018).

Gait adaptation reflects the ability to modify the gait pattern and navigate the environment. While steady-state walking is a highly automatized process that requires minimal attention in healthy subjects (Patel et al., 2014), gait adaptation involves the activation of multiple brain areas (Hinton et al., 2019). Biomechanical studies have shown that PD patients are unstable and need more time to overcome an obstacle and hit it multiple times (Smulders et al., 2016). Gait adaptation can be particularly difficult in subjects with PD due to difficulties resisting external interference and task-switching (Amboni et al., 2013). This condition is known as "higher-level gait disorder" and presents typically with short cadence, short steps with marked step length variability, and FOG with poor response to walking aids

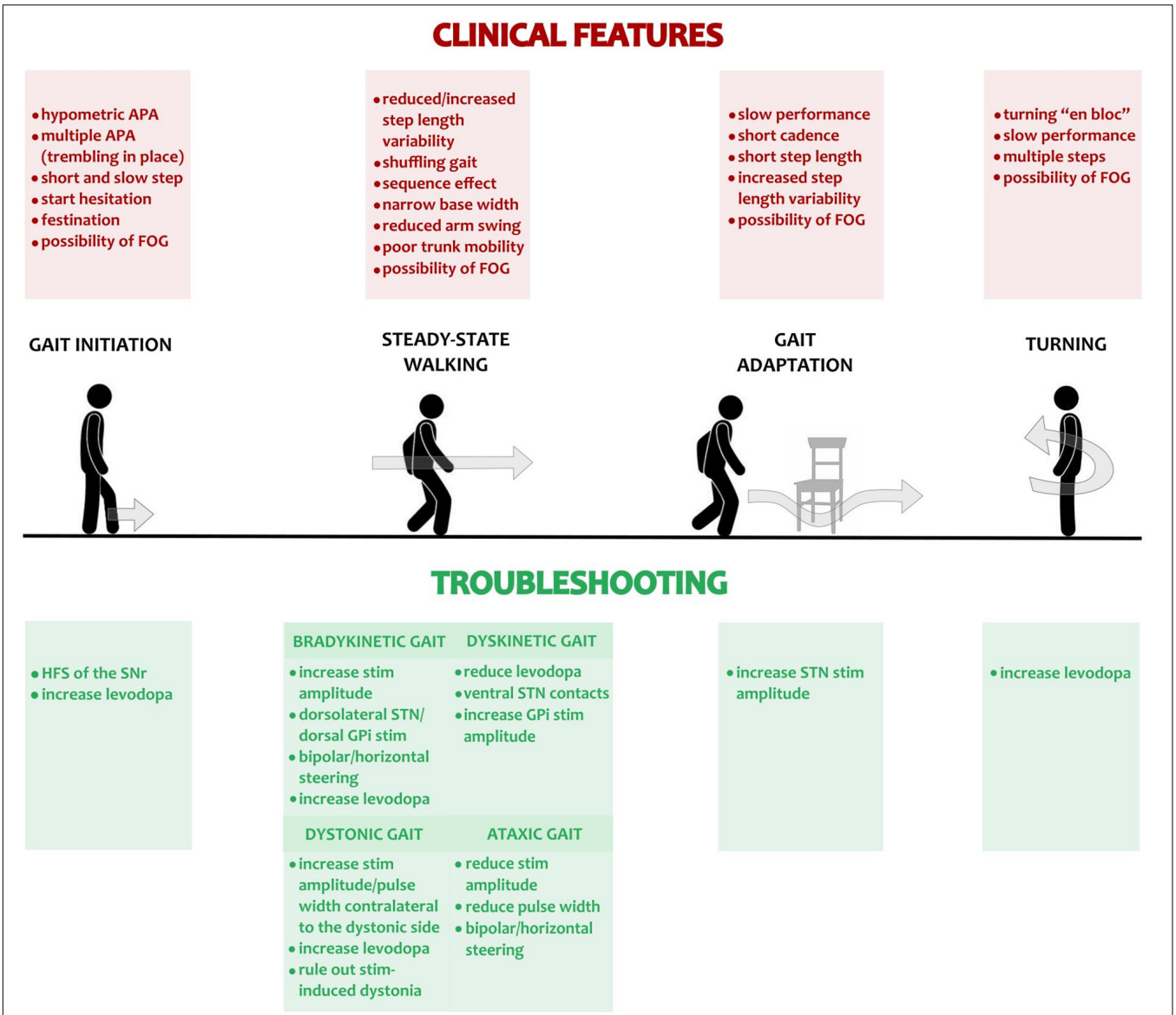

FIGURE 1 | Gait disturbances in PD and possible troubleshooting with DBS. The main gait conditions (i.e., gait initiation, steady-state walking, gait adaptation and turning) are displayed. The top red panels list the most frequent pathological abnormalities occurring in PD patients in meds-off condition and assessed clinically or with a kinematic gait analysis. The green panels at the bottom list the adjustment in DBS programming and medications for troubleshooting the pathological changes of the different gait components. For steady-state, unperturbed linear walking, we addressed separately the possible adjustments in case of bradykinetic, dystonic, dyskinetic, or ataxic gait. APA, Anticipatory postural adjustments; FOG, freezing of gait; HSF, high frequency stimulation (i.e., >130 Hz); STN, subthalamic nucleus; GPi, Globus pallidus pars interna.

(Nutt et al., 1993). Clinically, it may not be evident, but can be unmasked by obstacle crossing or dual-task walking. Patients should therefore be asked to walk through narrow passages (e.g., doors) or in a crowded space (Smulders et al., 2016; Pozzi et al., 2019). Another approach is to ask the patient to perform a cognitive task (e.g., backward counting) or a difficult motor task (e.g., carrying a tray) while walking. Under increased attentional demands, gait may become highly irregular or stop (i.e., "stops walking while talking" phenomenon) (Bloem et al., 2000; Hyndman and Ashburn, 2004). Alternatively, patients may neglect the onset of gait difficulties and focus on the cognitive task, thereby exhibiting reckless gait, a phenomenon more frequently observed in progressive supranuclear palsy (Ebersbach et al., 2013; Raccagni et al., 2019).

Freezing of Gait is an episodic and sudden interruption of the gait pattern with patients feeling the feet "glued to the ground" and the trunk is usually leant forward (Nieuwboer and Giladi, 2013). It occurs predominantly when the on-going locomotor pattern is interrupted (e.g., termination or initiation of gait), modulated (e.g., turning, obstacles navigation), or interfered

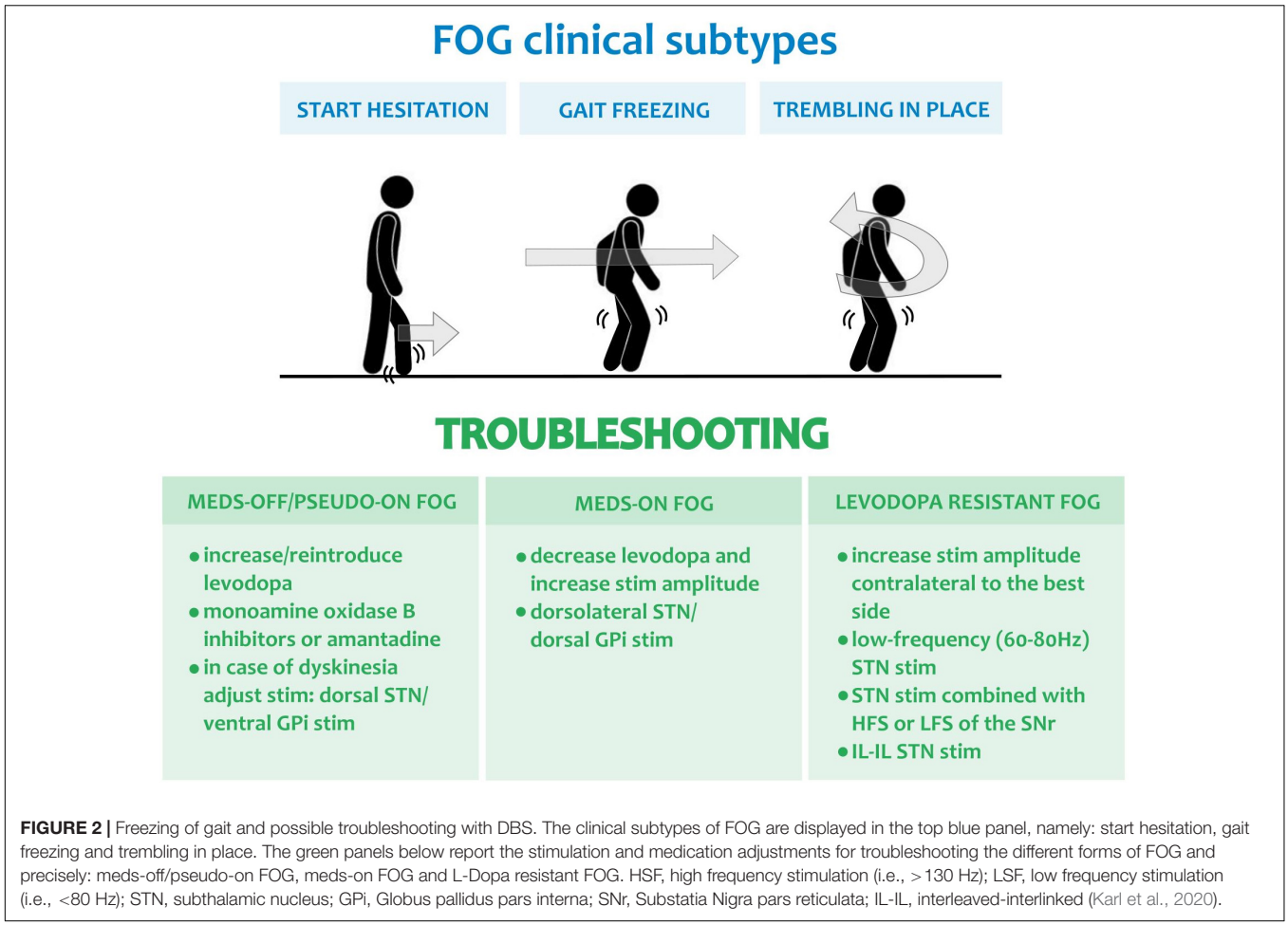

FIGURE 2 | Freezing of gait and possible troubleshooting with DBS. The clinical subtypes of FOG are displayed in the top blue panel, namely: start hesitation, gait freezing and trembling in place. The green panels below report the stimulation and medication adjustments for troubleshooting the different forms of FOG and precisely: meds-off/pseudo-on FOG, meds-on FOG and L-Dopa resistant FOG. HSF, high frequency stimulation (i.e., >130 Hz); LSF, low frequency stimulation (i.e., <80 Hz); STN, subthalamic nucleus; GPi, Globus pallidus pars interna; SNr, Substatia Nigra pars reticulata; IL-IL, interleaved-interlinked (Karl et al., 2020).

(e.g., dual-task walking), particularly under time constraints (Bekkers et al., 2018). Focused attention and external stimuli (cues) may instead facilitate the overcoming of a FOG episode (Nieuwboer and Giladi, 2013).

With disease progression, the majority of PD patients develop FOG. A recent meta-analysis of 9,072 PD patients showed a weighted prevalence for FOG of 50.6% with a marked increase with years of disease (37.9% for $\leq$ 5 years vs. 64.6% for $\geq$ 9 years from diagnosis of PD) (Zhang et al., 2021). Patients predisposed to develop FOG usually show an altered locomotor pattern with increased step length variability and poor coordination (Nieuwboer and Giladi, 2013). FOG is associated with a high risk of falling and hospitalization (Bloem et al., 2004; Okuma et al., 2018). Falls likely occur because of weight-shifting impairments with inadequate scaling and timing of postural responses (Bekkers et al., 2018). As such, it represents a major determinant of poor quality of life in subjects with PD (Moore et al., 2007; Perez-Lloret et al., 2014). The pathophysiological mechanism leading to FOG abrupt onset remains largely unknown, but it likely involves transient derangements of the supraspinal locomotor network (Weiss et al., 2020).

FOG can be classified according to the medication state into meds-off FOG, meds-on FOG (i.e., induced by dopaminergic medication) and levodopa-resistant FOG, which persist after a supratherapeutic dose of levodopa (Nieuwboer and Giladi, 2013). Pseudo-on FOG is seen during seemingly optimal meds-on state, but which nevertheless improves with stronger dopaminergic stimulation (Espay et al., 2012).

FOG can be accompanied by additional though distinctive phenomena such as *start hesitation*, which is the inability in generating effective stepping at the beginning of walking, or *trembling in place*, which is shaking of the knees with the forefoot attached to the floor and the heel in the air (Nieuwboer and Giladi, 2013). **Figure 2** shows the different clinical subtypes of FOG.

Festination represents a progressive increase in step cadence and gait speed with an excessive forward bending of the trunk that usually occurs during walking when approaching a destination. The pathophysiology of *gait festination* remains largely unclear, and it might be related to a defective production or processing of temporal cues at basal ganglia or cortical level (pre-SMA), respectively (Buhusi and Meck, 2005; Morris et al., 2008). Interestingly, a similar pathophysiological mechanism is shared by oral festination (Moreau et al., 2007; Ricciardi et al., 2016). A recent study advanced the hypothesis of a different subtype of festination in PD that derives from a postural abnormality

(Nonnekes et al., 2019a). In this case, festination would emerge as a compensatory attempt to avoid falling due to the forward-leaning of the trunk and inappropriately small balance-correcting steps (Nonnekes et al., 2019a).

Functional gait disorders are characterized by symptoms not compatible with organically determined gait patterns and an inconsistent presentation with susceptibility to distraction (Baik and Lang, 2007; Araujo et al., 2019; Nonnekes et al., 2020). Functional movement disorders have been described also in subjects with PD following DBS (Breen et al., 2018; Maciel et al., 2021). A detailed discussion of functional movement disorders has been reported elsewhere (Edwards and Bhatia, 2012).

TROUBLESHOOTING GAIT DISTURBANCES IN PARKINSON'S DISEASE PATIENTS WITH DEEP BRAIN STIMULATION

In all PD patients with DBS that develop early gait disturbances reprogramming should be attempted as it can lead to marked clinical improvement. DBS reprogramming is a complex procedure that requires customization of stimulation delivery, based on the symptomatology, anatomy, pathophysiology, and pharmacological condition of each patient (Volkmann et al., 2006; Picillo et al., 2016; Hell et al., 2019; Koeglsperger et al., 2019). For these reasons, there is no fixed algorithm that could work for every patient. Still, some basic concepts may facilitate the reprogramming process that, for sake of clarity, can be broken down into (1) changes of the stimulation parameters (i.e., amplitude, frequency and pulse width), (2) changes of the stimulation location (e.g., by modifying the active contacts or steering the stimulation), (3) changes of the paradigm of stimulation (e.g., interleaving stimulation) (Dayal et al., 2017). Of note, the optimization of pharmacological therapy is also essential to achieve a lasting improvement. In this regard, we suggest performing a clinical evaluation in meds-on condition after reprogramming, which should be performed in meds-off condition whenever possible. We also encourage to wait up to 10 min to assess the efficacy of any stimulation change as the effects may not be instantaneous, especially if performed in meds-on. Finally, we strongly suggest including exercise and physical therapy in the treatment of PD patients with gait disturbances (Mak et al., 2017; Gilat et al., 2021).

Gait Initiation Problems

Studies on the effects of DBS on gait initiation are few and with inconsistent results. Crenna et al. (2006) showed an improvement of both APA and the execution of the first step with unilateral and bilateral high frequency stimulation (HFS, i.e., > 130 Hz) of the STN, whereas Rocchi et al. (2012) reported an impairment of APA with bilateral STN- or GPi-DBS. The interesting observation that unilateral stimulation may improve bilateral symptoms led to the hypothesis of a "dominant" STN (Castrioto et al., 2011), which was documented in up to 50% of the patients with PD in one study (Rizzone et al., 2017).

STN-DBS and GPi-DBS did not improve compensatory stepping at gait initiation as compared to dopaminergic treatment (George et al., 2015). A selective improvement of gait disturbances at gait initiation was instead achieved with HFS of the SNr, which can be reached in some subjects with STN-DBS by selecting the most ventral contacts (Chastan et al., 2009; Scholten et al., 2017). This approach is still under investigation, but it might be used as a rescue strategy. Increasing dopaminergic medications can be also useful (Smulders et al., 2016) as levodopa showed to improve some APA (particularly the imbalance phase) and the stepping phases (Curtze et al., 2015; Palmisano et al., 2020a).

Troubleshooting

A summary is shown in **Figure 1**.

- Attempt HFS of the SNr (**Figure 1**; Chastan et al., 2009; Scholten et al., 2017).
- Adjust dopaminergic medications (e.g., increase levodopa) (Smulders et al., 2016; **Figure 1**).

Unperturbed Steady-State Walking Problems

A bradykinetic gait may arise after DBS due to an excessive reduction of dopaminergic medications (Castrioto et al., 2014). The reduction of dopaminergic medication may also be responsible for the development of dystonic contraction during walking (Krack et al., 1999; Castrioto et al., 2013). On the other hand, the presence of levodopa-induced dyskinesia might alter profoundly the gait pattern with jerky movements of the limbs that impair balance and walking (Krack et al., 1999; Castrioto et al., 2013). This condition has recently been described as lower body dyskinesias, which can be due to the synergic effect of dopaminergic medications and STN-DBS (Cossu and Pau, 2017).

STN-DBS may also directly induce a bradykinetic worsening of gait through an inadvertent stimulation to the pallido-thalamic tract that runs in the zona incerta region located dorsally and medially to the STN dorsal Zona incerta (dZi) (Castrioto et al., 2013; Fleury et al., 2016). This side effect can also affect GPi-DBS for current spread in the *ansa lenticularis* (Castrioto et al., 2013; Baizabal-Carvallo and Jankovic, 2016). The inadvertent stimulation of pallidal projections to the PPN may be a cause lateralized bradykinetic gait too (Baizabal-Carvallo and Jankovic, 2016; Cossu and Pau, 2017). In rare cases, dystonic gait might be secondary to HFS within the STN or to an inadvertent chronic overstimulation with current spread to the corticospinal tract (Castrioto et al., 2013; Baizabal-Carvallo and Jankovic, 2016). More often, STN-DBS directly induces dyskinetic gait, which may develop with delay (up to several hours) after stimulation adjustments (Krack et al., 1999; Baizabal-Carvallo and Jankovic, 2016). Balance impairment can be instead induced by inadvertent stimulation of the red nucleus or cerebellar fibers (Felice et al., 1990). This side-effect is more commonly seen in patients with essential tremor (ET) and thalamic DBS (Reich et al., 2016) but can be present also in PD (Felice et al., 1990). Clinically, it

manifests as an ataxic gait, with wide base width, high stride-to-stride and gait speed variability.

Troubleshooting

A summary of troubleshooting is shown in **Figure 1**.

- Bradykinetic gait
  - Increase stimulation amplitude (Volkmann et al., 2006; Koeglsperger et al., 2019). In case of lateralized bradykinetic gait, the brain side contralateral to the worst hemibody should be addressed first (**Figure 1**).
  - Try contacts at the dorsolateral margin of the STN (**Figure 1**; Herzog et al., 2004; Nickl et al., 2019). In case of GPi-DBS, a more dorsal stimulation is preferable (**Figure 1**; Bejjani et al., 1997; Rabin and Kumar, 2015; Baizabal-Carvallo and Jankovic, 2016; Au et al., 2020).
  - In case of suspected inadvertent stimulation (e.g., dZi) use a bipolar configuration or the horizontal steering of the stimulation, if supported by segmented leads (**Figure 1**; Steigerwald et al., 2019). Still, an increase of the stimulation amplitude might be required to maintain sufficient control of motor fluctuations. In this case the use of an *anodic block* may be attempted (**Figure 1**; Valente et al., 2010).
  - Adjust dopaminergic medications (e.g., increase levodopa; **Figure 1**) (Smulders et al., 2016).
- Dystonic gait
  - Increase the stimulation amplitude or pulse-width contralateral to the dystonic side (**Figure 1**; Volkmann et al., 2006; Koeglsperger et al., 2019).
  - Rule out the rare case of a stimulation-induced dystonia (**Figure 1**). Start with excluding pyramidal side-effects by reducing stimulation or performing a bipolar stimulation and beware that it may require a prolonged evaluation (up to few days). Eventually steer the stimulation outside the STN aiming to the dorsolateral border (**Figure 1**; Castrioto et al., 2013; Baizabal-Carvallo and Jankovic, 2016).
  - Adjust dopaminergic medications (e.g., increase levodopa; **Figure 1**) (Smulders et al., 2016).
- Dyskinetic gait
  - For STN-DBS, try dorsal contacts (**Figure 1**; Volkmann et al., 2006; Herzog et al., 2007; Aquino et al., 2019; Koeglsperger et al., 2019). In GPi-DBS an increase of the stimulation amplitude may suffice, otherwise test more ventral contacts (**Figure 1**; Bejjani et al., 1997; Krack et al., 1998; Rabin and Kumar, 2015; Baizabal-Carvallo and Jankovic, 2016; Au et al., 2020).
  - Reduce dopaminergic medications (e.g., reduce levodopa) and eventually increase STN/GPi stimulation to preserve sufficient control of motor fluctuations (**Figure 1**).
- Ataxic gait
  - Reduce the stimulation amplitude, but beware that this would come at the expense of the total electrical energy delivered (TEED) with likely worsening of motor fluctuations (**Figure 1**; Volkmann et al., 2006; Koeglsperger et al., 2019).
  - Try short pulse width (**Figure 1**; Reich et al., 2015). This would allow for a more selective stimulation based on different neuronal chronaxies and increase the therapeutic window. An increase in stimulation amplitude of ∼0.5 mA/10 μs would be likely required.
  - Use a bipolar configuration to limit the inadvertent current spread and TEED reduction (**Figure 1**). Still, an increase of the stimulation amplitude may be required to maintain sufficient control of motor fluctuations.
  - With a segmented lead, the horizontal steering of the stimulation may allow an improvement of the symptomatology and can prevent inadvertent stimulation of nearby structures (**Figure 1**; Steigerwald et al., 2019). To this aim, the use of an *anodic block* may also be attempted (Valente et al., 2010).

Turning Problems

STN-DBS has been reported to positively affect turning in PD by decreasing inter-segmental latencies (i.e., eye-head, eye-foot, and head-trunk) (Lohnes and Earhart, 2012). This benefit may be a specific effect of STN-DBS as dopaminergic medications improved turning during walking but not turning in place (Smulders et al., 2016). No data are available for GPi-DBS.

Troubleshooting

A summary is reported in **Figure 1**.

- No recommendation can be made due to the lack of evidence in the literature. We empirically suggest following the troubleshooting proposed for gait initiation, assessing the two hemibodies separately while the patient is asked to turn in place to the right and then to the left side (**Figure 1**).
- Adjust dopaminergic medications (increase levodopa to improve turning during walking; **Figure 1**) (Smulders et al., 2016).

Gait Adaptation Problems

STN-DBS can improve dual-task gait with a selective effect on gait, but not on cognitive performances (Seri-Fainshtat et al., 2013; Chenji et al., 2017). Dopaminergic medications also improve the gait performances under attentional demands but also induce a less cautious behavior (Smulders et al., 2016; Raccagni et al., 2019). No data are available for GPi-DBS.

Troubleshooting

A summary is shown in **Figure 1**.

- No recommendation can be made due to the lack of evidence in the literature. We empirically suggest increasing the amplitude of STN stimulation to support gait in dual-tasking performances (**Figure 1**; Seri-Fainshtat et al., 2013; Chenji et al., 2017).

Freezing of Gait

The effect of DBS on FOG is debated. Some studies showed an improvement of FOG with HFS STN-DBS up to 4-year follow-up, especially for meds-off FOG (Pötter-Nerger and Volkmann, 2013; Vercruysse et al., 2014). A re-evaluation of the EARLYSTIM trial also showed that STN-DBS with best pharmacological treatment was superior to best pharmacological treatment alone in preventing FOG in PD patients at 3 years from surgery (Barbe et al., 2020). No benefit has instead been shown on meds-on FOG (Schlenstedt et al., 2017). Acute development of levodopa-resistant FOG after STN-DBS surgery has also been described and possibly related to the inadvertent stimulation of the pallidal projections to the PPN, which are located dorsally to the STN in the Forel field (Tommasi et al., 2007; Adams et al., 2011; Cossu and Pau, 2017).

The management of FOG with DBS has been assessed in a few studies with different approaches ranging from changes in stimulation parameters (Moreau et al., 2008; Fasano et al., 2011), location (Weiss et al., 2013), or paradigm (Karl et al., 2020).

Fasano et al. (2011) reported an improvement in FOG when reducing the STN-DBS amplitude of 50% for the best hemibody (i.e., contralateral to the leg with longer step length). This approach aims to restore gait coordination by reducing the step length variability, but it might not be applicable in all subjects as other parkinsonian symptoms might arise under reduced stimulation amplitude (Meoni et al., 2019).

Moreau et al. (2008) achieved a remarkable improvement of FOG by reducing the frequency of stimulation to 80 Hz (low-frequency stimulation, LFS). The effect of LFS on human locomotion is not entirely clear, but it may be related to the modulation of STN fibers projecting to the PPN (Xie et al., 2017). LFS seems especially effective in PD patients who develop FOG with HFS, regardless of medication condition (Xie et al., 2017). A long-lasting positive effect of LFS can be expected in PD patients with more anterior stimulation of the STN (Zibetti et al., 2016). This can be achieved with horizontal current steering in subjects implanted with segmented leads (Steigerwald et al., 2019). However, in many cases, the benefit is only temporary and parallels a worsening of akinetic-rigid signs (Ricchi et al., 2012). Of note, unlike amplitude and frequency changes, increasing pulse-width is usually not associated with FOG improvement and might induce gait deterioration by increasing the current spread (Hui et al., 2020). Short pulse-width also showed no significant changes on FOG, while it was associated with an improvement of speech (Seger et al., 2021).

When changes in stimulation parameters are ineffective, a different stimulation location can be tested. Weiss et al. (2013) first reported a long-term improvement in FOG by combining STN- and SNr-HFS. Subsequently, FOG improvement was reported also for STN-HFS and SNr-LFS (Valldeoriola et al., 2019). Technological advances (e.g., vertically current steering and multiple independent current control) now more easily allow for such configurations (Andreasi et al., 2020), the efficacy of which is yet to be confirmed with large studies.

Finally, an improvement of FOG can be achieved by changing the stimulation paradigm. In particular, Karl et al. (2020) showed in a preliminary report in 25 PD patients a substantial benefit of interleaved-interlinked (IL-IL) STN-DBS on gait and FOG. This stimulation is a monopolar interleaved, overlapping, LFS of the STN generating a large stimulation field with peripherical LFS and central HFS (overlapping area).

Limited evidence is available for GPi-DBS in the management of FOG. GPi-DBS can improve FOG in meds-off condition with a sustained effect up to 4 years (Rodriguez-Oroz et al., 2005; Pötter-Nerger and Volkmann, 2013). However, in the meds-on condition, the improvement of GPi-DBS on FOG was limited to 1-year (Volkmann et al., 2004). An observational study specifically evaluating the effect of GPi-DBS on FOG in patients with PD is ongoing (NCT03227250) and more reports on this topic are encouraged.

Troubleshooting

A summary of troubleshooting is shown in **Figure 2**.

- Meds-off FOG and pseudo-on FOG:
  - Increase dopaminergic medications and consider prescribing monoamine oxidase B inhibitors or amantadine (**Figure 2**; Fasano and Lang, 2015; Nonnekes et al., 2015). In case of monotherapy with dopamine agonists, consider reintroducing levodopa. In the event of troublesome dyskinesia, an adjustment of stimulation might be needed: for STN-DBS more dorsal contacts should be tried (Volkmann et al., 2006; Herzog et al., 2007; Aquino et al., 2019; Koeglsperger et al., 2019), while for GPi-DBS an increase of the stimulation amplitude or more ventral contacts should be tested (**Figure 2**; Bejjani et al., 1997; Krack et al., 1998; Rabin and Kumar, 2015; Baizabal-Carvallo and Jankovic, 2016; Au et al., 2020).
- Meds-on FOG
  - Reduce dopaminergic medications (Fasano and Lang, 2015; Nonnekes et al., 2015) and consider increasing the amplitude of stimulation (**Figure 2**). For STN-DBS dorsolateral contacts should be selected (Volkmann et al., 2006; Herzog et al., 2007; Aquino et al., 2019; Koeglsperger et al., 2019), while dorsal contacts are preferrable for GPi-DBS (**Figure 2**; Bejjani et al., 1997; Krack et al., 1998; Rabin and Kumar, 2015; Baizabal-Carvallo and Jankovic, 2016; Au et al., 2020).
- Levodopa-resistant FOG:
  - Reduce the STN-DBS amplitude contralateral to the best hemibody (Fasano et al., 2011) or bilaterally in case of stimulation-related FOG in patients with GPi-DBS (**Figure 2**; Sketchler and Shahed, 2019).
  - Try STN-DBS with low frequency (60–80 Hz; **Figure 2**) (Moreau et al., 2008). An increase in stimulation amplitude may be needed to maintain a comparable TEED (Hui et al., 2020).
  - Combine STN with SNr-HFS (Weiss et al., 2013) or -LFS (**Figure 2**; Valldeoriola et al., 2019).

- Test IL-IL STN-DBS (**Figure 2**; Karl et al., 2020).

Functional Gait Disorders

The occurrence of functional movement disorders after DBS is not common, but it has been reported (Breen et al., 2018; Maciel et al., 2021).

Troubleshooting

- Functional gait disorders are not organically determined, therefore should be treated with diagnostic counseling. Changes in DBS parameters are not suggested, but a careful reevaluation of the stimulation should be performed anyhow as suboptimal programming (e.g., inadvertent stimulation of the anterior part of the STN in STN-DBS) may worsen non-motor symptoms (Castrioto et al., 2014; Petry-Schmelzer et al., 2019).

LEAD REVISION AND ALTERNATIVE DEEP BRAIN STIMULATION TARGET FOR GAIT DISTURBANCES: WHEN REPROGRAMMING IS NOT ENOUGH

Despite optimized pharmacological and stimulation treatments gait disturbances might still determine a significant burden for some PD patients. When all reprogramming options have been exploited, a surgical revision of the leads can be considered. Beside suboptimal lead placement, a supportive criterion to lead revision is the presence of an optimal levodopa response. In these patients, we reported a marked motor improvement after lead repositioning, even years after DBS surgery. However, the main improvement was achieved on rigidity or tremor (Nickl et al., 2019). As such, the repositioning of the lead in case of gait disturbances must be critically and individually discussed.

Treatment-resistant gait disturbances also promoted the investigation of alternative targets for DBS, such as the MLR or the field of Forel.

Stefani et al. (2007) first reported a remarkable improvement of gait and axial symptoms in six PD patients with combined STN-HFS and PPN-LFS (i.e., 25 Hz) at 6-month follow-up. This finding was initially confirmed (Moro et al., 2010; Peppe et al., 2010; Welter et al., 2015), but more recent studies have reported only a marginal benefit for PPN-DBS, limited to FOG (Ferraye et al., 2010), and only up to 3 months post-intervention (Wang et al., 2017; Yu et al., 2020). Caution is needed when interpreting these results due to the small and heterogeneous sample size as well as to the variability in the surgical placement of the leads. Some controversy remains also on unilateral vs. bilateral PPN-DBS as randomized, double-blinded studies showed FOG improvement with unilateral stimulation only (Rahimpour et al., 2020). It is still unclear which stimulation frequency should be preferred as benefits were reported for a wide range spanning from 15 to 130 Hz (Rahimpour et al., 2020). Furthermore, less is known on the effect of PPN-DBS on non-motor, which might be relevant as PPN stimulation can impact alertness and sleep (Sharma et al., 2018).

Encouraging results on FOG in PD have also been reported for stimulation of another MLR structure, namely the CN (Goetz et al., 2019). A prospective pilot trial of directional CN-DBS is ongoing (NCT04218526). An alternative promising target has recently been proposed by Rocha et al. (2021), who reported a marked and lasting motor improvement with amelioration of PIGD in 13 PD patients with Filed of Forel DBS.

Finally, a combined GPi- and PPN-DBS was investigated in a recent study that showed an improvement of FOG in three out of five PD patients at 6-month but not 1-year follow-up (Molina et al., 2021). The subsequent attempt in the same patients of an adaptive DBS with the stimulation triggered by an increase in power of the 1–8 Hz band from the PPN region was not successful (Molina et al., 2021). Despite the negative result, this study is of great value as it highlights the relevance that an accurate and stable neurophysiological biomarker of gait may have in advancing the treatments of gait impairment in PD. To this end, the management of non-neuronal artifacts will be also essential (Neumann et al., 2021; Thenaisie et al., 2021).

CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Gait disturbances are among the most relevant determinates of poor quality of life in PD and remain a therapeutic challenge, representing a cause of dissatisfaction after DBS surgery. While chronic gait impairments may be related to disease progression and require a combined and multidisciplinary therapy, early gait disturbances arising in the first 3 years after surgery may be secondary to treatable causes. In all these patients reprogramming of DBS should be attempted as it can lead to marked clinical improvement.

Advances in the neurophysiological understanding of gait control will soon lead to the development of novel DBS devices that can monitor the neuronal correlates of gait or its alterations and possibly adapt the stimulation delivery accordingly (Little and Brown, 2020; Gilron et al., 2021). Meanwhile, the optimization of DBS parameters needs to be performed clinically and it is based on proper classification of the gait disturbances. The clinical characterization of gait disturbances gives insight into their pathophysiological mechanism and can guide reprogramming, which has led to a marked improvement of the clinical outcome in a considerable number of PD patients. Alternative brain targets for DBS remain investigational but might be used as rescue therapy in selected cases.

AUTHOR CONTRIBUTIONS

NP and IUI contributed to study design and planning. NP, CHP, PC, and MR contributed to literature analysis and search. CLP,

JV, and IUI contributed to data interpretation and collection of funds. NP drafted the manuscript. NP and CHP prepared the figure. PC, MR, CLP, JV, and IUI critically reviewed and contributed to preparation of the manuscript. All authors contributed to the article and approved the submitted version.

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