Compensation strategies for gait impairment in Parkinson's disease

Towards personalized gait rehabilitation

Anouk Tosserams

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Compensation strategies for gait impairment in Parkinson's disease

Towards personalized gait rehabilitation

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Contents

1

General introduction and outline

Introduction

Gait impairments are common in persons with Parkinson's disease (PD; Box 1 Parkinson's disease) and are reckoned among the most disabling motor symptoms. [1] The gait deficits can typically be divided into those that are more or less constantly present, versus those that occur only episodically (i.e. these are only intermittently present, intermingled with episodes during which gait is much better). A reduced stride length, increased gait variability or a reduced arm swing are typical examples of continuously present gait deficits, [2] and can even be the first detectable motor signs of PD. [3,4] As the disease progresses, episodic gait deficits can also come into play. These episodic deficits include festination and freezing of gait. Festination is characterized by rapid, progressively smaller steps in combination with an involuntary forward-leaning of the trunk. [5,6] Freezing of gait is operationally defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk. [7] Both continuous and episodic gait impairments generally become increasingly more severe over the course of the disease, markedly affecting a person's mobility, independence and quality of life, and causing falls and associated injuries. [8-10]

Box 1 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder, and it is currently the fastest growing neurological condition in the world. A progressive loss of dopaminergic neurons in the substantia nigra and putamen gives rise to the main motor features of PD, being: tremor, rigidity, bradykinesia, hypokinesia, as well as abnormal posture and impaired postural reflexes.[11] Non-motor symptoms are also a prominent part of the overall phenotype, and these include hyposmia, fatigue, autonomic dysfunction, mood disorders, and cognitive deficits. These non-motor symptoms can also significantly impact quality of life.[12]

Besides the hallmark dopaminergic denervation within the nigrostriatal system, which represents the main target for the pharmacological management of PD symptoms, other structures are also affected by the disease, including the (noradrenergic) locus coeruleus, (cholinergic) substantia innominata, and (serotonergic) raphe nuclei.[13] These focal disruptions can ultimately cause dysregulation of entire networks, further contributing to the complex presentation of motor and non-motor symptoms in PD.[14]

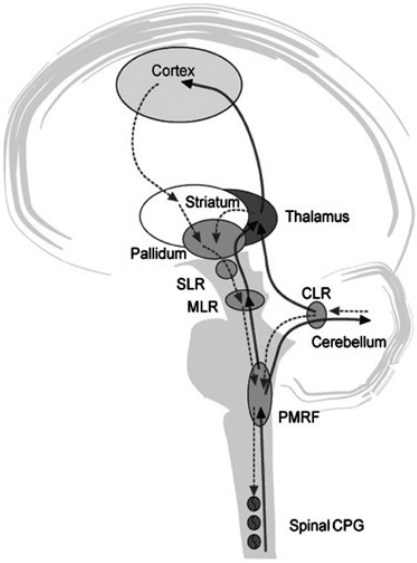
To date, it is impossible cure PD, and there is no effective treatment to slow down the progression of this disease. Symptomatic management consists of pharmacotherapy (e.g., levodopa or dopamine agonists), deep brain stimulation or continuous

pump therapies (in selected patients), and multidisciplinary care provided by a team of (allied) healthcare professionals (e.g., neurologists, PD nurses, physical-, occupational- and speech-language therapists).[15,16] Notably, persons living with PD and their near ones are critical members of this multidisciplinary team, which is why education, and providing support in self-management are so important.

Gait partly depends on a basic 'locomotor network', involving spinal central pattern generators, brainstem mesencephalic and cerebellar locomotor regions, as well as striatal input projecting to the primary motor cortex (Figure 1).[17,18] Additionally, frontoparietal and supplementary motor areas, alongside other distributed cortical areas, are engaged in gait adaptation and adjustment.[19] The precise pathophysiology underlying gait impairment in PD is highly complex and supposedly involves dysfunction of multiple cortical and subcortical structures within this locomotor network. Typically, persons with PD experience more difficulties when walking in an automated manner (i.e. without consciously paying attention to it), compared to when producing goal-directed behavior (often facilitated by an external stimulus, such as the steps of a staircase).[20] This difference between automatic and goal-directed behavior is likely related to the region-specific variation in dopaminergic depletion within the basal ganglia. The posterior putamen, which has been associated with the control of automatic (habitual) behavior, is subject to greater loss of dopaminergic innervation compared to the relatively preserved rostromedial striatum, which is primarily involved in goal-directed behavior.[21,22] As a consequence, persons with PD increasingly rely on making a compensatory shift from the primary automated to a more goal-directed mode of control to maintain functional mobility.

The deliberate application of so-called compensation strategies is believed to facilitate the above-mentioned shift from automated to goal-directed gait control.[23] These strategies are typically spontaneously invented by people with PD in an effort to overcome their walking difficulties. Such creative 'detours' can be very diverse, ranging from walking to the rhythm of a metronome or resorting to an adapted walking pattern (e.g. walking backwards, lifting up the knees high), to using alternative ways to move forwards, such as riding a bicycle or roller skating. The broad spectrum of available strategies has been proposed to consist of seven overarching categories of compensation. These comprise: external cueing, internal cueing, changing the balance requirements, altering the mental state, action observation and/or motor imagery, adopting a new walking pattern, and alternatives to walking (Table 1).[23] To date, a wide range of different compensation strategies has been reported, typically in the form of anecdotal case reports.[24-27]

Figure 1. Locomotor control from cortex to spinal cord. [18]



Gait is based on an automated rhythmic motor pattern generated by spinal central pattern generators (CPG). Besides sensory input from proprioceptive and skin afferents, these spinal CPGs receive descending input from supraspinal structures that are essential for the initiation and modulation of a stereotyped locomotion pattern. [17] The most important of these supraspinal structures are the mesencephalic locomotor region (MLR) and its descending projections to the ponto-medullary reticular formation (PMRF), the subthalamic locomotor region (SLR), and the cerebellar locomotor region (CLR). Input from the cortex (particularly the supplementary motor area), cerebellum and basal ganglia contribute to the fine regulation of gait. [19]

Reprinted from: *Jahn K, Deutschländer A, Stephan T, et al. Supraspinal locomotor control in quadrupeds and humans. Progress in Brain Research.* [18] Copyright 2008, with permission from Elsevier.

Non-pharmacological interventions, such as the application of compensation strategies form an essential element of the overall management of gait impairments in PD, as pharmacological treatment alone rarely suffices to adequately ameliorate gait quality. [28,29] A complementary treatment approach becomes even more important as the disease progresses, presumably because (1) non-dopaminergic lesions start to gradually dominate the underlying pathophysiology; [30,31] and (2) the increasingly higher necessary dosages of dopaminergic medication may no longer be tolerated due to debilitating side effects, such as dyskinesias, orthostatic hypotension or psychiatric complications. However, in contrast to conventional pharmacological and neurosurgical treatments, the efficacy and underlying mechanisms of compensation strategies for gait impairments in PD have rarely been studied in a systematic manner (with the exception of external cueing[32]). The lack of fundamental knowledge on this topic significantly hampers the development of a much-needed personalized approach to gait rehabilitation in PD, as clinical observations suggest that the efficacy of different compensation strategies varies greatly between individuals.

Another important condition of achieving a more personalized approach to gait rehabilitation is adequate representation of the diverse PD population in clinical

trials. Clinical trials should generally preferably be designed to be broadly inclusive in terms of age, sex, race, and other personal characteristics that may potentially affect the efficacy of targeted interventions. Historically however, this has proven to be challenging in medical research as a whole. In recent years, it has been established that women in particular are consistently underrepresented in clinical trials. In the field of PD, such a 'gender gap' could have important clinical implications, given the role played by sex in the pathophysiology and expression of the disease.

Table 1. Classification of compensation strategies for gait impairments in Parkinson's disease. [23]

Compensation strategy	Suspected principal mechanism	Phenomenology
External cueing	Introduction of goal-directed behavior by introducing a movement reference or target;	• Walking to the rhythm of music; • Stepping over lines on the floor; • Bouncing a ball.
Internal cueing	Assist in achieving focused attention toward specific components of gait, to shift from automatic to goal-directed motor control.	• Mental singing or counting; • Focusing on a specific component of the gait cycle (e.g. making a heel strike).
Changing the balance requirements	Facilitate the ability to make lateral weight shifts, thereby easing the swing phase of the unloaded leg, particularly in gait initiation or turning.	• Using walking aids; • Making a volitional weight shift before gait initiation; • Making wider turns.
Altering the mental state	Enhance general alertness and arousal. This may help shift from automatic to goal-directed motor control.	• Reducing anxiety (e.g. mindfulness); • Increasing motivation (e.g. encouraging oneself); • Kinesia paradoxa.
Action observation and motor imagery	Activate the mirror neuron system which may facilitate cortically generated movement.	• Observing or visualizing and mimicking the gait pattern of another person.
Adopting a new walking pattern	Use alternate motor programs that may be less overlearned and less dependent on the automatic mode of motor control.	• Skipping; • Walking backwards or sideways; • Running; • Making skating movements.
Alternatives to walking	Walking difficulty may be a task-specific problem.	• Riding a bicycle; • Skateboarding; • Riding a scooter; • Roller skating.

Adapted from: *Nonnekes J, Ruzicka E, Nieuwboer A, et al. Compensation strategies for gait impairments in Parkinson's disease: a review. JAMA Neurology 2019.* [23]

Outline of this thesis

The aim of my thesis was to generate a deeper understanding of compensation strategies for gait impairment in PD, in order to pave the way towards a more personalized approach to gait rehabilitation in persons with PD.

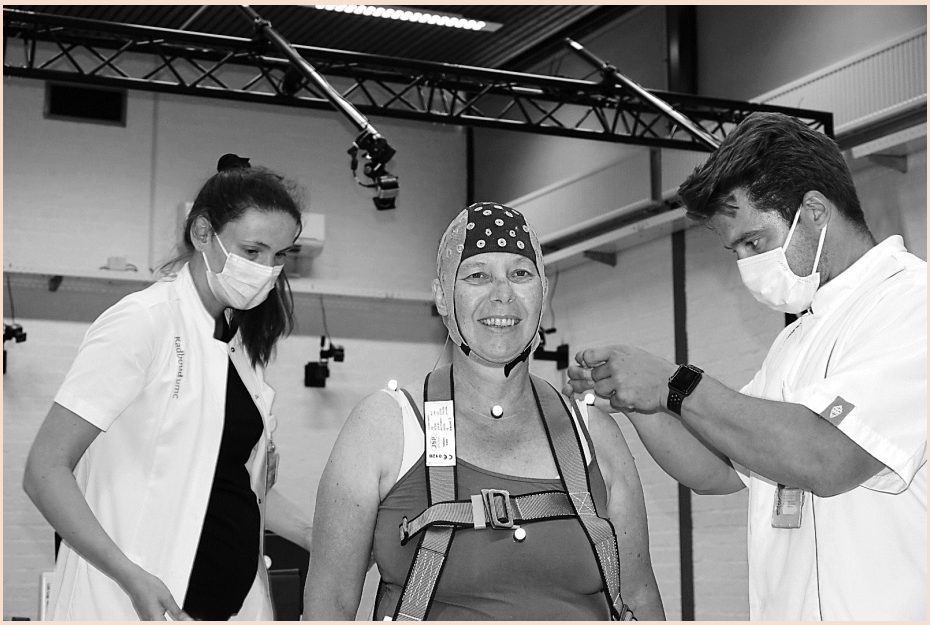
Part I of this thesis is meant to lay a foundation for the requisites of personalized care, specifically focused at the potential differences that may exist between male and female patients. In order to provide the best possible care to both men and women with PD, it is crucial that clinical intervention trials include a representative set of study participants that include both men and women. I hypothesized that women are currently underrepresented in PD clinical research. In a systematic review and meta-analysis, I explored this for all recent major randomized clinical trials concerning PD (**Chapter 2**), and separately for all recent intervention studies targeting freezing of gait in PD (**Chapter 3**).

In **Part II** of this thesis, I report on two survey studies that I conducted to make an inventory of the perception and use of compensation strategies for gait impairments in PD among healthcare professionals (**Chapter 4**), and persons with PD (**Chapter 5**). I hypothesized that compensation strategies are commonly used in daily life and clinical practice, but that the general knowledge on the full spectrum of available strategies is limited among both healthcare professionals and persons with PD. Second, I investigated the efficacy of different categories of compensation strategies in improving gait in PD, using patient-reported (**Chapter 5 & 6**) as well as objective lab-based measures (**Chapter 6**) in a clinical study using a within-subject design. I also explored whether certain patient characteristics are associated with the efficacy of specific strategies. I hypothesized that the application of compensation strategies in general can be highly effective, but that the effects of specific strategies differ significantly between individual patients.

In **Part III**, we delve deeper into the potential mechanisms underlying compensation strategies for gait impairments in PD. In an exploratory study using ambulatory electroencephalography (Box 2: Electroencephalography), I studied the cortical correlates of external cueing, internal cueing and action observation (**Chapter 7**). I hypothesized that the application of these compensation strategies would elicit an increase in central motor activation compared to usual gait. I also hypothesized that other cortical areas (e.g. frontal and parietal areas) would become more active, with distinct cortical 'fingerprints' for each of the three strategies. In the subsequent chapter I elaborate on the potential mechanisms underlying the 'Altering the Mental

State' category of compensation strategies, in which I propose a central role for the noradrenergic locus coeruleus in modulating arousal, as well as mediating network-level functional integration across the brain, to optimize gait performance in PD (**Chapter 8**).

Box 2 Electroencephalography



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Electroencephalography (EEG) is a non-invasive method to record voltage fluctuations arising from the cerebral cortex, using multiple electrodes that are placed on the scalp. These voltage fluctuations reflect synchronized activity of large neuronal networks, rather than changes in local activity of the cortex related to sensory stimulation or specific motoric or cognitive functions of the brain. Despite its limited spatial resolution compared to neuroimaging techniques such as functional magnetic resonance imaging (fMRI), it offers excellent (millisecond-range) temporal resolution and – importantly – allows for the recording of cortical activity during actual movement rather than imagined movement inside of a scanner.

In **Part IV**, I present a practical guide to the evaluation of compensation strategies for gait impairments in PD in clinical practice, based on the main findings of this thesis and my learnings from my own clinical observations (**Chapter 9**). The thesis is concluded by a summary and general discussion, in which I place the results of this work into a broader context and offer directions for future research (**Chapter 10 & 11**).

On a final note, the use of very large study populations is increasingly becoming the norm in the era of 'big data' we live in today. At the same time, it is still essential to recognize the unique value of meticulous observations made in considerably smaller groups of research participants, sometimes even as small as a single patient. [33] A striking observation in a single patient can help to advance the field by sparking new hypotheses and generating ideas for further investigations. Serving as a source of inspiration and contemplation, each of the four parts of this thesis therefore begins with a brief, video-illustrated **clinical vignette**, highlighting such n=1 observations.

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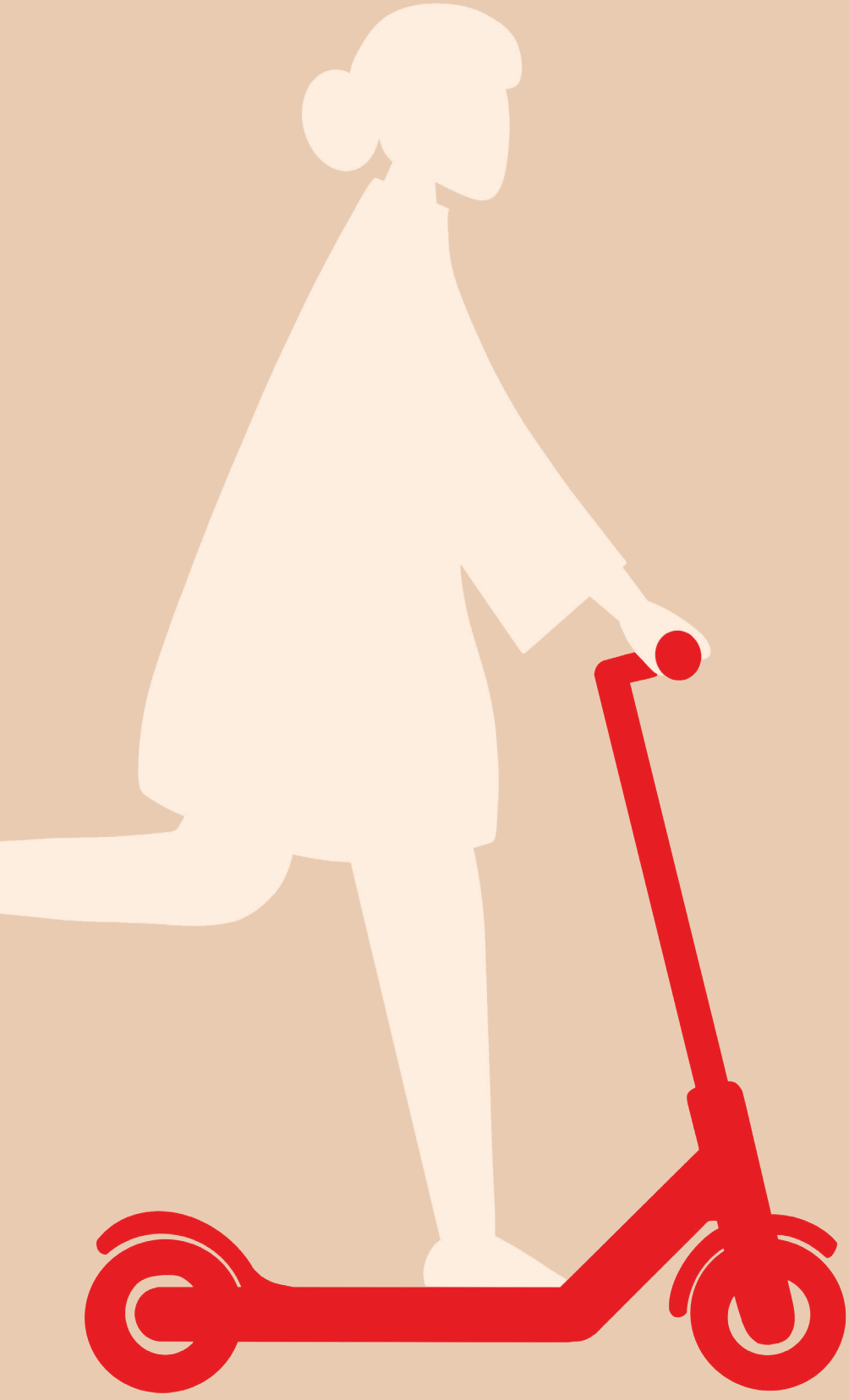

Part I

Prerequisites for personalized care: representation matters

Video vignette I

If you have ever seen a video of a person with Parkinson's disease and freezing of gait, chances are that person was a man. While both men and women with Parkinson's disease can experience gait impairments – including freezing, images on the topic are typically male-dominated. This skew in representation could mislead people into thinking that men are at greater risk of developing this symptom. Video vignette I shows a compilation of women experiencing freezing of gait.

2

Underrepresentation of women in Parkinson's disease trials

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Tosserams A., Araújo R., Pringsheim T., Post B., Darweesh S.K.L., IntHout, J., Bloem B.R. Underrepresentation of women in Parkinson's disease trials. Movement Disorders 2018;33(11):1825-1826.

There is growing recognition that women are underrepresented in clinical trials.[1,2] Concerning Parkinson's disease (PD), gender representation in clinical trials has not been assessed formally. If present, such a gender gap could have important implications in light of the role played by gender in the pathophysiology, natural history, and management of PD. We analyzed the male-to-female ratio of participants in PD randomized clinical trials (RCTs) published since 2010 and compare those to existing data from PD prevalence studies.

We searched the PubMed database in December 2016 for PD RCTs. PD prevalence data were obtained directly from a recent meta-analysis of population-based studies by Pringsheim and colleagues.[3] Included studies met the following criteria: (1) included > 50 subjects; (2) participants included both men and women; (3) no patients with secondary or drug-induced parkinsonism. "Parkinson" was used as search term, intended to be broadly inclusive. In addition, the following filters were employed: RCT [PTyp], From 2010/06/01-2016/12/06 [Pdat], Humans [MeSH Terms], English [Lang].

Of 685 potentially relevant clinical trials, 122 met our inclusion criteria. In total, 32,607 participants were randomized. The overall prevalence of male PD patients in the meta-analysis by Pringsheim and colleagues was estimated at 53.1%. In RCTs, men were consistently overrepresented. The overall skew toward more men in clinical trials was almost 7% (Table 1). We found that 55.7% of all major PD trials published since 2010 recruited > 59% men. Only 14.9% of a total of 48 trials conducted in Northern America consisted of a more neutral recruitment by gender, highlighting the impact of this issue.

Table 1. Estimated differences in percentage of men in PD trials in comparison with prevalence data,[3] presented by type of intervention - separately for all regions (All), European (EU), and Northern American (NA) studies

	Number of studies			**Mean difference (%)[a]**			**95% CI**	***p***
Intervention type	All[b]	EU	NA	All	EU	NA	All	All
Pharmacological	78	33	29	6.01	5.37	11.18	1.23-10.91	0.014
Neurosurgical	12	4	7	15.56	13.39	19.85	8.12-22.99	<.001
Other[c]	32	15	11	6.13	4.00	7.75	0.23-12.04	0.042
Total	**122**	**52**	**47**	**6.96**	**5.59**	**11.67**	**1.88-12.04**	**0.007**

[a] Mean difference was calculated as the percentage of men in PD trials minus the percentage of men in PD prevalence data.

[b] Comprising studies from EU, NA, Australia, and Asia.

[c] e.g. Exercise-based interventions.

To ascertain whether the high prevalence of men in clinical trials did not merely reflect the male predominance in certain age groups,[3] we looked at the overall age distribution in trials. PD patients in trials are globally younger than those in prevalence studies (63.8 vs 74.1 years). Consequently, we cannot rule out that some of the observed differences are the result of an overrepresentation of younger PD patients. However, there was no association with mean age and percentage of men included in trials. Finally, prevalence (as a metric) is an underestimate of lifetime risk, which is particularly relevant in this context because men tend to live shorter lives than women. As a consequence, the male-to-female difference between trials and "true" lifetime risk is conceivably considerably larger than 7%.

The background prevalence of women with PD is lower to begin with, but some evidence suggests that female patients are underrepresented in specialized clinics.[4] Consequently, they would be less likely to be invited to participate in trials initiated by such centers. Others have hypothesized that women may cope better than men with PD.[5] Indeed, in the outpatient clinic of our own Parkinson center, up to 70% of secondary and tertiary referrals are men (unpublished observations), clearly exceeding the prevalence in observational studies. However, we are unaware of previously published evidence for this.

Regardless of precise explanations, these findings suggest that some caution is warranted when extrapolating results from PD trials to women. Efforts to include more female patients into future RCTs should now be undertaken to bridge this gender gap.

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3

Sex and freezing of gait in Parkinson's disease: a systematic review and meta-analysis

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Abstract

Objective

It is unknown how sex affects the prevalence of freezing of gait (FOG). We conducted a systematic review and meta-analysis to establish the sex-specific prevalence of FOG in persons with Parkinson's disease (PD). In addition, we investigated whether men and women were represented accurately in intervention trials targeting FOG.

Methods

We queried the EMBASE and PubMed databases and identified 2637 articles. Of these, 16 epidemiological studies were included in the meta-analysis, and 51 intervention studies were included in the comparative analysis.

Results

In total, 5702 persons were included in the final meta-analysis of epidemiological studies. The pooled estimate of overall FOG prevalence was 43% [95% CI 33–53%]. We found no difference in FOG prevalence between men [44% (34–54%)] and women [42% (31–52%)] with PD. However, women were markedly underrepresented in intervention trials targeting FOG, with an average proportion of only 29.6% of women in trial populations. The percentage of women included in trials was similar across intervention types but differed greatly across geographical regions.

Conclusion

Sex is not a predictor of FOG. This could aid clinicians in counseling persons with PD about FOG. Importantly, a global effort is needed to include more women into clinical trials. Given the skewed distribution of men and women included in intervention trials targeting FOG, caution might be warranted when extrapolating results from FOG trials to women.

Introduction

Freezing of gait (FOG) is a common and disabling phenomenon in people with Parkinson's disease (PD). It is characterized by brief episodes during which patients experience their feet as being "glued to the floor".[1] Presence of FOG is an important predictor of future falls and loss of independence, and reduces quality of life of affected individuals.[2,3] The exact mechanisms underlying FOG are not fully understood, but several factors seem associated, including longer disease duration, cognitive decline and presence of depression or anxiety.[4-7] Interestingly, most video-illustrated case reports and case series on FOG display footage of men.[8-12] This may suggest that FOG is more common in men compared to women. However, it remains unclear whether sex affects the prevalence of FOG.[13,14] Gaining more insight into potential sex differences in FOG prevalence could aid clinicians in counselling PD patients, as well as researchers in selecting an appropriate study population for clinical trials targeting FOG. In this systematic review and meta-analysis, we report pooled estimates of the sex-specific prevalence of FOG in persons with PD. We also investigate whether this sex distribution is adequately reflected in recent clinical trials targeting FOG.

Methods

Inclusion criteria

Main selection criteria and methods of analysis were specified and documented in advance. The systematic review was conducted in accordance with the PRISMA statement,[15] following an a priori protocol (available upon request). The criteria for eligibility are reported in Table 1. Key criteria for epidemiological studies included: observational cohort- or cross-sectional study design, ambulatory, outpatient or community-based setting, and a minimum of 100 male and female participants with FOG included. Key criteria for intervention studies included: intervention studies published between June 2014 and December 2019, ambulatory, outpatient or community-based setting, and a minimum of 10 participants with FOG included.

Search strategy

In June 2019 the PubMed (NLM) and EMBASE (Elsevier) databases were searched. The search strategy was determined with the help of a medical librarian and was used for the selection of both epidemiological studies and intervention studies. "Freezing of gait", "Parkinson's disease" and related terms were used. Reference lists of included studies were examined for additional relevant studies. An update search was conducted in December 2019, to check for relevant studies that were published since the original search.

Table 1. Criteria for eligibility, per arm of the systematic review

Epidemiological studies	Intervention studies
Inclusion criteria	
• Includes human participants diagnosed with idiopathic PD; • Includes both male and female participants; • Includes ≥ 100 participants with FOG in the final analysis; • Reports prevalence of FOG within the cohort; • Reports sex distribution within the cohort and within FOG subgroup; • Observational cohort studies (retrospective or prospective) and cross-sectional studies; • Ambulatory, outpatient or community-based settings only; • Published in English or Dutch.	• Includes human participants diagnosed with idiopathic PD and FOG; • Includes ≥ 10 participants with FOG in the final analysis; • Reports sex distribution of study participants; • Published between June 2014 – December 2019; • Published in English or Dutch.
Exclusion criteria	
• Studies that enroll participants who are receiving a particular intervention; • Inpatient or other acute care settings; • Other studies that cannot be expected to provide generalizable estimates of prevalence.	• Inpatient or acute care settings; • Interventions specifically targeted to either men, or women (e.g. hormonal therapy in women); • Interventions specifically targeted to a specific subgroup of PD patients with FOG (e.g. DBS populations).

FOG = freezing of gait; DBS = deep brain stimulation.

Study screening and selection

All records were assessed for eligibility by two independent reviewers (AT, MM). Any disagreement was resolved by a third independent reviewer (JN). Only unique nonoverlapping study populations were included. Reasons for exclusion of studies were logged throughout the process. In- and exclusion criteria were specifically designed to eliminate epidemiological studies with a high risk of bias. No formal quality assessment took place for the intervention studies, since the focus of this review was to investigate the sex distribution within the study sample, and not the actual effect of the intervention.

Data extraction

Data extraction was performed by two independent reviewers (AT, MM). Any discrepancies were resolved by consulting a third reviewer (JN). All data were recorded in a predefined data extraction form. When necessary, corresponding authors were contacted to provide missing or additional information.

For all included epidemiological studies, the following data were extracted: study location, study setting, primary outcome, manner of recruitment, criteria used to

establish presence of FOG, patient characteristics including mean age, mean disease duration, and mean (MDS-)UPDRS part III scores, total participants included, total male participants included, total participants with FOG included, and total male participants with FOG included.

For all intervention studies, the following data were extracted: study location, intervention type (e.g. physiotherapy/cueing, pharmacological), a short summary of the intervention, total participants with FOG included, and total male participants with FOG included.

Synthesis and statistical analysis

For each epidemiological study, both the overall and the sex-specific prevalence of FOG were calculated. Overall FOG prevalence per study was calculated as follows: (number of participants with FOG/total number of participants in the study) × 100. Sex-specific prevalence of FOG per study was calculated for both men and women as follows: (number of men or women included in the FOG subgroup)/(number of men or women included in the total sample) × 100.

Meta-analyses were performed to provide pooled estimates of overall FOG prevalence, and FOG prevalence among men and women separately. Analyses were performed in Stata (StataCorp LLC.. 2019. Stata Statistical Software 16. College Station, TX, USA), using the *metaprop* program for pooling binomial data.[16] Additionally, a multivariable meta-regression analysis was performed, to investigate the influence of sex on overall FOG prevalence, independently of disease duration and -severity. A random effects model was employed for all analyses, because of the clinical heterogeneity of included studies. The degree of statistical heterogeneity was assessed using the I^2 index. p values < 0.05 were considered to be significant.

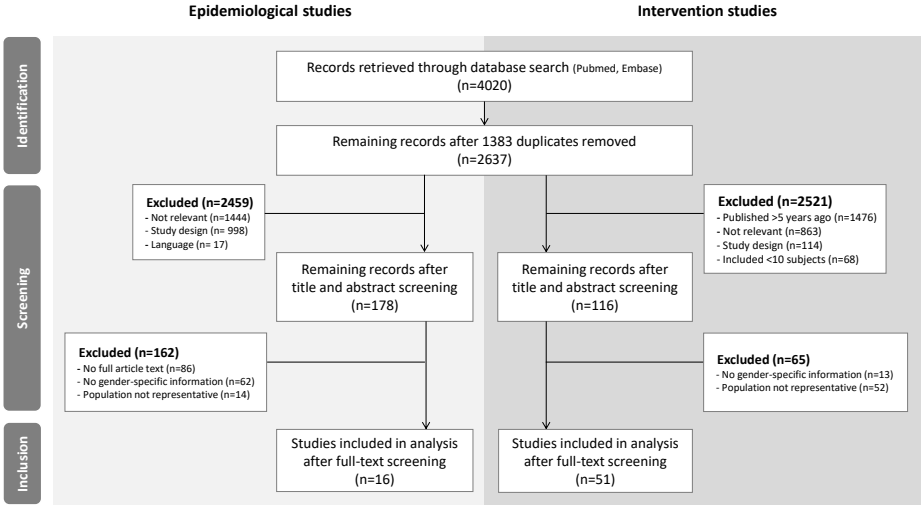
For each intervention study, sex distribution of included participants was calculated by: (number of men with FOG included/total number of participants with FOG included) × 100. Studies including < 45% male participants were marked as 'female-predominant', studies including 45–55% male participants were marked as 'neutral', and studies including > 55% male participants were marked as 'male-predominant'. Studies were categorized per intervention type, and geographical region.

Results

Literature search

In total, 2637 deduplicated records were retrieved from PubMed and EMBASE. After title and abstract screening, the full text of 178 articles was evaluated, after which 16 epidemiological reports were included in the final meta-analysis. In addition, 51 recent intervention studies on FOG were included for comparative analyses.

Figure 1. PRISMA flow diagram of the screening and selection process



No full article text (e.g. conference abstracts); Population not representative (e.g. preselected groups such as persons who had all received deep brain stimulation prior to FOG onset)

Figure 1 shows a flowchart of the screening and selection process. Conference abstracts were screened during the process, but excluded because (1) the information provided was too limited to determine whether the study met all the pre-defined inclusion criteria, or (2) a published final full article was also available, and part of the search result. Corresponding authors had to be contacted for additional information in ten cases. All queries concerned missing patient characteristics data for subgroup analyses (e.g. mean age or UPDRS motor score of the total cohort). One corresponding author responded. After three months, the remaining nine queries were marked as missing data.

Estimation of sex-specific prevalence of FOG

The 16 epidemiological studies in the final meta-analysis included a total of 5702 persons with PD. The average number of participants per study was 356

(range 100–990). Five studies included more than 500 participants. The average percentage of men included in the studies was 57.5% (range 41.1–66.1%). The mean disease duration of included participants was 7.0 years (range 4.8–12.1). Studies were conducted in Europe (n = 6), Asia–Pacific (n = 6), and North America (n = 4). In most studies, presence of FOG was identified using item 3 of the Freezing of Gait Questionnaire[17] (n = 7). In other studies, item 14 of the UPDRS part II[18] (n = 3), item 1 of the New Freezing of Gait Questionnaire[19] (n = 1), and other self-reported questionnaires (n = 3) were used to establish presence of FOG. In one study the presence of FOG was retrospectively extracted from medical records. One study did not report their method used to identify the presence of FOG.

Figure 2 presents the forest plots of pooled estimates of overall prevalence of FOG, as well as sex-specific prevalence of FOG. The pooled estimate of overall prevalence of FOG was 43% (95% CI 33–53%). The pooled estimate of FOG prevalence for men was 44% (95% CI 34–54%), and for women 42% (95% CI 31–52%). Included studies were highly heterogeneous (I2> 97%).

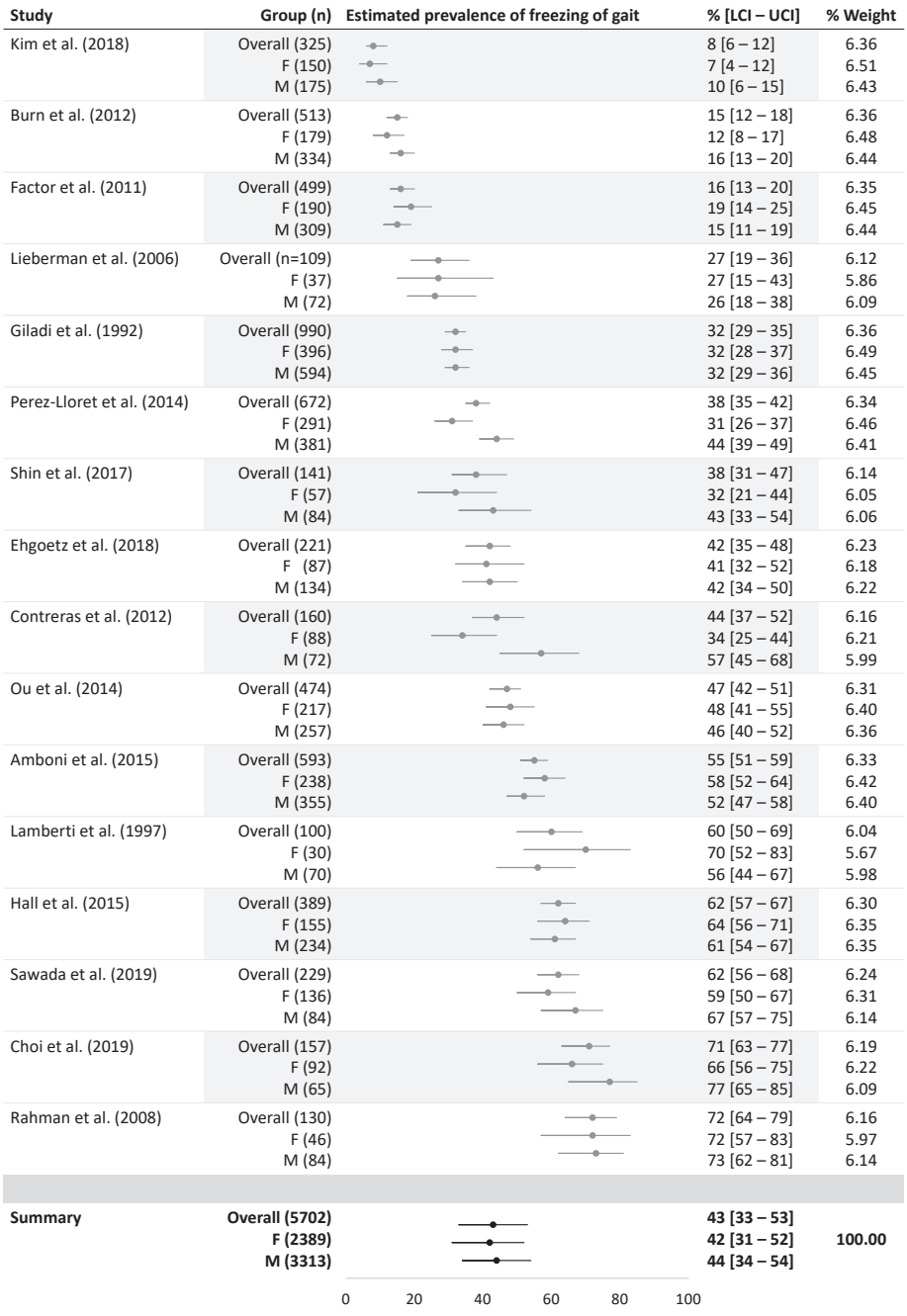
A multivariate random effects meta-regression did not demonstrate a relationship between sex and overall FOG prevalence (p = 0.333).

Sex distribution in recent intervention trials on FOG

A total of 51 intervention studies were included in the comparative analysis. Included studies were categorized per intervention type: physiotherapy/cueing (n = 32), non-invasive brain stimulation (n = 9), pharmacological treatment (n = 5), neurosurgical intervention (n = 4), or cognitive training (n = 1). Most studies were performed in Europe (n = 23), followed by Asia (n = 10), and North America (n = 9).

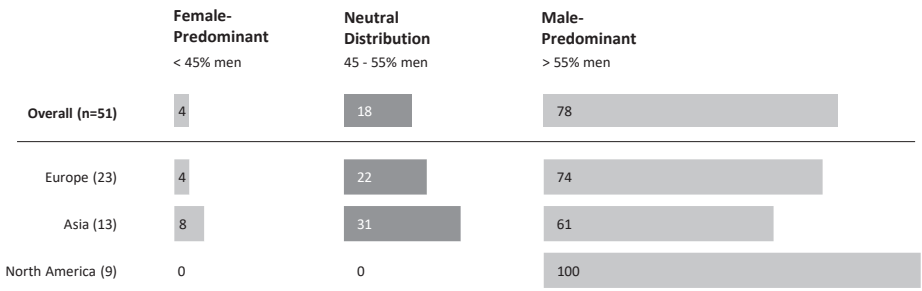
The overall sex distribution of included participants is presented in Figure 3. Out of 51 intervention studies, a mere 9 (17.6%) trials included a neutral sample in terms of sex distribution, whereas 40 (78.4%) trials were male-predominant. On average, 29.6% (range 0–56.7%) of study participants were women. The percentage of women included in trials was similar across intervention types: physiotherapy/cueing (mean: 29%, range 0–57%), non-invasive brain stimulation (mean: 34%, range 15–50%), pharmacological treatment (mean: 30%, range 14–52%), and neurosurgical interventions (mean: 29%, range 8–46%). Moreover, Figure 3 demonstrates the results stratified by geographical location, where a marked difference in the recruitment of women is apparent across regions. Notably, all trials performed in North America (n = 9) were male-predominant.

Figure 2. Forest plot of pooled estimates of overall and sex-specific prevalence of freezing of gait in Parkinson's Disease



F = female; M = male; LCI = lower limit of 95% confidence interval; UCI = upper limit of 95% confidence interval.

Figure 3. Overall sex distribution (%) in intervention studies on freezing of gait published in the last five years, stratified per geographical location



Due to the limited amount of studies performed in the Middle East, Pacific, South America, and intercontinental collaborations, these are not presented as separate subcategories. They are represented in the 'Overall' category. All studies concerned were male-predominant.

Discussion

Our main aim was to establish the sex-specific prevalence of freezing of gait (FOG) in PD. We also investigated whether recent intervention trials targeting FOG portrayed an accurate representation of the FOG disease population in terms of sex distribution. We found no difference in FOG prevalence between men and women with PD. However, women were markedly underrepresented in recent intervention trials targeting FOG.

The absent sex difference in FOG prevalence contradicts previous findings in a large cohort of 6,620 patients, where male sex was identified as a predictor of FOG in PD (OR 1.19 [1.04–1.35]).[13] This study by Macht et al. was not included in the present meta-analysis because it did not report the sex distribution within the FOG subgroup. An obvious strength of their study was the large number of respondents, and the fact that the included men and women were similar in terms of age and disease duration–the latter features are well-known determinants of FOG prevalence.[20] However, the outcomes of the study by Macht et al. should be interpreted with some caution, for various reasons. First, the study was originally designed to investigate the predictors of sudden onset of sleepiness, and the observed FOG prevalence resulted from post hoc analyses. Second, the definition of freezing that was used differed from validated self-reported questionnaires, such as the NFOG-Q and FOG-Q. Specifically, their definition was not limited to FOG, but encompassed freezing in a broader sense, also including upper limb freezing and freezing of speech. Third, the five possible answer options as to how often respondents experienced freezing

were dichotomized. In doing so, respondents who reported freezing less than twice a month were not included in the freezing subgroup, which might have affected the prevalence estimate. In the present meta-analysis, we were able to provide a similar sample size, with enough power to study potential sex differences in FOG prevalence among people with PD, by pooling data from a myriad of smaller studies.

Our results show that the sex distribution in recent intervention trials targeting FOG in PD is skewed towards men by nearly 20%. There are several explanations for this observed difference. First, PD is slightly more prevalent in men compared to women, but this cannot fully explain the difference in inclusion of men and women in FOG trials. In 2016, approximately 6.1 million individuals worldwide had PD, of whom 2.9 million (47.5%) were women and 3.2 million (52.5%) were men.[21] While the age-standardized prevalence of PD is higher in men,[21] the lifetime risk of developing PD is 4.4% for men and 3.7% for women.[22] The sex difference we observed in FOG intervention studies was much greater. Second, women might be less likely to be invited to participate in FOG trials, because they may be underrepresented in specialized clinics, which generally initiate such investigations .[23] According to a retrospective observational study investigating the predictors of specialist care utilization, women are less likely to receive neurologist care compared to men.[24] Third, women may theoretically be less inclined to participate in FOG trials, because they might cope differently with their disease.[25] For example, women could be better at self-management, and therefore less likely to seek neurology care. Fourth, women are more likely to experience depression and anxiety,[26] which may negatively affect both their interest to partake in clinical trials, as well as their chances to fulfil fit the inclusion criteria. The latter notion could explain why the observed sex gap in FOG research is considerably larger than what was previously noted for PD research as a whole (20% gap in FOG research versus 7% in general PD research),[27] since depression and anxiety are both factors associated with FOG.[6,7] Finally, regardless of disease-specific reasons, underrepresentation of women in clinical trials appears to be a generic challenge, which is increasingly recognized across other fields of clinical research as well, including cardiology and oncology.[28,29] A systematic search of nine prominent medical journals regarding randomized controlled trials concluded that the median enrollment of women in the 56 included studies was a mere 37%.[30]

As an incidental finding, we found that the inclusion of women in trials differed between study regions. Consistent with a previous study on sex distribution in PD clinical trials, studies conducted in Asia included relatively more women compared to studies conducted in Europe or North America.[27] Examining whether e.g. potential

cultural differences in gender roles contribute to this difference in female recruitment is an interesting topic for further investigation.

There are some precautions to take into account when interpreting the results of the present study. First, this review may not be exhaustive due to the limitations of the search strategy. Second, most of the included observational studies identified FOG through self-reported questionnaires. The question therefore remains whether possible differences in the prevalence of FOG were masked by differences in the way men and women might experience and report their motor symptoms. Future work should therefore also focus on patients with FOG that is objectively verified by an experienced examiner. Additionally, cognitive status should be taken into account.

The present finding that sex is not a predictor of FOG could aid clinicians in counselling persons with PD about FOG. Our findings also raise the question whether results from PD trials can be fully extrapolated to women with PD, as women were underrepresented.[27] Future studies may establish the exact impact of this sex data gap, e.g. by investigating whether sex differences affect the efficacy of different FOG interventions. Most importantly, a global effort must be undertaken to include a more representative proportion of women into future clinical trials.

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4

Perceptions of compensation strategies for gait impairments in Parkinson's disease: a survey among 320 healthcare professionals

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Abstract

Compensation strategies are an essential part of managing gait impairments in people with Parkinson's disease (PD). We conducted an online survey among 320 healthcare professionals with specific expertise in PD management, to evaluate their knowledge of compensation strategies for gait impairments in people with PD, and whether they applied these in daily practice. Only 35% of professionals was aware of all categories of compensation strategies. Importantly, just 23% actually applied all seven available categories of strategies when treating people with PD in clinical practice. We discuss the clinical implications, and provide recommendations to overcome this knowledge gap.

Introduction

Gait impairments are common and disabling in Parkinson's disease (PD). These impairments range from shuffling to outright "freezing" of gait, characterized by sudden, often brief, episodes when patients feel as if their feet are glued to the floor.[1] Considering that dopaminergic treatment usually only has limited effect, supplementary non-pharmacological interventions, including the application of compensation strategies, are essential in the management of gait impairments.[2] These compensation strategies cover a wide range of "detours" to overcome gait impairments and thereby enable better functional mobility in daily life. Examples of such strategies include walking to the rhythm of a metronome, walking, jumping, or mimicking the walking pattern of another person. An international group of experts recently summarized all strategies available based on reviews of video recordings of strategies invented by patients. A classification into seven categories of compensation strategies was proposed: external cueing, internal cueing, changing the balance requirements, altering the mental state, action observation/motor imagery, adapting a new walking pattern, and alternatives to walking.[3] Since one strategy that works well for one patient can have no, or possibly even a negative, effect on gait in another patient, a one-size-fits-all approach is unlikely to be effective. Additionally, even within one individual, one strategy may have different effects during different activities, or in different contexts (e.g., when preparing food in the kitchen vs. when walking outside).[4,5] Finally, even though robust evidence is lacking, there are concerns that the efficacy of particular compensation strategies may taper off over time, necessitating a switch to an alternative strategy. Consequently, patients will often require multiple strategies in order to perform their daily activities, over many years. Healthcare professionals should therefore focus on all available strategies, to ensure the optimal strategy can be determined for each individual patient and context. Here, we conducted an online survey among Dutch healthcare professionals who are regularly treating persons with PD in the Netherlands, to evaluate their knowledge of the various compensation strategies for gait impairments in patients with PD, and to investigate whether they applied these strategies in daily clinical practice.

Methods

The study was approved by the Institutional Review Board of the Radboud University Medical Center in Nijmegen, the Netherlands (Ref: 2019-5737). The survey was distributed via ParkinsonNEXT (http://www.parkinsonnext.nl), an online platform

that aims to unite patients, researchers and clinicians wanting to contribute to research and innovation in PD or parkinsonism. ParkinsonNEXT provides information about ongoing studies and facilitates the recruitment of patients. In the survey, each category of compensation strategies was briefly explained, and illustrated by several practical examples. Then, participants were queried whether they were previously aware of the existence of said category of strategies, and whether they had ever applied it in their daily practice. Since different professional disciplines can assume different roles in the management of gait impairments in PD, we made sure that our survey was broadly inclusive (e.g., PD nurses can inform patients about the existence of the strategies, while physical therapists specifically instruct patients how to apply the various strategies). Descriptive statistical analyses were performed using IBM SPSS 25 (SPSS, Inc., Chicago, IL, USA). The difference between ParkinsonNet affiliated professionals and non-affiliated professionals was assessed using an independent-samples Mann-Whitney U test.

Results

In total, 365 Dutch healthcare professionals completed the survey, of whom 45 were excluded because they treated less than one person with PD per month. The included study sample of 320 professionals consisted of physical therapists (71%), general nurses (9%), occupational therapists (8%), movement disorder specialists (4%), specialized PD nurses (4%) and miscellaneous (allied) healthcare professionals (e.g., general practitioners, 3%). The predominance of professionals worked in multiple care settings, including: primary care practices (63%), nursing homes (30%), general hospitals (13%), or rehabilitation facilities (10%). Notably, 70% of respondents was affiliated with ParkinsonNet, a nation-wide network of healthcare professionals specifically trained in the management of PD.[6]

Table 1 shows the median and range of the amount of categories known and applied by healthcare professionals. Only 35% of respondents was aware of the existence of all seven categories of compensation strategies, and 23% of professionals applied all seven available categories of strategies in practice when working with people with PD. The knowledge of, and the application of the strategies varied per profession, with physical therapists scoring highest, and movement disorders specialists and general nurses scoring lowest within the spectrum. Additionally, professionals affiliated with ParkinsonNet were better acquainted with the available strategies than professionals who were not affiliated ($p=0.007$). Of all available strategies, external and internal cueing were best known among healthcare professionals (96%), and were also applied

in practice by most respondents (by 94%, and 93% respectively). However, action observation and motor imagery was the least known category among professionals (60%), and was applied in clinical practice by less than half (45%) of the respondents. When asked which strategy they most often applied in clinical practice, 77% of healthcare professionals reported either internal or external cueing.

Table 1. Perceptions of compensation strategies for gait impairments, among 320 Parkinson's disease healthcare professionals

	Categories Known (n)		Know all 7 categories		Categories applied in practice[a] (n)		Apply all 7 categories in practice	
Profession	**Median**	**Range**	**n**	**%**	**Median**	**Range**	**n**	**%**
Physical therapists (n=228)	6	[1-7]	98	43	6	[1-7]	68	30
General nurses (n=30)	3	[0-6]	2	7	3	[0-6]	0	0
Occupational therapists (n=27)	5	[3-7]	5	19	5	[2-7]	1	4
Movement Disorders specialists (n=14)	5	[2-7]	1	7	4	[0-6]	0	0
Specialized PD nurses (n=12)	4	[1-7]	2	17	4	[1-7]	1	8
Miscellaneous professionals (n=9)	7	[3-7]	5	56	3	[2-7]	4	44
Total (n=320)	**6**	**[0-7]**	**113**	**35**	**5**	**[0-7]**	**74**	**23**
ParkinsonNet affiliated (n=224)	6	[1-7]	86	38	5	[0-7]	59	26
Not affiliated (n=96)	6	[0-7]	27	28	5	[0-7]	15	16

[a] Referring to the application of the strategies in general, not within one individual person with Parkinson's disease.

Most respondents (55%) indicated that a lack of knowledge and skills concerning certain categories of compensation strategies was the main reason why they did not apply all categories in practice. Interestingly, while the majority of professionals reported their search for a suitable strategy to be a trial-and-error process (87%), which is a time-consuming approach, lack of time was not an important reason to refrain from applying all seven categories in clinical practice (8%).

Finally, a striking 88% of professionals indicated that they would like to receive additional training in the available compensation strategies for gait impairments. Also, 86% of professionals reported a need for additional patient information on the available strategies.

Discussion

These findings identify a knowledge and skills gap concerning the application of compensation strategies for gait impairments in PD.

Compared to a previous study conducted in 2009, internal and external cueing strategies for gait impairments in PD are currently applied by a higher percentage of physical therapists (94% now vs. 73% then).[7] Unfortunately, the other categories of compensation strategies are less widely known, and certainly less widely applied. This discrepancy between cueing strategies and the five remaining categories of compensation strategies may reasonably be explained by the fact that internal and external cueing have been most extensively studied and reported, whereas a category such as action observation and motor imagery is still relatively new. Because the efficacy of different strategies may well vary between PD patients, and even vary within a single patient depending on the context, it is especially important to broaden the professionals' treatment palette of available strategies beyond internal and external cueing.

Undoubtedly, the effectiveness and feasibility of different categories of strategies, as well as possible personal preferences, will affect a healthcare professional's decision to apply certain strategies while treating patients with PD and gait impairments. This may explain our finding that professionals often do not apply all categories known to them in daily practice. Further studies may focus on the experiences of patients to identify the efficacy and usability of the different categories of compensation strategies. They should also explore whether the efficacy of the different strategies could be predicted based on individual patient characteristics (e.g. presence of a specific phenotype of freezing of gait, or severity of any cognitive impairments). That way, a more personalized approach to gait rehabilitation in PD could be achieved, and be integrated in evidence-based protocols.[8-9] Such an inventory could be achieved by taking advantage of online opportunities such as the Fox Insight cohort from the Michael J Fox Foundation (USA), or ParkinsonNEXT (NL).

Considering the study design, which included a high risk of selection bias, and the fact that this study was conducted in a country with a high-standard network such as ParkinsonNet, our current findings may overestimate the global knowledge and application of compensation strategies among healthcare professionals. The relatively high level of awareness regarding compensation strategies most probably is due to the increased attention that has long been paid to the complex therapy of PD in the Netherlands. Examining whether the knowledge and application of

compensation strategies for gait impairments in PD is less widespread in countries without such a network may be a topic of future research. Integrating the use of compensation strategies into educational programs, or developing a dedicated online platform about the various available strategies, might facilitate finding a suitable strategy for every person with PD who experiences gait impairments.

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1 2 3 4

Part II

Systematic evaluation of compensation strategies

Video vignette II

Most people with Parkinson's disease, and Parkinson's disease healthcare providers have heard of using cues to improve gait. Examples include: stepping over lines, or walking to the beat of music. However, this is just the tip of the iceberg of the broad and ever-expanding spectrum of available compensation strategies. Video vignette II shows a compilation of creative strategies that people with Parkinson's disease have discovered on their own.

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Perception and use of compensation strategies for gait impairment by persons with Parkinson's disease

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Abstract

Background

Gait impairments are common and disabling in Parkinson's disease (PD). Applying compensation strategies helps to overcome these gait deficits. Clinical observations suggest that the efficacy of different compensation strategies varies depending on both individual patient characteristics and the context in which the strategies are applied. This has never been investigated systematically, hampering the ability of clinicians to provide a more personalized approach to gait rehabilitation.

Objective

We had three aims: (1) to evaluate patients' awareness and actual use of compensation categories for gait impairments in PD; (2) to investigate the patient-rated efficacy of the various compensation strategies, and whether this efficacy depends on the context in which the strategies are applied; and (3) to explore differences in the efficacy between subgroups based on sex, age, disease duration, freezing status, and ability to perform a dual task.

Methods

A survey was conducted among 4,324 adults with PD and self-reported disabling gait impairments.

Results

The main findings are: (1) compensation strategies for gait impairments are commonly used by persons with PD, but their awareness of the full spectrum of available strategies is limited; (2) the patient-rated efficacy of compensation strategies is high, but varies depending on the context in which they are applied; and (3) compensation strategies are useful for all types of PD patients, but the efficacy of the different strategies varies per person.

Conclusions

The choice of compensation strategies for gait impairment in PD should be tailored to the individual patient, as well as to the context in which the strategy needs to be applied.

Introduction

Gait impairments are common and are reckoned among the most disabling symptoms of Parkinson disease (PD). They often give rise to falls and fall-related injuries and decreased functional mobility, independence, and quality of life.[1-3] Gait disturbances in PD can be continuously present (i.e., smaller step length, slower gait speed, or higher gait variability) or, as the disease progresses, become more episodic in nature (e.g., bouts of festination or freezing of gait [FOG]).[4,5] Episodic gait deficits such as FOG may occur when the patient initiates gait, turns, or attempts to cross a narrow space (e.g., passing a doorway); when the patient is anxious; or when the patient performs a concurrent task while walking (e.g., talking or carrying a tray).[6-8]

Dopaminergic treatment alone is seldomly satisfactory in ameliorating these disabling gait impairments, especially with increasing disease duration.[9,10] Remarkably, patients often spontaneously invent creative "detours" to overcome their walking difficulties in order to remain mobile and independent. These so-called compensation strategies can be very diverse; examples include walking paced by the rhythm of a metronome or by imaginary counting, mimicking the gait of another person, resorting to an adapted walking pattern (e.g., walking backward, lifting the knees up high), or using alternative ways to move forward such as roller skating. A wide range of different compensation strategies has been reported, typically in the form of anecdotal case reports, describing a typically self-invented solution that apparently worked very well for that particular individual.[11-13] Recently, a comprehensive overview of compensation strategies to overcome gait impairments was published in which a conceptual framework of seven separate overarching categories of compensation strategies was proposed based on their suspected underlying working mechanisms (Table 1).[14]

Clinical observations suggest that a certain compensation strategy may be highly effective in one person but may have no effect on or even aggravate gait disability in another person. Furthermore, even within one individual, a specific strategy may have different effects depending on the context in which it is applied (e.g., when preparing food in the kitchen vs when walking outside).[15-17] To date, this has not been systematically investigated, hampering the ability of health care professionals to provide a more tailored, personalized approach to gait rehabilitation for persons with PD. Consequently, in current daily practice, the search for appropriate compensation strategies for a given person with PD remains a time-consuming trial-and-error process. Moreover, individual patients are rarely offered an opportunity to systematically try out the multiple different variants of compensation strategies until they find a specific one that suits their needs and abilities best.

Table 1. Proposed categorization of compensation strategies[14]

Compensation category	Description	Phenomenology
External cueing	Typically rhythmic external stimuli, that may be auditory, somatosensory, or visual.	Walking to the beat of a metronome; wearing vibrating socks; stepping over lines.
Internal cueing	Focusing attention on (predetermined components of) gait.	Self-prompting; mental arithmetic.
Changing the balance requirements	Facilitating the ability to make lateral weight shifts.	Shifting weight in place prior to stepping; making wider turns; using walking aids.
Altering the mental state	Enhancing general alertness and arousal, leading to increased motivation or relaxation.	Breathing exercises; other measures to limit anxiety or fear of falling.
Action observation and motor imagery	NA	Mimicking another person walking; Visualizing the desired movement.
Adopting a new walking pattern	Changing the straight gait pattern, or using other forms of locomotion.	Scissoring; knee lifting; jumping; running; walking backwards.
Other forms of using the legs to move forward	NA	Bicycling; skateboarding; crawling.

NA = not applicable.

To address this issue, we conducted an international web-based survey among persons with PD experiencing gait impairments. The aim of this study was three-fold: (1) to evaluate the participants' awareness and use of the various compensation categories for gait impairments in PD, (2) to investigate the patient-rated efficacy of compensation strategies and whether this depends on the context in which the strategies are applied, and (3) to explore whether different patient subgroups (defined by sex, age, disease duration, freezing status, and ability to perform a dual task) might respond differently to certain types of compensation strategies.

Methods

Study design

A web-based survey was distributed among 6,700 participants within the Fox Insight cohort, as well as 1,573 Dutch participants via ParkinsonNEXT (the Netherlands). Fox Insight is a longitudinal, virtual, patient-centered observational study on PD led by the Michael J. Fox Foundation. Data used in the preparation of this article were obtained from the Fox Insight database on June 1, 2020. For up-to-date information on the study, interested readers should visit the Fox Insight website. ParkinsonNEXT

is an online platform that aims to unite patients, researchers, and clinicians wanting to contribute to research and innovation in PD or parkinsonism. The online survey was accessible from March to June 2020. Respondents >18 years of age with a self-reported diagnosis of PD and self-reported disabling gait impairments were included in the analyses.

The survey consisted of three parts. The first part asked about sex, age, time since PD diagnosis, and the presence and severity of gait impairments. Moreover, the presence and severity of FOG were assessed with the New Freezing of Gait Questionnaire.[18] They were also asked about their fall history over the preceding 12 months. The second part of the survey addressed the seven main categories of compensation strategies (Table 1).[14] One by one, each specific category was explained and illustrated by several practical examples. Participants were then queried whether they were aware of the category of strategies, whether they had ever applied a strategy belonging to that category, and, if so, how application of this strategy had affected their gait in a variety of contexts. These contexts included gait initiation, turning, stopping, passing a doorway, walking in narrow spaces, walking outdoors, walking in a crowded area, walking while talking, walking while carrying something, performing activities of daily living, and time-pressure situations. Respondents could indicate whether applying the strategy in that specific context improved their gait, had no effect on their gait, or worsened their gait. The third part of the survey examined the participants' interest to learn more about compensation strategies for gait impairments in PD. At the end of the survey, respondents were given an open-ended opportunity to share any new compensation strategies other than the ones already presented in the overview. In all cases, the mentioned strategies fitted into one of the seven proposed categories and were therefore migrated to the corresponding categories.

For Fox Insight respondents, data from a preexisting Fox Insight questionnaire, Your Cognition and Daily Activities, were also included in the analyses. No data on cognition were available for respondents from the ParkinsonNEXT cohort.

Data processing and analysis

According to the free-text entries that respondents had provided, data were verified and manually corrected by two independent researchers (AT, LW) to ensure that all recorded compensation strategies were completed under the appropriate corresponding category. All (descriptive) statistical analyses were performed in IBM SPSS 25 (SPSS, Inc, Chicago, IL). Any missing values were excluded from the analyses.

Independent t tests (means) and χ2 tests (proportions) were performed to assess subgroup differences. Values of $p < 0.05$ were considered to be statistically significant.

Results

Study population

In total, 4,987 responses were collected via Fox Insight (response rate 74.4%) and 845 via ParkinsonNEXT (response rate 53.7%). The 1,508 persons who did not report disabling gait impairments were excluded. Characteristics of the included sample of 4,324 respondents are presented in Table 2. Differences in the main characteristics of responders vs non-responders from the ParkinsonNEXT cohort were not clinically relevant in terms of sex distribution (62.1% vs 64.6% men), age (66.4 years vs 64.5 years), and disease duration (6.5 years vs 5.9 years since diagnosis). These data were not available for the Fox Insight sample.

Of the 4,324 persons with gait impairments who were included, 35.3% found that their walking difficulties negatively affected their ability to perform their usual daily activities. Of note, 52.4% of respondents had experienced ≥1 falls in the preceding 12 months, resulting in injury that had required medical attention in 385 cases.

Table 2. Characteristics of included respondents

	Total cohort	Fox Insight	ParkinsonNEXT	*p*-value
Respondents (n)	4324	3663	661	
Men (n (%))	2387 (55.3)	1960 (53.6)	427 (64.6)	<0.001[a]
Age (years)	67.8 ± 9.0	68.0 ± 9.0	66.4 ± 8.6	<0.001[a]
Time since diagnosis (years)	6.7 ± 5.3	6.7 ± 5.4	6.5 ± 4.6	0.51
Respondents with FOG (n (%))	1851 (42.8)	1652 (45.1)	199 (30.1)	<0.001[a]
NFOG-Q score[b] (median [range])	17 [1-28]	17 [1-24]	17 [5-28]	0.03[a]

Values are represented as mean ± SD, unless otherwise specified. NL = Netherlands; FOG = Freezing of gait; NFOG-Q = New Freezing of Gait Questionnaire (score range 0-28).[18]

[a] Statistically significant difference between Fox Insight cohort and ParkinsonNEXT cohort, as determined by independent samples t-test (means) or chi-square test (proportions).

[b] Among respondents with freezing of gait, defined by a non-zero NFOG-Q score.

Data from the Fox Insight questionnaire Your Cognition and Daily Activities were available for 3,586 of 3,663 (97.9%) respondents from the Fox Insight cohort enrolled in the present study. The majority of these respondents had little to no difficulties

performing cognitive tasks in daily life. Specifically, most respondents had little to no difficulties reading the newspaper or a magazine (88.7%); keeping track of time (e.g., using a clock) (96.1%); counting the correct amount of money when making purchases (96.8%); reading or following complex instructions (e.g., directions for a new medication) (90.9%); handling an unfamiliar problem (e.g., getting the refrigerator fixed) (88.0%); explaining how to do something involving several steps to another person (84.0%); remembering a list of four or five errands without writing it down (69.1%); using a map to tell where to go (92.1%); remembering new information such as phone numbers or simple instructions (77.2%); doing >1 thing at a time (76.0%); learning to use new gadgets or machines around the house (84.2%); understanding their personal financial affairs (92.5%); maintaining or completing a train of thought (92.5%); discussing a TV show, a book, a movie, or current events (88.5%); or remembering what day and month it is (93.8%). Fewer than 1% of respondents indicated that they were completely incapable of performing ≥1 of these daily activities.

Awareness of compensation strategies

Of all respondents, 16.7% had never heard of any of the compensation strategies before. Only a small group (3.5%) was aware of all seven categories of compensation strategies. The median number of categories that respondents were aware of was three. Apart from the use of walking aids and alternatives to walking, external cueing was the most widely known category of compensation strategies (46.9% had heard of it), followed by internal cueing (44.8%). Action observation and motor imagery was the least known category (14.3%). Dutch respondents from the ParkinsonNEXT cohort generally knew more categories of strategies (median: 4) compared to respondents from within the Fox Insight cohort (median 3; $p < 0.001$).

Most respondents had read about the strategies themselves (35.0%), had heard about the strategy from their physical therapist (29.6%), or had invented the strategies themselves (12.5%). One in three participants (32.2%) had ever received targeted advice from a professional focused on the use of compensation strategies for gait impairments in PD. Notably, 75.2% of respondents indicated that they would be interested to learn more about the available compensation strategies.

Use of compensation strategies

Of all respondents, 22.8% had never tried any form of compensation strategies before, despite experiencing clear and sometimes disabling gait impairments. Fewer than 1% of respondents had tried all seven categories of compensation strategies. The median number of categories that respondents had ever tried was two. Adapting a new walking pattern was tried most often (78.4% of respondents who were aware of it had ever tried it), followed by internal cueing (76.8%). Alternatives to walking was the least tried category (28.3%).

Overall, 64.7% of respondents still used one or more compensation strategies in daily life. Compensation strategies were most often used when walking outdoors or in time-pressure situations and were least often applied when attempting to stop walking or cross a doorway. The median number of categories used in daily life was one. Changing the balance requirements was the most widely used category. Among the 1,729 users of this category, 429 (24.8%) respondents used walking aids only, whereas 1,300 (75.2%) also used other balance strategies (e.g., making a volitional weight shift to initiate gait). After changing the balance requirements, internal cueing was most often applied in daily life (71.7% of respondents who had tried it continued to use it), followed by altering the mental state (70.5%). External cueing was the least used category (55.3%).

Among the respondents using compensation strategies, 12.4% reported that they had felt obliged to switch to different strategies over time. Most often, this was due to PD progression, rendering some strategies too difficult or dangerous to apply (e.g., riding a bicycle). Another illustrative example included switching from walking over lines pasted to the floor to using a specialized Parkinson wheeled walker that is able to project a laser line on the floor. We found no suggestion that the effect of a certain strategy tapered off over time due to habituation.

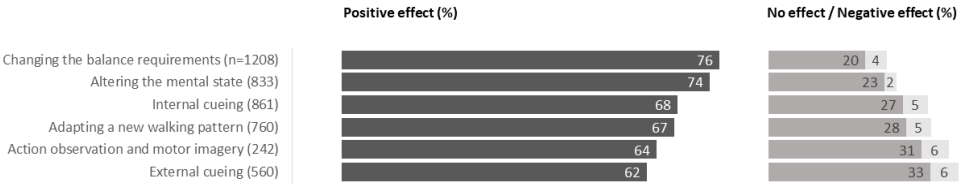
Patient-reported efficacy of compensation strategies

The patient-reported efficacy of the different categories of compensation strategies is presented in Figure 1. While most respondents reported that the application of compensation strategies positively affected their gait, not every respondent seemed to benefit from every category of strategies. When the efficacy of the strategies was averaged across contexts, changing the balance requirements had the highest success rate in improving gait (76%), whereas external cueing showed the relatively lowest success rate (62%).

The efficacy of compensation strategies varied greatly, depending on the context in which they were applied (Figure 2). Internal cueing, for example, seemed highly effective during gait initiation (73% success rate) but was deemed to be less useful when attempting to stop walking (47%). Similarly, action observation and motor imagery could be a successful strategy when walking outdoors (83% success rate) but seemed to be less helpful when applied in a narrow space (55%). In general, compensation strategies were most effective when walking outdoors (84% success rate) or during gait initiation (79%). Strategies were deemed least effective during an attempt to stop walking (54% success rate) or cross a doorway (65%). While reports of negative effects of compensation strategies were relatively scarce (this occurred in ±3% of cases), paradoxical aggravation of gait deficits was occasionally reported in stress-inducing or dual-task situations, including time-pressure situations (6%), walking in narrow spaces or crowded areas (7%), and walking while talking or carrying something (7%).

Sample size represents the number of respondents who indicated that they had ever tried that specific category of strategies. Values represent the percentage of respondents experiencing a positive effect averaged across all contexts to provide an overall indication of efficacy.

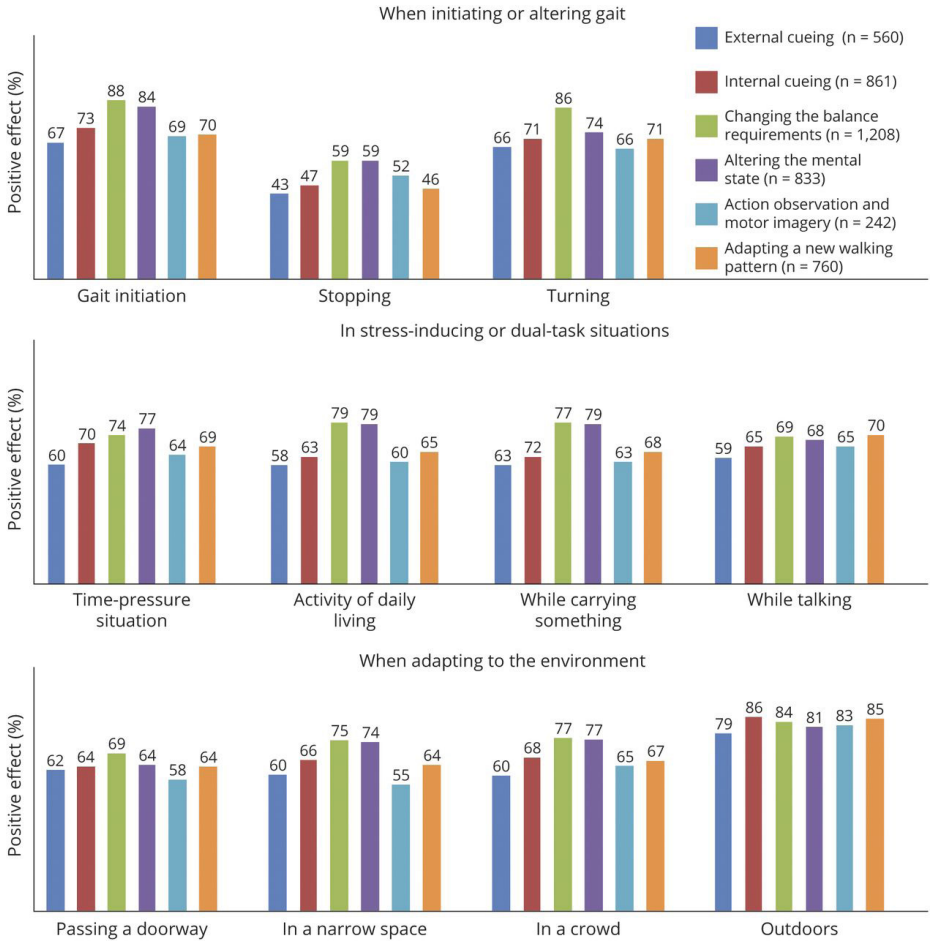
Figure 1. Overall patient-reported efficacy of different compensation strategies for gait impairment in Parkinson's disease



Subgroup data

The awareness and use of compensation strategies for gait impairments in PD did not differ between subgroups based on sex, freezing status, age (cut-off: 65 years), time since diagnosis (cut-off: 5 years), and the ability to perform a dual task (persons with little to no difficulties vs persons with more severe difficulties). There were also no differences in the reported efficacy of different strategies between these subgroups except for a slightly higher success rate among younger patients for external cueing and adopting a new walking pattern and among persons who had little to no difficulty dual tasking for motor imagery and action observation (Table 3).

Figure 2. Patient-reported efficacy (% positive effect) of different compensation strategies, depending on the context in which they were applied



Values represent the percentage of users experiencing a positive effect on gait impairments while applying a specific strategy in a specific context.

Table 3. Subgroup-reported efficacy (% positive effect) of different compensation strategies

	Men	Women	FOG+	FOG-	<65yrs old	>65yrs old	<5yrs since PD diagnosis	>5yrs since PD diagnosis	No/little difficulties dual tasking[a]	More difficulties dual tasking[a]
External cueing (n=560)	60.2	63.2	62.4	58.9	**66.4**[b]	**59.4**[b]	63.0	61.6	63.3	59.7
Internal cueing (n=861)	67.0	68.6	67.8	66.6	71.9	65.7	68.5	67.4	69.5	68.3
Changing the balance requirements (n=1208)	73.4	79.3	76.6	75.1	76.7	75.9	77.1	75.4	78.2	74.6
Altering the mental state (n=833)	72.7	76.1	75.9	71.4	73.5	74.6	73.6	74.5	76.3	72.5
Action observation & motor imagery (n=242)	65.8	60.0	61.8	65.5	66.9	62.0	66.8	60.9	**69.4**[d]	**58.8**[d]
Adapting a new walking pattern (n=760)	66.5	67.8	67.6	66.0	**71.9**[c]	**65.2**[c]	69.5	66.0	69.6	68.0

Sample sizes represent the number of respondents who indicated to have ever tried that specific category of strategies. Values represent the percentage of respondents experiencing a positive effect averaged across all contexts to provide an overall indication of efficacy. Comparative analyses were performed using a chi-square test. FOG+ = freezers; FOG- = non-freezers; PD = Parkinson's disease.

[a] Based on the Fox Insight questionnaire "Your cognition and daily activities": how much difficulty do you experience doing more than one thing at a time?

[b] p=0.04

[c] p=0.05

[d] p=0.01

Discussion

A web-based survey among 4,324 persons in the Fox Insight and ParkinsonNEXT (the Netherlands) cohorts was conducted to make an inventory of patients' perceptions of compensation strategies for gait impairments in PD. The main findings of this study were as follows: (1) compensation strategies are commonly used by persons with PD and gait impairments, although their awareness of the full spectrum of available strategies is limited; (2) the patient-rated efficacy of compensation strategies is high but varies depending on the context in which they are applied; and (3) the efficacy of compensation strategies varies per person, emphasizing the need for a more personalized approach to gait rehabilitation in PD. We discuss these findings in further detail below.

First, considering the severity of walking difficulties that respondents expressed, we consider the awareness of the full spectrum of compensation strategies among persons with PD to be rather limited. The median number of known categories was three of seven, and a striking one in five patients had no prior awareness of any of the compensation strategies for gait impairments. About half of the respondents had acquired this knowledge themselves through reading or personal experience. Notably, only one in three patients had ever received targeted advice from a professional, focused specifically on strategies to overcome gait impairments. Moreover, only 1% of patients had tried strategies from all seven categories available. A previous study among health care professionals in the Netherlands demonstrated that only 23% of PD health care professionals (i.e., physiotherapists, occupational therapists) apply all seven categories of compensation strategies in clinical practice when working with patients with PD experiencing gait impairments due to the lack of specific knowledge and skills in this field.[19] Considering that PD care in the Netherlands is organized in a high-standard professional network of therapists who have received dedicated PD-specific training and treat large numbers of patients (ParkinsonNet),[20] this percentage might be an overestimation of the global knowledge and application of compensation strategies among PD health care professionals. This may also explain why Dutch respondents from ParkinsonNEXT knew more strategies than respondents from Fox Insight.

Regardless of the underlying explanations, it is evident that both persons with PD and PD health care professionals[19] are interested in learning more about compensation strategies. Integrating the use of compensation strategies into educational programs or developing a dedicated online platform about the various available strategies might facilitate finding a suitable strategy for every person with PD who experiences

gait impairment. This notion is underscored by the present findings showing that the application of a single strategy is often insufficient because different contexts may require different types of strategies or because individual patients simply respond better to one specific strategy compared to another. In addition, our findings show that the feasibility of a previously successful strategy may diminish over time because of progression of disability, emphasizing the need to have a broader spectrum of compensation strategies available so that a customized renewed approach can be identified for any given individual patient. In the present work, we did not investigate whether knowing more compensation strategies positively affected a person's perceived quality of life, but this could be a topic of future investigations.

Second, the overall patient-rated efficacy of compensation strategies is high across all seven categories. While the main body of scientific work on compensation strategies has thus far focused on external cueing, perhaps because external cueing is easily controllable in a laboratory setting,[21-24] it is the least effective category according to patients. Unsurprisingly, because it is the most commonly known and applied category among PD health care professionals,[19] the existence of external cueing was widely known among respondents. Yet, only few patients actually applied external cues in their daily lives. In contrast, strategies changing the balance requirements and altering the mental state were deemed to be most effective and were accordingly most often used. These categories may be more accessible and feasible for persons with PD because they typically do not require specific devices (e.g., laser shoes, a metronome) or adaptations to the environment (e.g., 2- or 3-dimensional patterns on the floor). They may also be preferred because they are relatively less noticeable to bystanders, avoiding stigmatization or feelings of embarrassment.[25,26] Therefore, our findings reinforce the notion that all categories of compensation, not just external cueing, deserve further systematic investigation.

The effects of compensation strategies vary depending on the context in which they are applied, underlining the importance of a tailored approach to gait rehabilitation. We were struck by the relatively modest effect of compensations strategies during attempts to stop walking. More work is needed to clarify why gait termination is less influenced by the application of compensation strategies and what alternative strategies could be developed to ameliorate this.

Another notable finding was that some respondents experienced a negative effect of compensation strategies during stress-inducing or dual-task situations. In PD, gait deficits are generally exacerbated while dual tasks are performed because the need to concentrate on executing the concurrent task interferes with the patient's ability

to focus purposefully on gait.[27-29] Compensation strategies are believed to aid in prioritizing tasks and in allocating attention to gait.[14] However, the introduction of an additional task, namely the application of a compensation strategy, might exceed the attentional resources in certain individuals, causing a paradoxical aggravation of walking difficulties instead of an improvement.[17] This is also reflected in the present study by the slightly higher efficacy ratings of respondents with little to no difficulties with dual tasking compared to respondents with more difficulties with dual tasking.

Third, the efficacy of compensation strategies varies per person. Exploratory subgroup examinations based on age, sex, freezing status, and disease duration, however, did not demonstrate truly remarkable differences in the patient-rated efficacy of the different categories of compensation strategies. In general, compensation strategies seem to be useful in all types of patients with PD, and further work is needed to investigate optimal predictors of the effects of the different types of strategies for individual patients. Ideally, this would be investigated in a prospective clinical trial in which a clinician could also examine the severity of gait impairments present and the efficacy of the different strategies could be quantified with the use of more objective measures (e.g., improvement of spatiotemporal gait parameters, including gait variability).

Our study was not without shortcomings, and some of our findings should be interpreted with caution. Participants of both cohorts may well have been a selected and rather proactive sample of the overall PD population. Although the response rate was high for a survey study, particularly in the Fox Insight cohort, respondents may have been the most informed or motivated persons with PD. In addition, we were unable to retrieve information on the main characteristics of non-responders from within the Fox Insight sample. The self-reported nature of the survey is further reason for caution, for example, because the extent of the gait disability could not be confirmed by an independent neurologic examination. Because PD diagnosis is also self-reported, we cannot exclude the possibility that some patients in fact had a form of atypical parkinsonism, which may respond in a different way to compensation strategies than PD. At the same time, it is quite possible that persons with atypical parkinsonism will also benefit from compensation strategies, and such compensation may be particularly important for these patients because medication is generally much less effective in improving their gait impairments. Another limitation of our study is the lack of objective information about the respondents' cognitive status; cognitive deficits may impede the ability to use particular categories of compensation strategies.[17,30] It is possible that a certain degree of cognitive reserve

is imperative to be able to compensate for gait impairments.[31] The potential effect of impaired cognition might be particularly relevant for compensation strategies that are inherently cognitive tasks such as internal cueing (e.g., counting while walking). Further studies should aim to include a more heterogeneous study population in terms of cognitive status and include more objective measures of cognition (e.g., the Mini Mental State Examination or Montreal Cognitive Assessment) to gain more insight into the interplay between cognition and the ability to compensate for gait impairment in PD.

The present findings support the application of compensation strategies for gait impairments in PD and emphasize that a one-size-fits-all approach to gait rehabilitation is inappropriate. Persons with PD should be—and wish to be—more thoroughly informed about the range of available strategies. The choice of compensation strategies should be tailored to the individual patient and to the contexts in which the strategies need to be applied. Further prospective studies are vital to further crystallize these findings and eventually incorporate them into evidence-based protocols, thus paving the way toward a more personalized approach to gait rehabilitation in PD.

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Evaluation of compensation strategies for gait impairment in patients with Parkinson's disease

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Abstract

Background and Objectives

Compensation strategies are essential in Parkinson's disease (PD) gait rehabilitation. However, besides external cueing, these strategies have rarely been investigated systematically. We aimed to: (1) establish the patients' perspective on the efficacy and usability of five different compensation strategies; (2) quantify the efficacy of these strategies on spatiotemporal gait parameters; and (3) explore associations between the effects of specific strategies and patient characteristics.

Methods

We recruited persons with PD and self-reported disabling gait impairments for this lab-based, within-subject study. Clinimetrics included: questionnaires (NFOG-Q, VMIQ-2, GMSI), cognitive assessments (ANT, MoCA, Brixton), and physical examinations (MDS-UPDRS III, Mini-BEST, tandem gait, rapid turns test). Gait assessment consisted of six 3-minute trials of continuous walking around a 6-meter walkway. Trials comprised: 1) baseline gait; 2) external cueing; 3) internal cueing; 4) action observation; 5) motor imagery; and 6) adopting a new walking pattern. Spatiotemporal gait parameters were acquired using 3D motion capture analysis. Strategy efficacy was determined by the change in gait variability compared to baseline gait. Associated patient characteristics were explored using regression analyses.

Results

101 participants (50 men; median[range] age: 66[47-91] years) were included. The effects of the different strategies varied greatly among participants. While participants with higher baseline variability showed larger improvements using compensation strategies, participants without freezing of gait, with lower MDS-UPDRS III scores, higher balance capacity and better performance in orienting attention, also showed greater improvements in gait variability. Higher MoCA scores were associated with greater efficacy of external cueing.

Discussion

Our findings support the use of compensation strategies in gait rehabilitation for PD, but highlight the importance of a personalized approach. Even patients with high gait variability are able to improve through the application of compensation strategies, but certain levels of cognitive and functional reserve seem necessary to optimally benefit from them.

Introduction

Gait impairment is common and disabling in individuals with Parkinson's disease (PD). Reduced stride length, increased gait variability, and reduced arm swing are examples of continuous gait deficits that typically occur in persons with PD. As the disease progresses, episodic gait deficits, including freezing of gait (FOG) and festination, can also come into play.[1,2] The presence of gait impairment often leads to falls and fall-related injuries and significantly impacts functional mobility, independence, and quality of life.[3-5]

As dopaminergic medication and deep brain stimulation usually have an only moderate effect on gait impairment, the application of compensation strategies has become an essential part of gait rehabilitation in PD.[6-8] These strategies are typically self-invented by persons with PD, and comprise a wide range of 'detours' to overcome gait impairment and improve functional mobility. Examples include improved gait when walking to the beat of music, counting while walking, walking backwards, climbing stairs, or when walking on a floor with a specific visual pattern.[9,10] While often applied in the context of FOG, compensation strategies also improve continuous gait deficits.[11,12]

To date, compensation strategies in PD have usually been reported in the form of anecdotal case reports.[13-16] With the exception of external cueing (e.g. rhythmic auditory stimulation), the efficacy of these strategies has rarely been investigated in a systematic manner. In 2019, a comprehensive framework of seven distinct categories of strategies was proposed: external cueing, internal cueing, changing the balance requirements, altering the mental state, action observation or motor imagery, adopting a new walking pattern, and alternatives to walking.[9] This framework served as the basis for a large-scale survey on the perception of compensation strategies in 4,324 persons with PD and gait impairment, providing Class IV evidence that compensation strategies are effective.[11] However, the study also confirmed that the efficacy of specific strategies varies per person, highlighting the need for an individually tailored approach. It is still insufficiently understood what the underlying working mechanisms of these strategies are, and which patient characteristics may be associated with the individual efficacy of the various compensation strategies. This is hampering the ability of healthcare professionals to provide much-needed personalized gait rehabilitation.

In this study we evaluated the efficacy of five different categories of compensation strategies: external cueing, internal cueing, action observation, motor imagery, and

adopting a new walking pattern. We had three aims: (1) to establish the patients' perspective on the efficacy and usability of the different strategies; (2) to quantify the efficacy of the strategies on spatiotemporal gait parameters; and (3) to explore whether the effects of specific strategies on gait are associated with certain patient characteristics.

Methods

Study population

We predefined a target of 100 participants (grant proposal available upon request). Participants were recruited from a large on-going observational trial (PRIME-NL)[17], and ParkinsonNEXT (NL), an online recruitment platform for PD and parkinsonism research. Inclusion criteria were: presence of PD and self-reported gait impairment hindering usual daily activities. Exclusion criteria were: co-morbidity significantly impacting ambulation (e.g. stroke, orthopedic ailments); inability to walk unaided (or with a customary cane) for three minutes consecutively; severe auditory impairment hampering the perception of auditory cues; and severe cognitive impairment hampering the ability to comply to the study protocol.

Written informed consent was obtained from all study participants, in accordance with the principles of the Declaration of Helsinki. This study was approved by the local ethics committee CMO Arnhem-Nijmegen, and the Institutional Review Board of the Radboud University Medical Center in Nijmegen, the Netherlands (Ref: 2019-5710).

Experimental protocol

In a one-time study visit to the Radboud University Medical Center gait laboratory, participants completed three questionnaires, performed several clinical tests, and underwent detailed gait assessment. Participants did not have to withdraw from their dopaminergic medication prior to the visit, but refrained from taking renewed dosages of dopaminergic medication for the duration of the four-hour visit. Consequently, clinical tests were performed in the dopaminergic ON-state, but gait assessment - at the end of the visit - was performed in 'end-of-dose OFF'. We specifically opted for this approach, as persons with PD typically experience most gait difficulties during this period, making it the clinically most relevant state to employ any compensation strategies. Participants with deep brain stimulation (DBS) did not have to adjust their stimulation settings.

Questionnaires and clinimetrics

Participants completed three questionnaires: the New Freezing of Gait Questionnaire (NFOG-Q),[18] the Vividness of Movement Imagery Questionnaire (VMIQ-2),[19] and an adapted version of the Goldsmiths Musical Sophistication Index (to quantify one's musical abilities).[20] Cognitive assessment included the Montreal Cognitive Assessment (MoCA) as a measure of overall cognitive status,[21] the short version of the Revised Attentional Network Test (ANT) - a computerized test measuring three attentional processes (alerting, orienting, and executive attention, expressed as network scores),[22] and the Brixton Spatial Anticipation test as a measure of executive function - assessing rule detection and concept shifting (age- and education adjusted percentile scores).[23] These tasks have been used in PD populations before.[24] Physical examination comprised the MDS-UPDRS part III,[25] the Mini-Balance Evaluation Systems Test (Mini-BEST),[26] tandem gait (walking heel-to-toe in a straight line for ten consecutive steps without taking balance correcting side steps),[27] and the rapid turns test for FOG detection (making three 360° turns in place, in both directions).[28]

Gait assessment

Gait assessment consisted of six three-minute trials of continuous walking around a six-meter instrumented walkway. The first trial always entailed the baseline gait condition, in which participants walked without applying any compensation strategies. The remaining five trials comprised the compensation strategy conditions in which patients applied: (1) external cueing; (2) internal cueing; (3) action observation; (4) motor imagery; and (5) adopting a new walking pattern. The remaining three categories proposed by Nonnekes et al.[9] were not included: (1) altering the mental state (as it is difficult to control in a lab setting), (2) changing balance requirements (as it applies to turning and initiating gait) and (3) alternatives to walking (as gait variability is not an applicable outcome measure). The compensation strategy conditions were counterbalanced across participants, with the exception of motor imagery, which was always preceded by action observation. Participants were instructed to walk at a comfortable speed, and refrain from talking, consciously varying gait speed, or using a strategy other than the one specified.

The strategy choice within each category was based on feasibility: participants had to be able to apply them without extensive training, and they had to be easy to implement in daily life after the experiment. During external cueing, participants listened to a metronome (Metronome v1.2, BEIJING BULUOBANG CO., LTD) and synchronized their steps to the beat. Metronome pace was customized by a trained researcher, matching or optimizing the participant's natural cadence as determined during baseline gait. Participants had the final say in determining the optimal

pace. During internal cueing, participants silently counted in a rhythmic manner (e.g. 1-2-3-4-1-2-3-4) and synchronized their steps to the beat. During action observation, participants walked alongside a trained researcher and synchronized their steps. During motor imagery, participants consciously thought about the preceding action observation condition, and visualized the researcher walking alongside them, synchronizing their steps. During adopting a new walking pattern, participants walked with exaggerated arm swing. Participants practiced each strategy until they felt comfortable.

After each trial, participants indicated whether the strategy had any subjective effect (positive, negative, or no effect compared to baseline gait). Finally, participants rated the probability of them continuing to use that strategy in daily life, using a 5-point Likert scale (1: Very unlikely – 5: Very likely).

Motion data acquisition and analysis

Movement data were acquired using a motion capture system (VICON, Oxford, UK; sampling rate: 100Hz). Sixteen markers were placed following the Plug-in Gait Lower Body Model.[29]

Strategy efficacy was determined by the difference in gait variability between baseline gait and each of the compensation strategy conditions. Gait variability was the predefined primary outcome, as it is associated with fall risk in PD and other populations.[30-32] Variability was expressed as the coefficient of variation (CV) of stride time: stride time CV = (SD stride time/mean stride time)×100%. Stride time was defined as the time between subsequent heel strikes of the same foot, and computed using a custom MATLAB script. Heel strikes were identified as (local) minima of the vertical displacement of the heel markers within the gait cycle. To negate the effects of the 180° turns (and associated deceleration/acceleration) at both ends of the walkway, only the center three meters of the trajectory were included in the analysis.

Statistical analysis

Data analysis was performed in IBM SPSS 25 (SPSS, Inc., Chicago, IL, USA). Group-level differences in gait parameters between baseline gait and gait with compensation strategies were examined using paired two-tailed t-tests with Bonferroni correction for multiple comparisons. For each strategy, the relationship between the predetermined primary outcome measure (change in stride time variability from baseline) and change in gait speed from baseline was assessed using Pearson correlation.

We investigated the association between participant characteristics and strategy efficacy using a two-step approach. Exploratory analyses using unpaired two-tailed t-tests were conducted to compare the characteristics of responders (Q1 in terms of improvement in gait variability compared to baseline gait) to non-responders (Q4) for each compensation strategy, to identify potentially relevant variables. These variables were entered into a univariable linear regression analysis, adjusted for baseline gait variability. Finally, all associated variables were entered into a stepwise regression analysis with forward selection. $P<0.05$ was considered statistically significant.

Results

Study population

We included 101 participants. Participant characteristics are outlined in Table 1; reflecting the desired clinical heterogeneity for the purpose of this study. Three participants did not complete all six gait conditions due to fatigue. Consequently, data on external cueing and motor imagery were available for 99/101, and action observation for 100/101 participants.

Most participants (87%, 87/101) reported to have previously tried compensation strategies in daily life. The median number of strategies tried/currently used was two, most often entailing internal cueing strategies (e.g. counting).

Efficacy and usability of compensation strategies

The efficacy and usability of the five compensation strategies is presented in Table 2. The effect of the strategies on spatiotemporal gait parameters varied greatly across participants (see also: Figure 1), generating a relatively modest beneficial effect at group level. All strategies resulted in increased gait speed, predominantly due to an increase in stride length. While most strategies positively impacted stride time variability (i.e. elicited a decrease in variability), action observation actually led to an increase in gait variability at group level. Overall patient-rated efficacy of the strategies was high, with the exception of action observation which was most often considered to have no effect. Adopting a new walking pattern and internal cueing ranked highest regarding usability. Participants considered action observation to be the least usable strategy in daily life, as it relies on the presence of another person. Figure 2 displays the number of participants who were 'very likely' to continue using any of the investigated strategies in daily life. The median number of strategies for continued use was two per participant. Only 4% (4/101) would continue using all five strategies.

Participant characteristics associated with the efficacy of compensation strategies

For all strategies, the strongest predictor of efficacy was baseline gait variability (Figure 2). Participants with higher baseline variability (reflecting greater gait impairment) showed the largest improvements in gait variability while applying compensation strategies. For each strategy, the change in gait variability from baseline was linearly correlated with the change in gait speed from baseline (external cueing, internal cueing, adopting a new walking pattern: $p<0.01$; action observation, motor imagery: $p<0.05$).

Several other variables were associated with larger improvements, independent of baseline variability (Table 3). Participants with lower MDS-UPDRS part III scores (specifically PIGD items), higher balance capacity (higher Mini-BEST scores), faster Timed Up-and-Go (TUG) times, and better performance in orienting attention (higher ANT Orienting scores) showed greater improvements when applying strategies. Non-freezers also showed larger improvements in gait variability compared to freezers. Strategy-specific associations with efficacy included higher MoCA score for external cueing, and male sex for adopting a new walking pattern. All presented variables were entered in the stepwise regression analysis. Variables included in the final model are indicated in bold in Table 3. Coefficients of determination (R^2) per strategy ranged between 0.419 for motor imagery and 0.647 for external cueing.

Table 1. Participant characteristics.

	Median [range]
N	101
Age (years)	66 [47 - 91]
Sex (N % women)	51 (50.5%)
Years of education	15 [9 - 18]
Time since PD diagnosis (years)	6.2 [0.3 – 24.9]
Levodopa Equivalent Daily Dosage (mg)	694 [0 - 2500]
Presence of Deep Brain Stimulation (N %)	9 (8.9%)
Physical examination	
MDS-UPDRS part III score	33 [9 - 70]
Hoehn-Yahr stage	2 [1 - 3]
Subjective presence of freezing of gait [a] (N %)	39 (38.6%)
NFOG-Q score among freezers	16 [3 - 27]
Abnormal rapid turns test (N %))	26 (25.7%)
Mini-BEST total score	24 [7 – 28]
Anticipatory subscore	5 [0 – 6]
Reactive subscore	5 [0 – 6]
Sensory subscore	6 [0 – 6]
Gait subscore	8 [3 – 10]
TUG time (s)	7.7 [4.2 - 20.6]
Abnormal tandem gait [b] (N %)	18 (17.8%)
Cognitive assessment	
MoCA score	28 [18 - 30]
Brixton Spatial Anticipation Test percentile	40 [2 - 95]
ANT Orienting	58 [-51 – 130]
ANT Alerting	5 [-104 – 82]
ANT Conflict	133 [40 – 332]
VMIQ-2 score	91 [36 – 180]

Values are expressed as median [range], unless indicated otherwise. PD = Parkinson's disease; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; NFOG-Q = New Freezing of Gait Questionnaire; Mini-BEST = Mini Balance Evaluation Systems Test; MoCA = Montreal Cognitive Assessment; ANT = Attention Network Test; TUG = Timed Up-and-Go; VMIQ-2 = the Vividness of Movement Imagery Questionnaire.

[a] Defined by a non-zero score on question 1 of the NFOG-Q.[17]

[b] Defined by the inability to perform ten consecutive heel-to-toe steps, without taking any side steps.

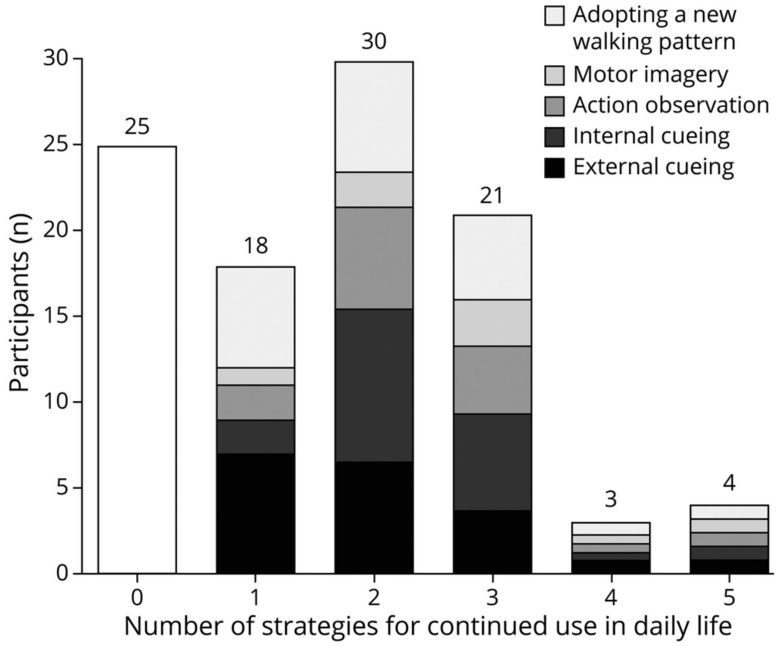
Table 2. Efficacy and usability of compensation strategies for gait impairment in Parkinson's disease

	Baseline gait(n=101)	External cueing (n=99)	Internal cueing (n=101)	Action observation (n=100)	Motor Imagery (n=99)	New walking pattern (n=101)
Stride time variability (CV)	3.26 ± 1.31	**2.72 ± 0.93***	**2.80 ± 0.98***	**3.64 ± 1.19***	3.00 ± 1.12	**2.90 ± 1.10***
Stride length variability (CV)	5.85 ± 2.40	5.61 ± 1.82	5.72 ± 2.41	**6.74 ± 2.53***	5.98 ± 2.27	5.69 ± 2.30
Stride time (s)	1.17 ± 0.13	1.17 ± 0.10	1.16 ± 0.11	1.16 ± 0.11	**1.14 ± 0.14***	1.15 ± 0.11
Stride length (m)	1.09 ± 0.23	**1.14 ± 0.22***	**1.14 ± 0.23***	**1.14 ± 0.20***	1.11 ± 0.22	**1.18 ± 0.23***
Gait speed (m/s)	0.94 ± 0.21	**0.98 ± 0.21***	**0.98 ± 0.24***	**0.99 ± 0.20***	**0.99 ± 0.21***	**1.03 ± 0.22***
Participant-rated efficacy [a]						
Positive effect (N %)		79 (80%)	80 (80%)	32 (32)%	69 (70%)	64 (63%)
Negative effect (N %)		5 (5%)	11 (11%)	2 (2%)	19 (19%)	22 (22%)
Usability [b]						
'Very likely' to use in daily life (N %)		35 (44%)	41 (51%)	9 (28%)	16 (23%)	38 (59%)
'Likely' to use in daily life (N %)		33 (42%)	33 (41%)	10 (31%)	32 (46%)	23 (36%)
'Undecided' (N %)		1 (1%)	1 (1%)	1 (3%)	0	0
'Unlikely' to use in daily life (N %)		8 (10%)	5 (6%)	4 (13%)	14 (20%)	2 (3%)
'Very unlikely' to use in daily life (N %)		2 (3%)	0	8 (25%)	7 (10%)	1 (2%)

Values represent mean ± SD unless indicated otherwise. CV = coefficient of variation. * Significant compared to baseline gait,after Bonferroni correction [a] Rating scale: positive effect/no effect/negative effect.

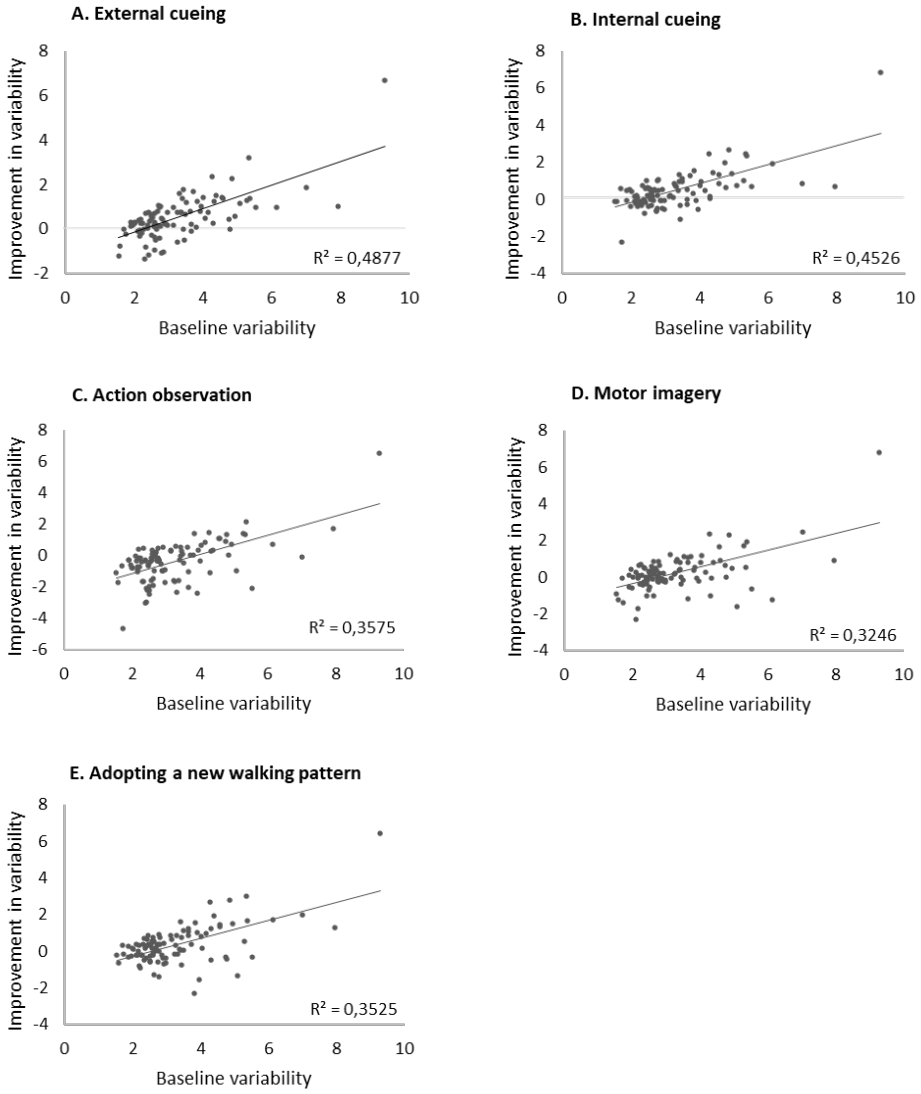
[b] Among participants that indicated the strategy had a positive effect on gait quality. Rated on a 5-point Likert scale: very likely/likely/undecided/unlikely/very unlikely.

Figure 1. Participants (n) who were 'very likely' to continue using a number of the five investigated compensation strategies in daily life.



Colors represent the strategies persons intended to continue using in daily life (e.g. in the group of participants who were 'very likely' to continue using 1 strategy, this most often comprised external cueing or adopting a new walking pattern).

Figure 2. Association of baseline gait variability and improvement in gait variability with (A) external cueing; (B) internal cueing; (C) action observation; (D) motor imagery; and (E) adopting a new walking pattern.



The efficacy of the strategy is presented as the improvement in gait variability compared to baseline gait. Gait variability is defined as stride time variability, expressed by the coefficient of variation (CV). Negative values correspond to an increase in variability compared to baseline, equaling a negative effect of the strategy.

Table 3. Patient characteristics associated with improvement in stride time variability, adjusted for baseline stride time variability.

	B	[95% CI]	*p*	R^2
External cueing				**0.647**
Baseline stride time variability	0.547	[0.438 – 0.655]	<0.001	
Hoehn-Yahr stage	-0.533	[-0.769 – -0.297]	<0.001	
Presence of FOG	-0.484	[-0.766 – -0.202]	0.001	
TUG (with dual task) time	-0.073	[-0.107 – -0.039]	<0.001	
Total MoCA score	0.073	[0.017– 0.129]	0.011	
ANT Orienting score	0.005	[0.001 – 0.009]	0.020	
MDS-UPDRS III	-0.021	[-0.033 – -0.009]	<0.001	
MDS-UPDRS III PIGD score	-0.692	[-1.009 – -0.655]	<0.001	
TUG time	-0.077	[-0.121 – -0.033]	0.001	
Internal cueing				**0.542**
Baseline stride time variability	0.513	[0.401 – 0.626]	<0.001	
ANT Orienting score	0.006	[0.002 – 0.010]	0.004	
Hoehn-Yahr stage	-0.441	[-0.693 – -0.189]	0.001	
Presence of FOG	-0.376	[-0.678 – -0.074]	0.015	
MDS-UPDRS III	-0.018	[-0.030 – -0.006]	0.004	
MDS-UPDRS III PIGD score	-0.516	[-0.861 – -0.171]	0.004	
TUG (with dual task) time	-0.042	[-0.080 – -0.004]	0.026	
Action observation				**0.471**
Baseline stride time variability	0.609	[0.446 – 0.773]	<0.001	
Presence of FOG	-0.677	[-1.106 – -0.248]	0.002	
Mini-BEST Subscore Anticipatory	0.300	[0.133 – 0.467]	0.001	
MDS-UPDRS III	-0.025	[-0.043 – -0.007]	0.006	
MDS-UPDRS III PIGD score	-0.863	[-1.356 – -0.369]	0.001	
Hoehn-Yahr stage	-0.658	[-1.025 – -0.291]	0.001	
Total Mini-BEST score	0.079	[0.033 – 0.125]	0.001	
Mini-BEST Subscore Reactive	0.155	[0.028 – 0.282]	0.017	
Abnormal tandem gait	-0.584	[-1.144 – -0.024]	0.041	
TUG (with dual task) time	-0.060	[-0.114 – -0.006]	0.030	
Motor imagery				**0.419**
Baseline stride time variability	0.464	[0.332 – 0.597]	<0.001	
ANT Orienting score	0.006	[0.002 – 0.010]	0.006	
MDS-UPDRS III	-0.021	[-0.035 – -0.007]	0.003	
MDS-UPDRS III PIGD score	-0.466	[-0.878 – -0.055]	0.027	
Hoehn-Yahr stage	-0.456	[-0.760 – -0.152]	0.004	

Table 3. Continued

	B	[95% CI]	*p*	R^2
New walking pattern				**0.500**
Baseline stride time variability	0.488	[0.356 – 0.620]	<0.001	
Male sex	0.442	[0.107 – 0.777]	0.010	
Presence of FOG	-0.424	[-0.779 – -0.069]	0.019	
Hoehn-Yahr stage	-0.486	[-0.784 – -0.188]	0.002	
MDS-UPDRS III PIGD score	-0.428	[-0.841 – -0.015]	0.042	
Total Mini-BEST score	0.039	[0.003 – 0.075]	0.036	
Mini-BEST Subscore Gait	0.145	[0.048 – 0.242]	0.004	
TUG (with dual task) time	-0.048	[-0.092 – -0.004]	0.032	

Bold variables represent the variables that were included in the stepwise regression by means of forward selection, determining the R^2 per strategy.

Discussion

We systematically evaluated the efficacy of five categories of compensation strategies (external cueing, internal cueing, action observation, motor imagery and adopting a new walking pattern) in 101 persons with PD and gait impairment. Our main findings were: (1) the beneficial effects on gait varied greatly across participants for the different types of strategies, highlighting the importance of an individually tailored approach to gait rehabilitation in PD; (2) a similar interindividual variation was noted in terms of patient-rated efficacy and usability of the specific strategies, again highlighting a strong personalized element; (3) for all five strategies, higher baseline gait variability was associated with greater strategy efficacy, implying that persons with significant gait impairment are still able to improve gait quality by applying compensation strategies; and (4) the patient characteristics associated with the efficacy of specific strategies provide some insight into the possible underlying mechanisms of compensation, and potentially explain why specific strategies seem to work better in certain patients.

Regarding the efficacy of specific compensation strategies to reduce gait variability, results varied greatly across individual participants. While one person showed dramatic improvement while using a certain strategy, the next would show no change, or even an increase in gait variability when applying the same strategy. These individual differences are in line with the observations from clinical practice, and are consistent with the results of a recently published survey study about the perception of compensation strategies in 4,324 persons with PD and gait impairment.[11] Our

findings emphasize the importance of trying out a variety of options to identify the optimal strategies in terms of efficacy and usability for each individual patient. Using this approach in the present study, 75/101 (75%) of participants was 'very likely' to continue the use of at least one newly-acquired strategy in daily life. However, only 4/101 (4%) of participants deemed all five strategies to be both effective and usable, again underlining the need to find an optimal personal fit. Trying out a variety of strategies is especially important considering that patients will often require multiple strategies in order to perform their daily activities over many years. Even within one individual the same strategy may have different effects depending on the situation or environment in which it is applied (e.g. indoors vs. on a busy market square).[11] In addition, although robust evidence is lacking, there are concerns that the efficacy of a strategy may taper off (or 'habituate') over time, necessitating a switch to alternative strategies.

Expectedly, the average baseline stride time variability of our participants was higher than the average reported for healthy adults of a similar age (mean±SD: 3.26±1.31 vs. 2.20±1.10).[33] For all five strategies, higher baseline gait variability was associated with higher strategy efficacy. While it is certainly expected that persons with the largest baseline impairment have the greatest opportunity to portray the largest improvements, this finding contains an important clinical implication. Namely, persons with significant gait impairment are still able to improve gait quality by applying compensation strategies; i.e. even among persons with the greatest gait difficulties, there is still 'room' for improvement via compensation. This needs to be examined further in a population with more severely affected individuals. While participants all experienced hindering gait impairment, all were able to walk independently for at least three consecutive minutes, representing a group with relatively good functional mobility. Presumably, a certain level of functional and cognitive reserve is necessary to be able to successfully compensate for gait impairment.[34] This is also supported by our finding that participants without freezing of gait (FOG), with lower MDS-UPDRS part III scores, higher balance capacity, faster TUG times, and better performance in orienting attention, demonstrated greater improvements in gait variability using compensation strategies.

The strategy-specific associations provide some insight into the possible mechanisms underlying compensation. It has been postulated that the application of compensation strategies ameliorates gait by facilitating a shift from automatic to goal-directed motor control, thereby bypassing the most affected basal ganglia circuitries.[9,35-37] Moreover, their underlying mechanisms are hypothesized to at least partly differ for each category, potentially explaining why the efficacy of a specific

strategy varies between patients.[9,11] This is supported by a recent EEG study that presented distinct cortical correlates for external cueing, internal cueing and action observation.[38] We will highlight three interesting strategy-specific associations that we identified in the present study.

First, participants with higher performance in orienting attention, i.e. the ability to selectively attend to specific sensory input,[39] showed larger improvements with external cueing, internal cueing and motor imagery compared to participants with lower performance. This is in line with the presumed major role of attention in compensation for gait impairment, specifically in external and internal cueing.[9]

Second, a previous study on auditory cueing and the factors associated with increased gait speed in thirty-nine non-demented PD patients revealed that persons with poorer cognitive flexibility, using the Wisconsin Card Sorting Test (WCST), showed largest improvements.[40] Using the Brixton Spatial Anticipation Test, similar to the WCST,[23,41] we were unable to replicate this finding for improvement in gait variability. Contrastingly, we found better overall cognition (MoCA) was associated with larger improvements with external cueing. As proposed, this may be an indication that a certain level of cognitive reserve is imperative for successful compensation.[34,42]

Third, previous studies on auditory cueing in PD populations demonstrated an association between rhythmical ability and increased gait speed.[40,43] Again, we were unable to replicate this association for gait variability. Years of musical training and self-perceived musicality (adapted Goldsmiths Index) showed no association with the efficacy of external auditory cueing in our population. Presumably, a more objective quantification of perceptual and motor timing abilities is necessary to reveal a potential connection to cueing efficacy.

In addition to the study limitations already discussed, several other points should be considered. First, the associated patient characteristics are specific to the strategy efficacy on gait variability, and may have been different had a different parameter been selected. However, we specifically chose gait variability for its association with fall risk.[30-32] Moreover, we found an evident correlation between the change in gait variability from baseline and the change in gait speed from baseline for each of the five strategies, which is important considering that patients often find gait speed one of the most important measures of their perceived gait quality.

Furthermore, the associations are also specific to the strategy we selected to represent the category of compensation strategies as a whole (e.g. auditory cueing,

rather than visual or tactile cueing in the category external cueing). Different strategies within a category of compensation strategies may have yielded different results. For example, while external auditory cueing seems to target temporal aspects of gait (e.g. stride time), external visual cueing more likely targets spatial aspects of gait (e.g. stride length) and may therefore appeal to a different type of patient.[44] While the investigated strategies are a representation of the type of strategies that are usually evaluated by a physical therapist in clinical practice, persons with PD often employ highly personalized strategies, that may be a combination of strategies from different categories (e.g. counting while lifting the knees up high). In addition, imposed strategies may have a different (i.e. less outspoken) effect on gait compared to compensation strategies that are spontaneously invented by patients themselves.

Finally, the efficacy of compensation strategies is highly dependent on the context in which strategies are applied,[11] so the reports of efficacy, as well as the associated patient characteristics are specific to continuous gait in a lab-based setting. The lab-based setting may have particularly influenced the efficacy of action observation in this study. Because of the length of the walkway (6 meters, with 180 degree turns on each end), participants were forced to walk alongside, rather than behind the person they were instructed to mimic. This meant they had to walk with their gaze directed to one side, rather than straight ahead. In addition, the need to take corrective steps to get back in sync after the 180 degree turns may have caused the detrimental effect on stride time variability at group-level. Presumably, continuous gait along a straight path may have led to an overall better response to the strategy at both the individual and the group level.

To conclude, the present findings support the use of compensation strategies for gait impairment in PD, but underline the reality that one size does not fit all. The application of an individually tailored, personalized approach to gait rehabilitation is imperative to facilitate finding a suitable strategy for every person with PD.

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Part III

Underlying mechanisms of compensation strategies

Video vignette III

Compensation strategies for gait impairment in Parkinson's disease can have spectacular effects, but it remains relatively unknown how these creative 'tricks' establish such great improvements in gait. People with Parkinson's disease - like the person demonstrating his self-invented strategies in video vignette III - often cannot explain why certain strategies are helpful to them either.

7

Cortical correlates of gait compensation strategies in Parkinson's disease

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Abstract

Objective

Gait impairment in persons with Parkinson disease is common and debilitating. Compensation strategies (eg, external cues) are an essential part of rehabilitation, but their underlying mechanisms remain unclear. Using electroencephalography (EEG), we explored the cortical correlates of 3 categories of strategies: external cueing, internal cueing, and action observation.

Methods

Eighteen participants with Parkinson disease and gait impairment were included. We recorded 126-channel EEG during both stance and gait on a treadmill under 4 conditions: (1) uncued, (2) external cueing (listening to a metronome), (3) internal cueing (silent rhythmic counting), and (4) action observation (observing another person walking). To control for the effects of sensory processing of the cues, we computed relative power changes as the difference in power spectral density between walking and standing for each condition.

Results

Relative to uncued gait, the use of all 3 compensation strategies induced a decrease of beta band activity in sensorimotor areas, indicative of increased cortical activation. Parieto-occipital alpha band activity decreased with external and internal cueing, and increased with action observation. Only internal cueing induced a change in frontal cortical activation, showing a decrease of beta band activity compared to uncued gait.

Interpretation

The application of compensation strategies resulted in changed cortical activity compared to uncued gait, which could not be solely attributed to sensory processing of the cueing modality. Our findings suggest there are multiple routes to control gait, and different compensation strategies seem to rely on different cortical mechanisms to achieve enhanced central motor activation in persons with Parkinson disease.

Introduction

Gait impairment is a common and disabling manifestation of Parkinson's disease. The nature of this impairment can be present both continuously (i.e. decreased step length, reduced arm swing, and increased gait variability) as well as episodic (e.g. festination or freezing of gait).[1,2] Gait impairment limits functional mobility and may lead to falls and subsequent injuries.

The pathophysiology underlying gait impairment in Parkinson's disease is complex and presumably involves dysfunction of multiple supraspinal components within the locomotor network, including corticostriatal loops. The pathophysiology of episodic and continuous gait deficits is not identical, but does overlap.[3] Persons with Parkinson's disease generally experience more difficulties when walking in an automated manner (i.e. without consciously paying attention), compared to when producing goal-directed behaviour (often facilitated by the presence of a clear external or sometimes an internal stimulus).[4] Studies in animals and humans revealed that these differences between automatic and goal-directed behaviour are likely related to greater loss of dopaminergic innervation in the posterior putamen, which has been associated with the control of automatic (habitual) behaviour, in contrast to the relatively preserved rostromedial striatum, which is primarily involved in goal-directed behaviour.[5,6] Consequently, persons with Parkinson's disease may increasingly rely on making a compensatory shift from the automated to the goal-directed mode of action control to maintain functional mobility. Recently, Gilat et al. published an excellent model diagram of gait control in Parkinson's disease.[7]

The application of compensation strategies forms an essential part of gait rehabilitation. These strategies involve a wide variety of 'detours' that are typically spontaneously invented by persons with Parkinson's disease to overcome their walking difficulties. Examples of compensation strategies include: stepping over lines on the floor, counting while walking, skipping, and mimicking the movements of another person. They can be employed to alleviate freezing of gait episodes, but are also commonly applied in clinical practice to ameliorate gait rhythmicity, gait speed and step length in persons with Parkinson's disease with and without freezing of gait.[8,9] A comprehensive framework of seven distinct categories of compensation strategies was recently proposed, based on a review of hundreds of patient videos collected over a four-year period.[10] It is hypothesized that the mechanisms underlying these strategies may be different for each proposed category, potentially explaining why the efficacy of a specific strategy tends to vary between patients.[9] The general idea is that the application of compensation strategies facilitates the shift from

automatic to goal-directed motor control, thereby bypassing the most affected basal ganglia circuitries. This switch to goal-directed control of gait is postulated to lead to increased recruitment of cortical areas including (pre-)frontal and parietal areas.[11,12]

To date, the cortical correlates of compensation strategies for gait impairment in Parkinson's disease remain relatively unclear. Recent technological advances now allow for the study of cortical activity during actual walking rather than imaged gait, using brain imaging techniques such as electroencephalography (EEG). The interpretation of earlier EEG studies on this topic is complicated by their lack of control conditions, hampering the ability to distinguish the cortical signature of compensation strategies in motor control from the cortical activity related to the sensory or attentional processing of the cueing modality. In the present study, we overcome this limitation through the use of a novel approach comprising of high-density EEG recordings during both gait and stance to explore the cortical correlates underlying three categories of compensation strategies: (1) external cueing, (2) internal cueing, and (3) action observation. We hypothesized that each of the different types of compensation strategies would present with a distinct pattern of cortical activation.[10] Based on previous studies, external cueing was postulated to assist in filtering information and prioritizing a stimulus through improvement of executive attention, regulated by frontostriatal circuitries.[10] Internal cueing was hypothesized to aid in orienting or focusing attention towards gait, and thought to involve prefrontal- and parietal areas.[10,13] Finally, action observation was hypothesized to compensate for reduced automaticity through activation of the mirror neuron system, involving the supplementary motor area (SMA), the dorsal premotor cortex, the supramarginal gyrus and superior parietal lobe.[10,14,15]

Methods

Participants

Twenty persons with Parkinson's disease and self-reported disabling gait impairment (i.e. negatively affecting their ability to perform their usual daily activities) participated in this study. All had previously participated in an experiment aimed at evaluating the efficacy of compensation strategies for gait impairments in Parkinson's disease. Persons were eligible for inclusion if they had demonstrated beneficial effects of external cueing, internal cueing, and action observation on gait quality. A beneficial effect was defined as any decrease in stride time variability compared to uncued gait (without any compensation strategy), assessed during three-minute trials of continuous overground walking, in combination with a subjective improvement in

gait compared to uncued gait according to the participant. Exclusion criteria were: inability to walk unaided for five minutes consecutively, presence of comorbidities significantly influencing gait capacity (i.e. history of stroke, orthopaedic ailments), and deep brain stimulation (DBS).

Measurements took place in the morning. Disease severity was assessed at the start of the measurement, in the dopaminergic 'ON' phase, using the MDS-UPDRS part III.[16] The presence and severity of freezing of gait was determined using the New Freezing of Gait Questionnaire.[17] Participants were to refrain from taking their scheduled dosages of dopaminergic medication for the duration of the experiment (±four hours). Consequently, due to the long EEG preparation time, EEG recordings were performed while participants were in the dopaminergic end-of-dose phase. This was confirmed by debriefing the participants, who all indicated a clear worsening of their symptoms which would normally have necessitated the intake of dopaminergic medication. We specifically designed this element of our study to mimic the daily life situation, since the end-of-dose phase would be the time of day in which the application of compensation strategies would be most useful.[18]

Informed consent was obtained from each participant, in accordance with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Radboud University Medical Centre in Nijmegen, the Netherlands, and the local Medical Ethics Committee Arnhem-Nijmegen (ref:2019-5710).

Experimental protocol

Participants stood on a treadmill in a quiet, non-distracting environment, and were equipped with a safety harness. The experiment consisted of EEG recordings during standing and during gait, under four conditions: (1) uncued; (2) external cueing; (3) internal cueing; and (4) action observation (see Figure 1 and the descriptions below). The uncued conditions (uncued stance and gait) were recorded at the beginning of the experiment. The order of the remaining conditions within the stance and gait blocks was counterbalanced across participants. The duration of each recording was four minutes, except for uncued stance (quiet stance), which lasted one minute. Treadmill speed was set at the participant's preferred comfortable speed and kept constant for all gait recordings. Each condition was individually explained, practiced if necessary, and then recorded. General instructions to the participants included: focusing their gaze on a fixation cross projected on the screen in front of them, refraining from talking during the recordings, and refraining from actively suppressing any tremors, dyskinesia or dystonia that may occur. Participants were encouraged to take unrestricted breaks in between recordings to prevent fatigue.

Uncued condition

During the uncued conditions, participants were explicitly instructed not to apply any compensation strategies. During uncued gait, the participant's natural cadence was estimated by the researcher using a freely available beats-per-minute app on a smartphone (BPM, version 3.04, CHEEBOW).

External cueing

During the external cueing conditions participants listened to the sound of a metronome that was played through speakers. The metronome was developed for an in-house treadmill operations application (D-flow, Motek Forcelink, Amsterdam, the Netherlands) and recorded in parallel as a trigger line for data synchronization. The pace of the metronome was set to the uncued gait cadence. During gait, participants were to synchronize their steps to the rhythm of the metronome (i.e. make a heel strike at every beat), without counting along, or using any other compensation strategies.

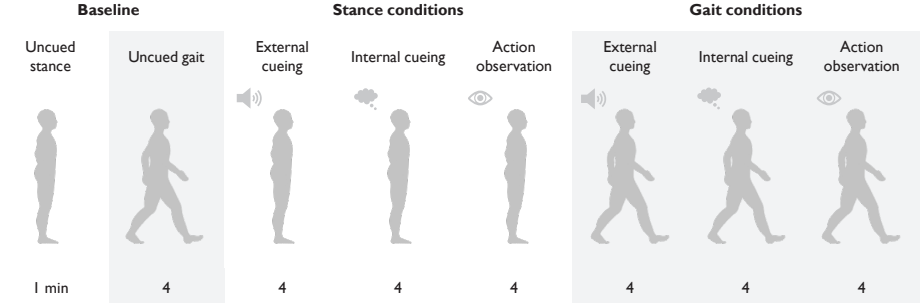
Internal cueing

During the internal cueing conditions participants silently counted in a rhythmic manner (e.g. 1-2-3-4-1-2-3-4). During gait, participants were to synchronize their steps to their counting (i.e. make a heel strike at every count), without using any other compensation strategies. Due to the nature of the internal cueing condition, synchronization of the cue with motion- and EEG data was not possible.

Action observation

For the action observation conditions, participants watched a pre-recorded video of a healthy person walking on the same treadmill. The video was projected onto a large screen in front of them. The person in the video walked on the treadmill, synchronizing their steps with the rhythm of a metronome. A set of videos with cadences between 80-120 steps per minute (increments of five steps per minute) was available, to ensure the projected video would closely match the natural cadence of every participant, as measured during uncued gait. During gait, participants were to synchronize their steps to the steps of the person in the video, without counting along, or using any other compensation strategies. The audio signal of the metronome in the video was muted, but its digital signal was recorded in parallel as a trigger line for data synchronization.

Figure 1. Experimental tasks and conditions.



The experimental conditions consisted of external cueing, internal cueing and action observation during stance and gait. Stance conditions always preceded the gait conditions, but the order of the conditions was counterbalanced within stance/gait blocks and across participants. Each condition lasted four minutes, with exception of uncued stance (commonly referred to as quiet stance). Prior to the main experiment, participants practiced walking on the treadmill at a comfortable speed to determine their preferred cadence. The corresponding belt speed remained constant throughout the experiment. Resting breaks were encouraged between all conditions.

Data acquisition

High-density EEG data was acquired using 126-channel Ag-AgCl electrodes embedded in an electrode cap (WaveGuard, ANT Neuro, the Netherlands), with electrode distribution according to the five percent electrode system.[19] The ground electrode was placed on the left mastoid. EEG was sampled at 2048 Hz using a biosignal amplifier (REFA Systems, TMSi, The Netherlands) with a built-in antialiasing low-pass filter (552Hz) and average reference. Electrode impedance was ≤10kΩ.

Movement data was acquired using a ten-camera 3D motion capture system (VICON, Oxford, United Kingdom), with a sampling rate of 100Hz. Thirty-five reflective markers were placed on anatomical landmarks as defined by the PlugInGait Full Body Model,[20] excluding the head markers for EEG purposes. In addition to the trigger line for external cueing and action observation, a digital trigger signal was simultaneously recoded by the EEG and motion capture systems for data synchronization.

Data processing and analysis

Movement data

The motion capture data was analysed to determine the difference in gait variability between uncued gait and each of the three gait conditions with compensation strategies. Gait variability is associated with fall risk in a broad variety of populations,

including persons with Parkinson's disease.[21-24] Gait variability was expressed as the coefficient of variation (CV) of stride time:

Stride time was computed with a custom MATLAB (Mathworks, Natick, MA, USA) script and was defined as the time between two subsequent right heel strikes (same for the left). Heel strikes were identified as (local) minima of the vertical displacement of the heel markers within a gait cycle. A similar procedure was used to determine toe offs from the toe markers. The sequence of gait events within the gait cycle was checked for order and aberrant cycles were discarded. The latency between gait events was computed and outliers were rejected.

Electroencephalogram

EEG data were processed using the EEGLAB toolbox (UC San Diego, Swartz Center for Computational Neuroscience, La Jolla, USA),[25] and custom MATLAB scripts.

Pre-processing and artefact reduction

EEG data were combined with gait events (i.e. heel strikes and toe-offs for each foot). EEG data were bandpass filtered between 2-200Hz (5120th order FIR filter, Hamming window, zero-phase shift) and down-sampled to 512Hz. Afterwards, EEG data from all conditions were concatenated.

The *clean_rawdata* plugin (v2.3) from EEGLAB was used to reject channels with low correlation (<0.6) with neighbouring channels, and correct for bursts of high-amplitude activity (e.g. muscle artefacts) using artefact subspace reconstruction (ASR v0.13; threshold: 15SD).[26] The artefact-reduced participant-specific EEG dataset was segmented into consecutive, non-overlapping epochs (0.5s). Epochs containing high-amplitude artefacts were removed from the dataset using the *pop_jointprob* function from EEGLAB (threshold: 6SD). Finally, using Infomax independent component analysis (ICA),[27] EEG data were decomposed to estimate source-resolved brain activity and reduce the influence of physiological noise.[28] ICA performs a blind source decomposition of the dataset based on the assumption that the EEG sources are instantaneously near-independent. Each independent component is associated with a scalp map, representing the scalp projection of synchronous neural activity in a cortical domain. This map was used to approximate the cortical source of a given component by fitting an equivalent current dipole using the *dipfit* plugin (v3.7) from EEGLAB, with standard electrode coordinates and a standard three-shell boundary element head model (BEM). Independent components with an associated equivalent current dipole and a residual variance <15% were visually inspected considering their mean power spectra to exclude non-brain activity.

EEG datasets were segmented according to the participant-specific mean gait cycle duration, to compute the condition-specific mean power spectral density (PSD; average across the gait cycle) and mean gait cycle spectrograms. PSD was computed between 2-48Hz (45 frequencies, linearly distributed) using Morlet wavelets (1.2 cycles at lowest frequency, increasing 0.2 cycles with each step). Gait cycle spectrograms for individual gait cycles were time-warped via linear interpolation to standardize the gait cycle across participants. Gait events were aligned to 0-10-50-60-100% of the gait cycle, corresponding to the right heel strike (RHS), left toe off (LTO), left heel strike (LHS), right toe off (RTO), and right heel strike (RHS) respectively.[29]

Clustering independent components across participants

For group-level analysis, independent components were clustered across participants. Feature vectors were created by concatenating information about the location of the corresponding equivalent current dipole, the scalp projection, and the mean power spectral density (3-48Hz, across all conditions). Principal component analysis was used to reduce the feature vectors to nine principal components before using the k-means algorithm. The number of clusters was the average number of components per participant (k=13). Feature vectors located >5SD from the computed cluster centroids were considered outliers. Only clusters containing independent components from more than half of the participants (n>9) were considered for further analysis. Condition-specific PSDs and gait cycle spectrograms were averaged per cluster.

Assessment of cortical activation

To obtain a measure of cortical activation,[30,31] relative power changes were computed as the difference in PSD between standing and walking per condition. This measure indicates the relative change in cortical activation during the application of a compensation strategy during gait, compared to solely processing the same sensory input (external cueing, action observation), or engaging in a similar cognitive task (internal cueing) during stance. According to the traditional interpretation of event-related spectral modulations,[30-32] a relative power decrease indicates increased cortical activation, whereas a relative power increase may indicate reduced cortical activation or increased inhibition. Similarly, the difference between condition-specific spectrograms during gait and condition-specific PSD during stance resulted in a time-frequency representation of cortical activation throughout the gait cycle.[33,34]

Statistical analysis

Significant differences in cortical activation during the application of a compensation strategy versus uncued gait were evaluated using two-tailed t-tests for repeated measures and non-parametric permutation testing (5000 permutations, α=0.05).[35]

This was applied to each frequency line of the PSD (2-48Hz, 45 levels linearly spaced). Significant differences where only considered if present in at least two consecutive frequency lines.

Results

Study population

Of twenty participants, eighteen (10 men and 8 women, aged 66.2 ± 7.6 years) were included in the analysis, as the data from two participants had to be excluded (trigger line defect, n=1; inability to walk on a treadmill, n=1). Participant characteristics are presented in Table 1.

Effect of compensation strategies on gait variability

At group level, the mean stride time variability (CV; %) was 2.38 [SD: 0.82; range: 1.41-4.48] during uncued gait; 2.30 [0.73; 1.21-4.16] during gait with external cueing; 2.40 [0.74; 1.43-3.76] during gait with internal cueing, and; 2.27 [0.70; 1.33-4.13] during gait with action observation. The effect on gait variability was not confounded by changes in gait speed, as gait speed was controlled across all conditions. All participants reported a subjective improvement of gait during the application of all three strategies compared to uncued gait.

Clusters of independent components

In total, 222 independent components were selected for clustering (mean±SD:13±3.5; range: 6-18 per participant). Ten clusters containing independent components from more than half of the participants were identified (Table 2). For descriptive purposes, these clusters were categorized according to their anatomical localization: frontal (n=1), central/sensorimotor (n=3), parietal (n=3), and occipital (n=3).

Table 1. Participant characteristics.

	PD participants (n=18)
Age	66.2 ± 7.6
Sex (M / F)	10 / 8
Disease duration (years)	6.4 ± 2.7
LEDD (mg)	894.1 ± 309.5
MDS-UPDRS III score (median [range])	29 [11 - 42]
Hoehn & Yahr stage (median [range])	2 [1 - 3]
Presence of FOG[a] (Y / N)	6 / 12

Values represent the mean ± SD unless indicated otherwise.
PD = Parkinson's disease; LEDD = levodopa equivalent daily dosage.
[a] As defined by a non-zero score on question 1 of the New Freezing of Gait Questionnaire[17]

Table 2. Clusters of independent sources obtained with Independent Component Analysis.

Cluster	Location of cluster centroid	MNI coordinates (x, y, x)	Brodmann area	Subjects and ICs included (n)
Frontal				
1	Central frontal cortex	11, 32, 36	BA 32	10
Sensorimotor				
2	Left sensorimotor cortex	-29, -7, 57	BA 6	13
3	Central sensorimotor cortex	1, -22, 61	BA 4	12
4	Right sensorimotor cortex	38, -8, -47	BA 6	14
Parietal				
5	Left parietal cortex	-30, -46, 43	BA 40	15
6	Central parietal cortex	1, -57, 37	BA 7	13
7	Right parietal cortex	35, -44, 34	BA 40	14
Occipital				
8	Left occipital cortex	-34, 60, 11	BA 37	11
9	Central occipital cortex	1, -78, 19	BA 18	11
10	Right occipital cortex	33, -64, 9	BA 19	12

MNI = Montreal Neurological Institute; ICs = independent components

Cortical activation during the application of compensation strategies

Cortical activation spectra and time-frequency maps during the application of compensatory strategies relative to uncued gait are presented per cluster in Figures 2-5. We highlight the most important findings (all $p<0.05$) in this section.

Relative to uncued gait, all three compensation strategy modalities induced a stronger decrease of beta band activity in the sensorimotor left (external cueing: 23-31Hz; t(12)=3.19; internal cueing: 26-29Hz; t(12)=2.93; action observation: 24-30Hz; t(12)=3.33) and central (external cueing: 23-30Hz; t(11)=2.65; internal cueing: 26-37Hz; t(11)=2.45; action observation: 22-26Hz; t(11)=2.87) clusters during gait, indicative of increased cortical activation. Beta band activity displayed a distinct modulation across the gait cycle, with the largest appearing increase in cortical activation during the double support phase (Figure 2).

In the frontal cluster, applying internal cueing during gait induced a stronger decrease of beta band activity (17-23Hz; t(9)=2.39) compared to uncued gait, indicative of increased cortical activation. External cueing and action observation did not induce a significant change in cortical activation of the frontal cluster compared to uncued gait (Figure 3).

All parietal clusters displayed a stronger decrease in theta/alpha band activity during gait with internal cueing (left: 2-9Hz; t(14)=3.27; central: 2-7 Hz; t(12)=2.85; right: 2-8Hz; t(13)=2.76), indicative of increased cortical activation compared to uncued gait. The parietal left (19-20Hz; t(14)=2.94 and 25-27Hz; t(14)=2.65) and parietal right (33-38 Hz; t(13)=2.19) clusters also displayed a stronger decrease in beta band activity during gait with internal cueing. Contrastingly, the parietal left (11-14Hz; t(14)=-2.29) and parietal right (9-14Hz; t(13)=-2.84) clusters displayed a weaker decrease in alpha band activity during gait with action observation compared to uncued gait. Alpha and beta band activity of the parietal clusters was not significantly changed by the application of external cueing during gait (Figure 4).

In the occipital clusters, a decrease in alpha band activity was apparent for gait with internal cueing (left: 2-7Hz; t(10)=2.71; central: 3-11 Hz; t(10)=4.85; right: 4-8Hz; t(11)=2.62) and external cueing (central: 3-7Hz; t(10)=3.47; right: 4-6Hz; t(11)=2.50), but not for gait with action observation. Gait with action observation induced a weaker decrease in alpha band activity in the left occipital cluster (6-8Hz; t(10)=-2.50), indicative of a relative decrease in cortical activity in this area compared to uncued gait. Beta band activity showed a stronger decrease in the occipital central

(external cueing: 20-22Hz; t(10)=3.39; internal cueing: 19-29Hz; t(10)=3.28 and 32-35Hz; t(10)=2.76; action observation: 24-37Hz; t(10)=2.82) and occipital right (external cueing: 22-24Hz; t(11)=2.28; internal cueing: 12-15Hz; t(11)=2.49 and 20-44Hz; t(11)=3.21; action observation: 21-31Hz; t(11)=2.59 and 33-42Hz; t(11)=2.01) clusters during the application of all three compensation strategies during gait compared to uncued gait (Figure 5).

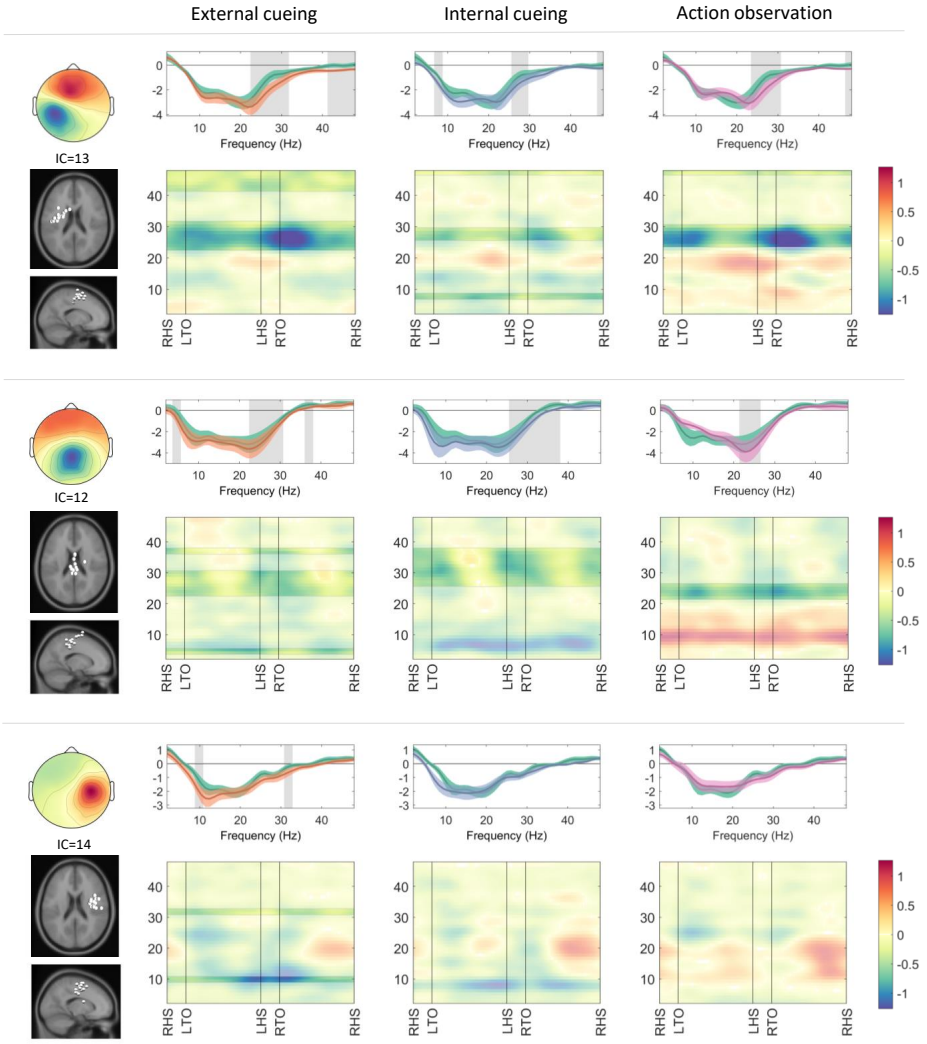
Discussion

We conducted a high-density EEG gait study of 18 persons with Parkinson's disease and gait impairment, aiming to explore the cortical correlates of three categories of compensation strategies: external cueing, internal cueing, and action observation. The main findings of the study are: (1) compared to uncued gait, the application of compensation strategies during gait resulted in altered cortical activity, which could not be solely attributed to sensory processing of the cueing modality; (2) beta band activity in the sensorimotor areas was decreased during gait while applying compensation strategies, indicating increased recruitment of this cortical area compared to uncued gait; (3) cortical activation patterns differed depending on the type of compensation strategy that was applied, suggesting that each of the strategies engages a distinct cortical network.

Compensation strategies change cortical activation

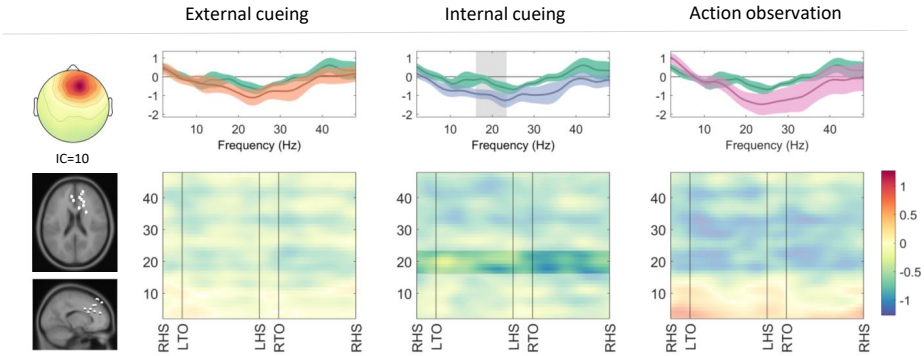
Compared to uncued gait, the application of external cueing, internal cueing and action observation during gait resulted in spectral power changes over sensorimotor, frontal, parietal, and occipital cortical areas, which is in agreement with previous findings of walking under goal-directed conditions (e.g., following internal or external cues).[33,36] In contrast to earlier work, we were able to confirm that the altered cortical activation we found was not merely attributable to increased cortical recruitment due to processing sensory input related to the cueing modality (i.e. listening to a metronome,[37] watching another person walking[38]), or engaging in a cognitive task such as rhythmic counting[39]). By including control conditions during stance (during which the same compensation strategies were applied) into our experimental protocol, we were able to correct for the stimulus-related cortical activity, and consequently distil the cortical activation patterns that were most likely contributing to gait control. To our knowledge, we are the first to apply this approach to study the cortical correlates of compensation strategies for gait impairment in Parkinson's disease.

Figure 2. Somatosensory clusters: cortical activation during gait with a compensation strategy.



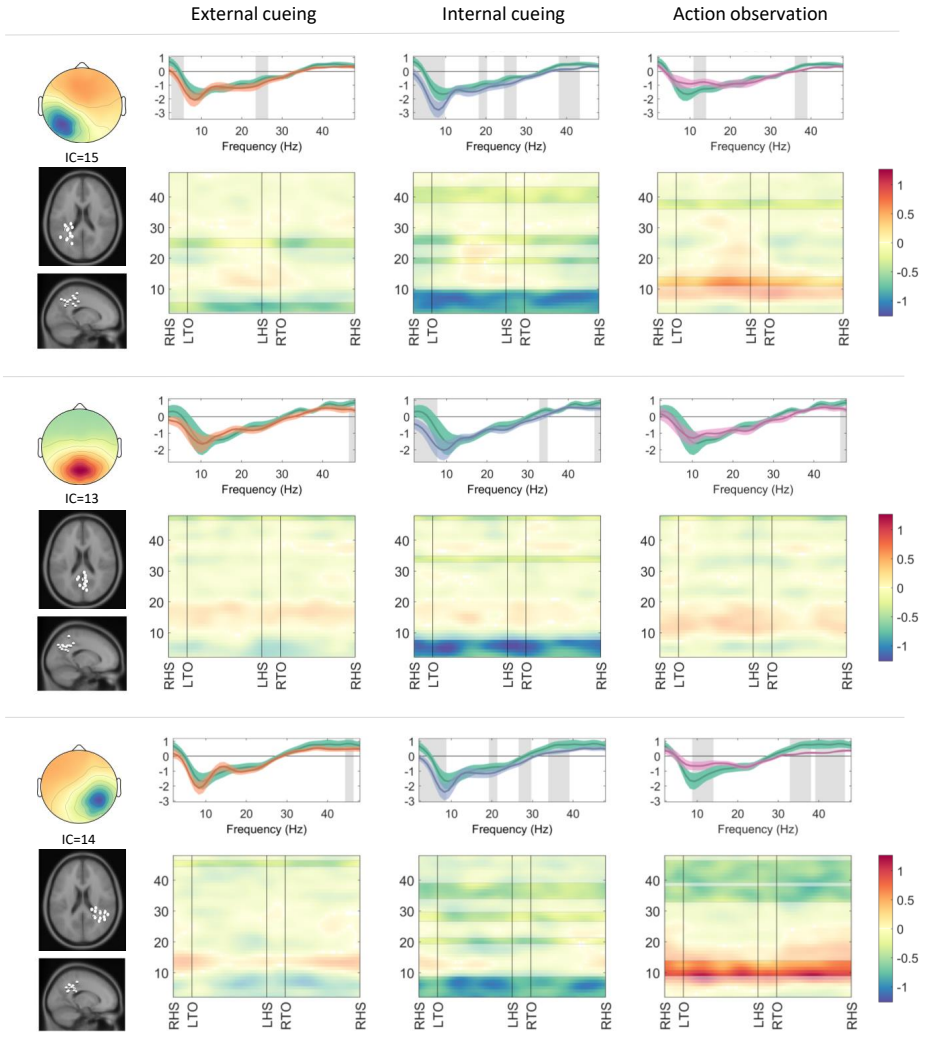
Cortical activation spectra (top row) showing power changes during gait conditions relative to stance conditions (mean ± standard error), and cortical activation time-frequency maps (bottom row) illustrating relative differences (compensation strategy gait minus uncued gait) across the gait cycle. The negative values around sensorimotor alpha (8-12 Hz) and beta (13-35 Hz) frequency bands indicate increased cortical activation during gait (top row, all conditions). Similarly, negative values around the beta frequency band (bottom row, all conditions) indicate stronger cortical activation during application of the compensation strategies. Significant effects ($p<0.05$) of a given compensation strategy (external cueing: orange, internal cueing: blue, action observation: pink) in contrast to uncued gait (green) are highlighted (spectra: grey background, maps: unmasked colours). RHS = right heel strike; LTO = left toe off; LHS = left heel strike; RTO = right toe off; IC = independent component.

Figure 3. Frontal cluster: cortical activation during gait with a compensation strategy.



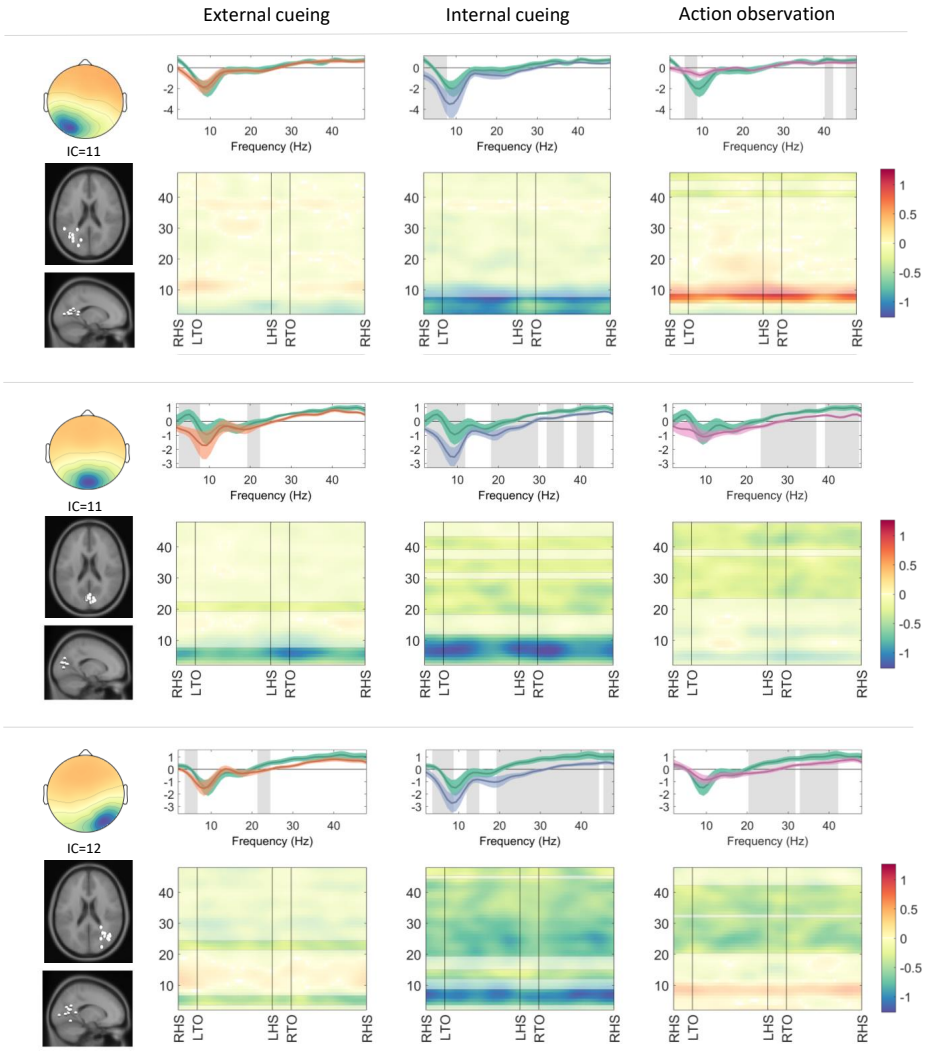
Cortical activation spectra (top row) showing power changes during gait conditions relative to stance conditions (mean ± standard error), and cortical activation time-frequency maps (bottom row) illustrating relative differences (compensation strategy gait minus uncued gait) across the gait cycle. Significant effects ($p<0.05$) of a given compensation strategy (external cueing: orange, internal cueing: blue, action observation: pink) in contrast to uncued gait (green) are highlighted (spectra: grey background, maps: unmasked colours). RHS = right heel strike; LTO = left toe off; LHS = left heel strike; RTO = right toe off; IC = independent component.

Figure 4. Parietal clusters: cortical activation during gait with a compensation strategy.



Cortical activation spectra (top row) showing power changes during gait conditions relative to stance conditions (mean ± standard error), and cortical activation time-frequency maps (bottom row) illustrating relative differences (compensation strategy gait minus uncued gait) across the gait cycle. The negative values, primarily around theta (3-7 Hz) and alpha (8-12 Hz) frequency bands indicate increased cortical activation during gait (top row, all conditions), which is sustained across the gait cycle (bottom row). Significant effects ($p<0.05$) of a given compensation strategy (external cueing: orange, internal cueing: blue, action observation: pink) in contrast to uncued gait (green) are highlighted (spectra: grey background, maps: unmasked colours). RHS = right heel strike; LTO = left toe off; LHS = left heel strike; RTO = right toe off; IC = independent component.

Figure 5. Occipital clusters: cortical activation during gait with a compensation strategy.



Cortical activation spectra (top row) showing power changes during gait conditions relative to stance conditions (mean ± standard error), and cortical activation time-frequency maps (bottom row) illustrating relative differences (compensation strategy gait minus uncued gait) across the gait cycle. Significant effects ($p<0.05$) of a given compensation strategy (external cueing: orange, internal cueing: blue, action observation: pink) in contrast to uncued gait (green) are highlighted (spectra: grey background, maps: unmasked colours). RHS = right heel strike; LTO = left toe off; LHS = left heel strike; RTO = right toe off; IC = independent component.

Compensation strategies facilitate the recruitment of sensorimotor areas

Gait is controlled through a complex supraspinal network.[40] It was previously concluded from an exploratory activation of likelihood estimation (ALE) meta-analysis of functional magnetic resonance imaging studies, that persons with Parkinson's disease have more difficulties recruiting cortical motor areas during gait compared to healthy controls, as illustrated by decreased cortical activation of the supplementary motor area (SMA).[41] Hypoactivity of the SMA has been associated with gait disturbances including increased cadence, decreased step length, and reduced arm swing in persons with Parkinson's disease.[42-44] Importantly, after normalization of SMA activity (e.g. through dopaminergic medication, deep brain stimulation, or transcranial stimulation of the motor cortex), movement amplitude improves.[45-47] A recent study revealed that walking with instructed arm swing (which is a type of compensation strategy[10]) increased step length and gait speed in persons with Parkinson's disease and restored deficient cortical activation over the putative SMA.[48] Movement execution (e.g. finger tapping, foot dorsiflexion and walking) is associated with a relative power decrease in sensorimotor beta rhythm.[31,49] In the present study we found a consistently larger decrease of beta band activity in sensorimotor clusters during the application of all three compensation strategies compared to uncued gait. This implies that the application of a compensatory strategy facilitates the recruitment of sensorimotor areas in persons with Parkinson's disease and gait impairment. Our findings provide evidence for the hypothesis that central motor activation could be achieved through cues by making use of alternative motor pathways.[7,10,50] These alternative pathways likely involve corticostriatal loops that rely on different modes of gait control (i.e. goal-directed or emotional) compared to the primary automatic mode of gait control via the posterior putamen, which is most affected by dopaminergic denervation in Parkinson's disease.[5,51]

Cortical correlates differ between compensation strategies

Another important result of the present study is the finding that the three types of compensatory strategies produced different patterns of cortical activation. This implies that specific compensation strategies have unique underlying cortical mechanisms. This is in line with earlier hypotheses regarding the distinctive underpinnings of different categories of gait compensation strategies,[10] as specified in the Introduction section.

Differences in cortical activation between strategies became most apparent through our finding that solely internal cueing elicited increased engagement of the frontal cluster compared to uncued gait. The use of auditory cues during walking did not

significantly alter frontal brain activation compared to uncued gait, which contradicts the presumed major role of executive brain areas in external cueing.[10] However, our findings are in agreement with a recent EEG study investigating the cortical correlates of external (visual) cueing in Parkinson's disease, which did not demonstrate involvement of the frontal cortices during gait with visual cues.[36] Furthermore, a functional near-infrared spectroscopy pilot study on tactile cueing in persons with Parkinson's disease also revealed that the use of (external) somatosensory cues does not increase activation of the prefrontal cortex compared to uncued gait.[52] Previously, the mechanisms underlying external cueing were postulated to improve gait by targeting frontostriatal circuitries.[5,10] Our findings do not provide support for this hypothesis, suggesting external cueing does not seem to rely on increased involvement of frontal executive areas.

Cortical activation in the parietal and occipital areas also differed between the three compensation strategies, especially in their elicited alpha band responses. Relative to uncued gait, alpha activity decreased during gait with internal and external cueing, but increased during gait with action observation. Alpha band oscillations in parieto-occipital areas are essential for attentional processes, by facilitating the selection of relevant information.[53] Indeed, external and internal cueing strategies have been hypothesized to work through aiding in filtering information and allocating attention to gait.[10] The relative alpha activity increase during gait with action observation may reflect active top-down inhibition or disengagement of visual areas to suppress the processing of irrelevant visual information to the task (i.e. anything besides the observed person's feet).[54]

Given the wide variety of unique compensation strategies within each of the seven proposed categories,[10] even different strategies within the same category may have distinct neural mechanisms (e.g. visual vs. tactile. vs. auditory cues in external cueing). Notably, patients often employ highly personalized strategies in daily life, comprising of a combination of different categories of compensation strategies (e.g. counting in combination with lifting the knees up high) rather than a 'pure' form of external cueing, internal cueing, or action observation as assessed in the present study.[10] The EEG correlates of these personalized strategies may differ from the strategies examined in this study, but this remains to be uncovered by future studies.

Study limitations

The following limitations should be considered when interpreting the results of this study. First, treadmill gait differs from overground walking. Since the EEG amplifier was too heavy to achieve true mobile recordings, we had to resort to treadmill

walking to enable the acquisition of high-density EEG data during actual gait. Moreover, treadmill walking allowed us to control for gait speed across conditions. However, walking on a treadmill most probably caused a substantial deflation of the positive effect of the compensation strategies on stride time variability, as stride time variability during gait on a treadmill is conceivably considerably lower compared to the variability during self-paced overground walking.[55] This deflation in the positive effect on gait variability may however be beneficial for the purpose of this study, as the mental effects of sudden gait improvement with a strategy (e.g. a decrease in anxiety compared to uncued gait) may also affect EEG results. Lastly, it can be argued that walking on a treadmill may act as a tactile cue for persons with Parkinson's disease and gait impairment, therefore causing an overestimation of sensorimotor recruitment during uncued treadmill gait compared to uncued overground gait. Combined, our results are likely to underestimate the actual increase in cortical activation evoked by applying a compensation strategy during self-paced overground gait.

Second, while EEG has excellent temporal resolution, spatial resolution is limited.[56] Consequently, the interpretation of the source localizations of brain activity only provide a rough estimation. It is difficult to reliably distinguish between the relative contributions of specific cortical areas of interest (i.e. the SMA, premotor cortex and primary motor cortex), and virtually impossible to explore the role of deeper, subcortical structures (i.e. the cerebellum and basal ganglia) in gait control and compensation. Regardless, the most important advantage of using EEG rather than neuroimaging techniques with greater spatial resolution is the ability to measure cortical activity during actual gait, instead of imagined gait in a scanner.

Future directions

The insights on the cortical correlates of compensation strategies may eventually be translated to more targeted therapeutic interventions for gait impairment in Parkinson's disease. Either as stand-alone treatments, such as closed-loop DBS, or in conjunction with physical therapy (e.g. by studying the potential benefits of the training of compensation strategies combined with transcranial direct current stimulation of relevant cortical areas[57]). At present, the results of this study can already be implemented in clinical practice in support of much-needed patient education on this topic.[9]

A topic of future investigations could be the exploration of the EEG correlates of alleviating a freezing episode with the use of a variety of compensation strategies. The cortical mechanisms at play may be different when strategies are applied

episodically as a way to alleviate a freezing episode, compared to when they are being applied during continuous walking. Another interesting topic of further research could be the evaluation of gait compensation strategies in persons with and without (severe) cognitive impairment using EEG. With disease progression, cognitive dysfunction may hamper the efficient switching from automated to goal-directed gait control,[58] potentially hindering a person's ability to benefit from the application of compensation strategies.

Conclusion

The present study highlights that compensation strategies in Parkinson's disease are likely to share an overarching working mechanism: using alternative pathways to achieve enhanced central motor activation. Our study also suggests that there is more than one route to control gait, and that different compensation strategies may rely on different cortical mechanisms. It is likely that humans in general use multiple routes to control gait (e.g. in the context of urgent situations, or when playing tennis),[59] but that the presence of such alternative routes to motor control only becomes apparent in persons with Parkinson's disease when the primary automatic motor pathway fails.[50]

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8

Modulating arousal to overcome gait impairments in Parkinson's disease: how the noradrenergic system may act as a double-edged sword

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Abstract

In stressful or anxiety-provoking situations, most people with Parkinson's disease (PD) experience a general worsening of motor symptoms, including their gait impairments. However, a proportion of patients actually report benefits from experiencing – or even purposely inducing – stressful or high-arousal situations. Using data from a large-scale international survey study among 4,324 people with PD and gait impairments within the online Fox Insight (USA) and ParkinsonNEXT (NL) cohorts, we demonstrate that individuals with PD deploy an array of mental state alteration strategies to cope with their gait impairment. Crucially, these strategies differ along an axis of arousal – some act to heighten, whereas others diminish, overall sympathetic tone. Together, our observations suggest that arousal may act as a double-edged sword for gait control in PD. We propose a theoretical, neurobiological framework to explain why heightened arousal can have detrimental effects on the occurrence and severity of gait impairments in some individuals, while alleviating them in others. Specifically, we postulate that this seemingly contradictory phenomenon is explained by the inherent features of the ascending arousal system: namely, that arousal is related to task performance by an inverted u-shaped curve (the so-called Yerkes and Dodson relationship). We propose that the noradrenergic locus coeruleus plays an important role in modulating PD symptom severity and expression, by regulating arousal and by mediating network-level functional integration across the brain. The ability of the locus coeruleus to facilitate dynamic 'cross-talk' between distinct, otherwise largely segregated brain regions may facilitate the necessary cerebral compensation for gait impairments in PD. In the presence of suboptimal arousal, compensatory networks may be too segregated to allow for adequate compensation. Conversely, with supraoptimal arousal, increased cross-talk between competing inputs of these complementary networks may emerge and become dysfunctional. Because the locus coeruleus degenerates with disease progression, finetuning of this delicate balance becomes increasingly difficult, heightening the need for mental strategies to self-modulate arousal and facilitate shifting from a sub- or supraoptimal state of arousal to improve gait performance. Recognition of this underlying mechanism emphasizes the importance of PD-specific rehabilitation strategies to alleviate gait disability.

Introduction

A person's mental state is an important intrinsic factor affecting the expression of a variety of neurological motor symptoms, from dystonia to hemiparesis after stroke.[1] Parkinson's disease (PD) is a prototypical example highlighting this captivating interaction, where alterations in the mental state often lead to immediate observable changes in motor symptoms. While tremor is the prime example of a PD motor feature that typically worsens during stressful situations and with increased cognitive load,[2-6] other motor symptoms, such as gait impairments, are also often aggravated by stress and anxiety.[6-8] Gait impairments in PD comprise both continuously present deficits (e.g. reduced step length and -height, reduced gait speed, and increased gait variability) as well as episodic deficits (i.e. festination and freezing of gait).[9] The detrimental effect of stressful, anxiety-inducing situations on the occurrence and severity of freezing of gait episodes has been particularly well-established.[10-16] Unsurprisingly, many people with PD and gait impairment use strategies to counteract stress or anxiety, in an effort to improve their walking ability. Of these approaches, mindfulness-based interventions have received the most attention in recent years.[17-20]

Paradoxically, in contrast to this negative impact on gait, some PD patients seem to actually benefit from experiencing - or even purposely inducing - stressful situations. The most extreme form is the well-known phenomenon of 'kinesia paradoxa': a sudden, transient ability to perform a task that a person was previously unable to complete, often in the context of grave, life-threatening situations.[21,22] A classic case example was offered by a group of 14 institutionalized Italian patients with advanced PD, who demonstrated an extraordinary motor improvement during the L'Aquila earthquake of 2009.[23] All of them were able to escape unaided from the collapsing nursing home, despite usually requiring assistance during daily activities because of severe gait difficulties and postural instability. While kinesia paradoxa may well be an entity on its own, it has been hypothesized that gait improvement under more mundane circumstances that increase motivation may share a similar underlying mechanism, namely a shift to optimally heighten arousal.[24] These common clinical observations raise an interesting question – how is it that heightened arousal can augment symptoms in some individuals, while alleviating their severity in others?

Here, we suggest that this paradox is related to inherent features of the ascending arousal system. Over a century ago, psychologists Yerkes and Dodson demonstrated that task performance is related to arousal (Figure 1).[25] The inverted u-shaped curve illustrates that task performance improves with increasing arousal, until an optimum

is reached. When the optimal level of arousal is surpassed, performance declines again as arousal increases further. Depending on where you are situated on this curve, a change in arousal could therefore be either beneficial or detrimental to performance of the task at hand. Translating this notion to gait impairments in PD, on the left-hand side of this curve (i.e., with suboptimal arousal), gait might be ameliorated by strategies that increase arousal levels. Conversely, on the right-hand side of the curve (i.e., with supraoptimal arousal) gait might benefit from strategies that decrease arousal.

Compensation strategies tapping into this mechanism of modulating arousal levels are typically attributed to a category entitled 'Altering the Mental State'. This is one of seven major categories of compensation strategies for gait impairment, based on a comprehensive review of several hundred videos of persons with PD who spontaneously 'invented' strategies to improve their gait. [24] The 'Altering the Mental State' category has thus far received relatively little attention, certainly when compared to other categories such as external or internal cueing. [26] For obvious reasons, it is not recommended to implement life-threatening situations in daily life to improve gait impairment. However, reports on 'everyday' variants of less drastic arousal strategies are scarce. Indeed, PD healthcare professionals rarely apply strategies from the 'Altering the Mental State' category in their clinical practice, [27] even though persons with PD find it a valuable way to cope with their gait impairments in daily life. [28] Furthermore, the mechanisms underlying this category of strategies remain poorly understood.

Here, we introduce a novel theoretical framework regarding the potential underlying mechanisms of modulating one's arousal to optimize gait performance in PD. To this aim, we first present an array of ready-to-use 'Altering the Mental State' strategies for gait impairment, informed by data from a large-scale international survey study among over 4,000 persons with PD and gait impairments, [28] illustrating our hypothesis that the noradrenergic system may act as a double-edged sword in PD gait control.

Methods

Study population

The present study is a secondary analysis of a web-based survey that was distributed among 6,700 participants within the Fox Insight cohort (USA), as well as 1,573 Dutch participants within the ParkinsonNEXT cohort (NL). [28] Fox Insight is a longitudinal,

virtual, patient-centered observational study on PD led by the Michael J Fox Foundation. Data used in the preparation of this article were obtained from the Fox Insight database on June 1st 2020. For up-to-date information on the study, visit https://foxinsights-info.michaeljfox.org/insight/explore/insight.jsp. ParkinsonNEXT (http://www.parkinsonnext.nl) is an online platform that aims to unite patients, researchers and clinicians wanting to contribute to research and innovation in PD or parkinsonism. The online survey was accessible from March – June 2020. Respondents above the age of 18 years with a self-reported diagnosis of PD and self-reported disabling gait impairments were included in the analyses.

Survey

Details on the design and content of the original survey, which consisted of three parts, have been previously reported. [28] We will reiterate the elements relevant to the present study. The survey addressed the seven main categories of compensation strategies, including 'Altering the Mental State'. [24] This category was explained and illustrated by several practical examples. Participants were then queried whether they had ever applied a strategy belonging to the 'Altering the Mental State' category, and – if so – what specific strategy they had used (free-text entry).

Data processing and -analysis

Based on the free-text entries that respondents had provided, data were verified and manually corrected by two independent researchers, to ensure that all recorded compensation strategies were completed under the appropriate corresponding category. 'Altering the Mental State' strategies were then classified into being either 'strategies that reduce arousal' (e.g., relaxation techniques, mindfulness) or 'strategies that increase arousal' (e.g., experiencing high-pressure situations, getting angry). Strategies that were difficult to intuitively place into one of two categories were discussed among all study investigators until consensus was reached. All (descriptive) statistical analyses were performed in IBM SPSS 25 (SPSS, Inc., Chicago, IL, USA). Independent t-tests and chi-square tests were performed to assess group differences in demographic characteristics. Values of $P<0.05$ were considered to be statistically significant.

Ethical approval

The study was approved by the Institutional Review Board of the Radboud University Medical Center in Nijmegen, the Netherlands (Ref: 2019-5737). Written informed consent was not necessary for this work.

Results

Study population

In total, 5,832 respondents successfully completed the questionnaire. We collected 4,987 responses via Fox Insight (response rate: 74.4%), and 845 via ParkinsonNEXT (response rate: 53.7%), of which 1,508 persons were excluded as they did not experience disabling gait impairments. Characteristics of the remaining final sample of 4,324 respondents, of whom 1,343 (31.1%) reported to have ever used 'Altering the Mental State' strategies, are presented in Table 1. Notably, the sample of respondents who used 'Altering the Mental State strategies' comprised of relatively more women (47.4% vs. 43.6%, p=0.022), and the prevalence of freezing of gait (49.2% vs. 41.6%, p<0.001) and falls (58.4% vs. 49.7%, p<0.001) was higher in this group compared to the sample of respondents who did not use 'Altering the Mental State strategies' strategies.

'Altering the Mental State' strategies

As expected, we were able to identify a clear divide between those strategies that seemed to reduce arousal (i.e. through reducing stress or anxiety) at one end of the spectrum versus those strategies aimed at purposefully increasing arousal (i.e. through increasing stress levels or motivation) at the other end. An overview of the specific 'Altering the Mental State' strategies that the 1,343 respondents employed to overcome their gait impairments in daily life is presented in Table 2. Some of the examples represent strategies that include a clear element of 'Altering the mental state' in combination with elements of other known categories of compensation (e.g., motor imagery or internal cueing). [24]

Table 1. Respondent characteristics.

	Total cohort	Have used 'Altering the Mental State' strategies	Have never used 'Altering the Mental State' strategies	*P*-value[b]
Respondents (N %)	4324	1343 (31.1)	2981 (68.9)	
Men (N %)	2387 (55.3)	706 (52.6)	1681 (56.4)	0.022*
Age (years)	67.8 ± 9.0	67.5 ± 9.0	68.6 ± 9.0	0.371
Time since diagnosis (years)	6.7 ± 5.3	7.0 ± 5.3	6.5 ± 5.2	0.004*
Respondents with FOG (N %)	1900 (43.9)	661 (49.2)	1239 (41.6)	<0.001*
NFOG-Q score[a] (median [range])	17 [1-28]	18 [1-27]	17 [1-28]	0.005*
Fallen last year (N %)	2266 (52.4)	784 (58.4)	1482 (49.7)	<0.001*

Values are represented as mean ± SD, unless otherwise specified. FOG = Freezing of gait; NFOG-Q = New Freezing of Gait Questionnaire (score range 0-28).[75]

[a] Among respondents with freezing of gait, defined by a non-zero NFOG-Q score.

[b] Respondents who have ever used 'Altering the Mental State' strategies vs. respondents who have never used 'Altering the Mental State' strategies, assessed by independent t-tests and chi-square tests.

Strategies that reduce arousal

Among all reported 'Altering the Mental State' strategies, strategies to reduce arousal were most common (76.5%). They most frequently entailed: breathing exercises (n= 593); mindfulness and meditation (n=522); stretching before walking (n=190); and praying (n=31). Respondents reported many creative ways to achieve a sense of general relaxation to improve gait before going out for a walk, ranging from listening to soothing music to playing a game of digital solitaire before going anywhere: *"I recite the 7 countries of Central America and the 13 countries of South America, this relaxes me. I'm learning Europe next".* Others reported to specifically focus on tackling negative emotions or cognitions surrounding gait right before or during walking: *"I have always been a believer in the individual's ability to get more from their mental attitude than they otherwise do. I focus on the mental reasons I freeze, such as a fear of falling, and tell myself quite profoundly that it is only a fear and I must, simply must overcome it".* Some respondents reported to walk better when they feel like they are well-prepared and have a back-up plan in case gait difficulties (e.g. freezing of gait) emerge: "*I always take a 'test walk' in the family room before going outside"; "I always carry around a cane, even though I do not actually use it for support. Just having it with me gives me more confidence to walk, as I will have something to help me in case I freeze. I feel like I freeze more often when I do not bring the cane with me."*

Strategies that increase arousal

Strategies that seemed to purposefully increase arousal (23.5%) most often comprised: getting oneself angry or 'pumped' (n=59) and forceful (often abusive) self-talk to motivate oneself to move (n=86). Multiple respondents mentioned that they had noticed a marked improvement in their ability to move when they experienced stress or 'a rush of adrenalin': *"When my adrenaline is high, I am suddenly able to perform actions that I could not do before"; "Stress increases my focus and the fear factor makes me perform and walk better".* Some indicated that they would simulate this feeling by getting themselves very angry: *"When I get very angry I feel my power increasing, it even enables me to run";* or by challenging themselves: *"If I imagine a twisty trail with rocks and roots and other obstacles while walking, I'm more alert and I walk better".* Another respondent even reported to purposefully inflict pain on herself to achieve an improvement in gait: *"I find that if I slap my right wrist really hard with my left hand, that for the next hour or more, my mind is confused and will concentrate on the wrist pain and forget the leg issues."*

Table 2. Reported 'Altering the Mental State' strategies for gait impairments in Parkinson's disease.

Principle mechanism	Phenomenology	Examples
Reducing arousal	Facilitating general relaxation	• Mindfulness; • Breathing techniques; • Meditation; • Yoga; • Qigong; • Tai chi; • Self-hypnosis; • Spirituality; • Low-intensity physical exercise; • [a]Doing something one loves; • Being on holiday; • Being somewhere one loves; • Listening to one's favourite music; • Taking anxiolytic drugs, or medicinal cannabis.
	Eliminating negative emotions and cognitions surrounding gait	• Focussing on what you CAN do; • Rationalize stressful events; • Consciously stop worrying; • Thinking about one's most positive experiences; • Using mantra's, or positive affirmations; • Visualizing a successful situation; • Taking antidepressants.
	Decreasing external (social) pressure	• Avoiding feeling rushed by other persons; • Communicating beforehand how one is feeling, so people can take it into account; • Pretending to be the only person around.
	Having a back-up plan in case of gait difficulties	• Carefully planning out the walk beforehand; • 'Crisis rehearsal' of bottleneck areas of the route beforehand; • Walking a 'test round' indoors before heading outsideWearing laser shoes, without having to look at the projections; • Holding a cane, without using it for support; • Having someone close by.
Increasing arousal	Internal factors	• Getting angry at oneself and using that energy to walk; • Inflicting pain on oneself; • Getting 'pumped' through forceful self-talk or high-intensity physical exercise*; • Purposefully creating a time-pressure situation; • Pretending to be on stage, ready to perform in front of a large audience; • Challenging oneself to make each step better than the one before.
	External factors	• Being in 'test' situations, such as at the doctor's office; • Being in an emergency, or otherwise thrilling situation.

[a] While low-intensity exercise is typically applied to facilitate general relaxation (i.e. decrease arousal), some persons employ higher intensity physical exercise to 'get pumped' (i.e. increase arousal).

In addition to these examples of inducing arousal with negative valence, high arousal states with positive valence were reported to improve gait performance in a similar matter. Specifically, respondents mentioned to benefit from inducing a state of 'flow' (a state of being fully absorbed by a task, established by an optimal match between the person's skills and the task challenges[29]) through doing something they enjoyed: *"After an intense programming session on my computer, I found myself being 'freed' of my Parkinson's disease for several hours".* Physical exercise before walking was also frequently reported to improve overall gait performance. Physical activity is a special example of 'Altering the Mental State' strategies, as it can be employed to facilitate general relaxation with low-intensity exercises (i.e. a decrease in arousal), as well as induce general excitement with higher intensity exercises (i.e. an increase in arousal). While some respondents reported to prefer to relax through yoga or tai chi exercises, others preferred to exercise in order to 'kickstart' themselves, for example by performing a quick set of push-ups before going out for a walk.

Subgroup characterization

A characterization of the subgroups of respondents based on the type of strategies they had ever tried is presented in Table 3. Most respondents had only ever tried strategies aimed at reducing arousal (83.5%). Notably, the subgroup of respondents that had used strategies to increase arousal comprised of more men (65.2% vs. 52.6%) and more individuals with freezing of gait (58.7% vs. 43.9%) compared to the subgroup of respondents that had used strategies to reduce arousal.

Table 3. Subgroup characteristics.

	Have used strategies that reduce arousal	Have used strategies that increase arousal	Have used both types of strategies
Respondents (N%)	4324	1343 (31.1)	2981 (68.9)
Men (N%)	2387 (55.3)	706 (52.6)	1681 (56.4)
Age (years)	67.8 ± 9.0	67.5 ± 9.0	68.6 ± 9.0
Time since diagnosis (years)	6.7 ± 5.3	7.0 ± 5.3	6.5 ± 5.2
Respondents with FOG (N%)	1900 (43.9)	661 (49.2)	1239 (41.6)
NFOG-Q score[a] (median [range])	17 [1-28]	18 [1-27]	17 [1-28]
Experienced ≥1 falls in preceding year (N%)	2266 (52.4)	784 (58.4)	1482 (49.7)

Values are represented as mean ± SD, unless otherwise specified. FOG = freezing of gait; NFOG-Q = New Freezing of Gait Questionnaire (score range 0-28).[75]

[a] Of respondents who had ever tried 'Altering the Mental State' strategies. NB: 31 respondents (2.3%) did not specify what kind of mental state strategy they had ever used.

[b] Among respondents with freezing of gait, defined by a non-zero NFOG-Q score.

Discussion

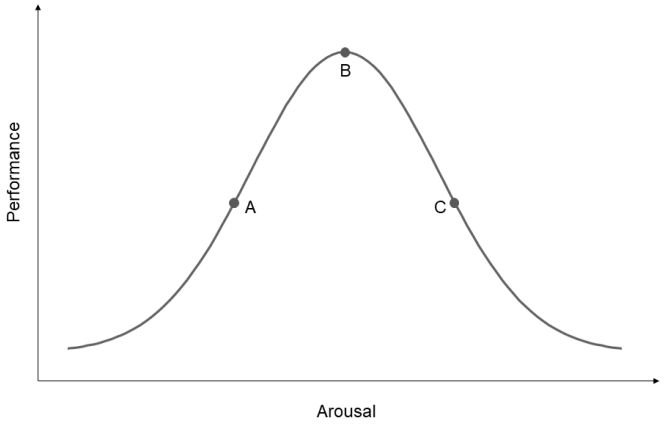
Here, we presented an overview of 'Altering the Mental State' strategies that persons with PD applied in an effort to overcome their gait impairments in daily life. Approximately one in three patients with gait impairments report altering their mental state as a compensatory strategy. While most persons with PD reported to have used strategies that reduced arousal (e.g., by diminishing stress, or promoting general relaxation), a smaller group actually reported to have purposely increased their arousal to improve gait. We will next elaborate on our theoretical framework regarding the potential underlying mechanisms and address the clinical implications of self-modulating arousal to optimize gait performance in PD.

From a neurobiological perspective, the concept of fine-tuning one's arousal level to optimizing one's ability to compensate for gait impairments in PD is tightly connected to the functions of the locus coeruleus. The locus coeruleus is a small nucleus located in the posterior area of the rostral pons, and represents the primary source of noradrenaline for the central nervous system. [30] Its widespread noradrenergic projections modulate cortical, subcortical, cerebellar, brainstem and spinal cord circuits, which makes it well suited to rapidly and globally modulate brain function in response to changes in the environment (e.g., stressful stimuli). [31] Moreover, locus coeruleus noradrenaline contributes to the reconfiguration of functional communication between distributed brain regions. [32] It is part of the ascending arousal pathway, and plays a major role in attentional and arousal response to threat. [33] Indeed, locus coeruleus activity displays an inverted u-shaped relationship with task performance, in accordance with Yerkes-Dodson's law. [34,35] Therefore, changes in the firing rate of the locus coeruleus may facilitate a shift in arousal that promotes optimal performance on the task at hand (Figure 1). The neuromodulatory impact of the locus coeruleus on the central nervous system is classically compared to tuning the volume of a radio, even though its precise adaptive role is more complex and dynamic, and more appropriately analogous to the bowing of a violin. [36] Much like the effect that a bow has on the strings of a violin, the locus coeruleus changes the way the 'notes' are expressed (e.g. their volume or tone quality) without affecting the specific string of notes in itself, in order to shape complex neuronal melodies. [36] Increased activity of the locus coeruleus (i.e. turning up the volume) increases the strength of functional interactions between brain regions that are otherwise largely segregated, [37,38] as noradrenaline elicits changes in the internal milieu of target cells to alter their 'neural gain' (i.e. their excitability and receptivity to incoming signals). [39] By mediating this increased network-level integration across the brain, the locus coeruleus can facilitate dynamic 'cross-talk' between different regions across the

cortex and subcortex that are critical for higher-order functions.[40,41] This functional integration is of particular importance in gait control in PD.

The pathophysiology underlying gait impairments in PD is complex and presumably involves dysfunction of multiple cortical and subcortical components. Gait partly depends on a basic 'locomotor network', involving spinal central pattern generators, brainstem mesencephalic- and cerebellar locomotor regions, along with the corticostriatal input projecting to the primary motor cortex.[42,43] In addition, distributed cortical areas, particularly the frontoparietal and supplementary motor areas, are normally involved in the adjustment and adaptation of walking.[44] During walking in an automated manner (i.e. without consciously paying attention to it), persons with PD typically have difficulties recruiting these cortical motor areas.[45] Adequate gait control therefore not only relies on the integrity and function of corticostriatal motor loops, but on compensatory input from cognitive, sensory and limbic systems as well (Figure 2).[46-49] Reinforcing the integration of these different neural networks may consequently facilitate optimal compensation for the PD-related loss of function in the motor circuitries. When locus coeruleus activity is too low (i.e., suboptimal arousal), the different compensatory networks may be too segregated to allow for adequate compensation of motor impairments. Overactivation of the locus coeruleus (i.e., supraoptimal arousal), on the other hand, may lead to a situation that allows for an element of increased, dysfunctional 'cross-talk' between competing inputs of these complementary networks.[50] In PD specifically, this has been associated with detrimental effects on motor function, particularly the occurrence of anxiety-induced freezing of gait.[51-53] Unfortunately, the ability to adaptively employ the locus coeruleus to optimally modulate the interaction of compensatory networks may be affected by the profound degeneration of the nucleus in PD, and this is compounded by dysfunction of cortical regions in charge of regulating arousal. Whilst well-established, this loss of noradrenergic neurons (ranging from 20-90% in PD patients[54,55]) has been relatively neglected,[56] even though it both precedes the onset and exceeds the extent of the hallmark loss of dopaminergic neurons in the substantia nigra pars compacta.[57-59] The application of 'Altering the Mental State' strategies to modulate arousal may therefore be necessary to facilitate shifts from sub- or supraoptimal states of arousal to optimize gait performance in PD.

Figure 1. The relationship between arousal and task performance, related to the effects of compensatory strategies targeting arousal. Based on Yerkes and Dodson (1908).[25]



A. Suboptimal state of arousal. In case of suboptimal arousal, a person with Parkinson's disease would likely benefit from applying a compensation strategy that aims to increase the level of arousal (e.g. by adding an element of time pressure), in order to optimize task performance. **B. Optimal state of arousal.** In case of optimal arousal, optimal task performance is expected. **C. Supraoptimal state of arousal.** In case of supraoptimal arousal, a person with Parkinson's

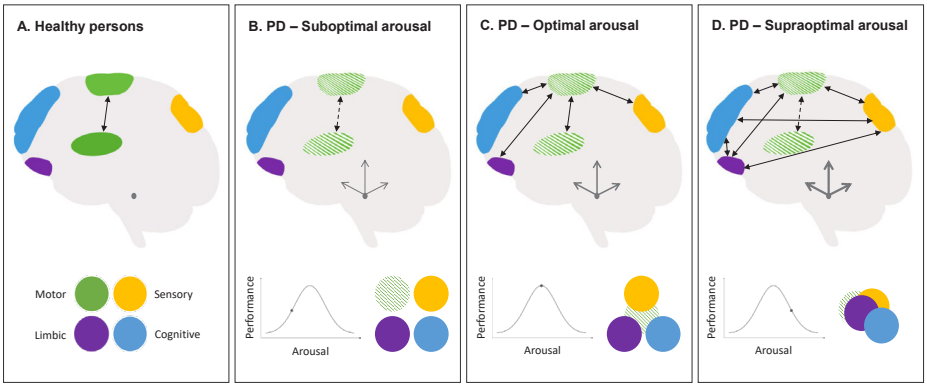
Importantly, the underpinnings of these strategies presumably do not only involve noradrenaline, but other neurotransmitters such as dopamine and serotonin as well.[60] The classic parallel model suggesting a direct correlation between changes in a single neurochemical system and a distinctive deficit is likely to be too simplistic. Rather, a convergent biochemical model in which the complex interactions between the different monoaminergic systems are taken into account would be more appropriate.[61] For example, the concept of reaching a "flow state", which respondents reported to be helpful in ameliorating gait, illustrates that striking the right balance between motivation (dopamine) and arousal (noradrenaline) can lead to optimized behavior.[62,63] Arousal levels are also influenced by a multitude of both internal and external factors (e.g., one's present emotions or physical environment). Even the presence of gait impairments in itself is likely to influence arousal levels in people with PD: introducing a vicious cycle of supraoptimal arousal due to anxiety related to falling, in turn leading to aggravated gait impairment, which further increases the fear of falling. However, while a person's 'baseline' position on the curve is likely to be partly trait-dependent (e.g., a chronic state of supraoptimal arousal in those with generalized anxiety or a debilitating fear of falling), it would presumably be predominantly dependent on the task, environment and context at hand (e.g., a sudden increase in arousal when a doorbell rings). In light of this, it is unsurprising

that a proportion of respondents reported to have used both types of 'Altering the Mental State' strategies in daily life. One can imagine that depending on the situation at hand, the state of arousal – and with that the appropriate type of strategy - may vary. Furthermore, depending on the complexity of the (gait) task at hand, the optimal level of arousal (i.e., the shape of the curve) could vary significantly across tasks. [25,64,65] These factors combined may make it particularly difficult to employ pharmacological interventions targeting the noradrenergic system as an add-on to dopaminergic medication to improve gait performance in persons with PD. [66-69] Any medication targeting the noradrenergic system would potentially impact the trait-dependent 'baseline' arousal level, rather than enabling the necessary dynamic adaptation in arousal that might be required over the course of the day. An advantage of the application of non-pharmacological compensation strategies is that it allows for such dynamic approaches that are tailored to the specific personal needs of individual patients under everchanging circumstances. Future studies could investigate whether a more personalized approach to the use of pharmacological agents targeting arousal could be beneficial in selected groups of patients (e.g., those with particularly high or low trait-dependent anxiety levels as measured by existing scales like the State-Trait Anxiety Inventory [STAI]). For example, if one occupies a highly aroused state the majority of their day, could 'resetting' their baseline arousal level help shift them to occupy an optimal part of the curve for a greater proportion of their daily activities? Quantifying baseline levels of locus coeruleus activity using techniques such as neuromelanin-sensitive MRI[70,71] may hold promise to stratify patients into clinical trials according to their level of noradrenergic (dys)function. [72]

The survey data that we used to support our hypothesis rely on the self-reported presence of a PD diagnosis, presence of gait impairment, and the efficacy of the applied mental strategies. The potential presence of selection bias, given the selected and rather proactive subpopulation of PD patients that is typically involved in online cohorts, must also be taken into account when interpreting the survey data. However, these data were merely used to probe the presence of examples of strategies at two ends of the arousal spectrum, rather than aim to provide an accurate percentage of the prevalence of specific strategies. Nevertheless, future clinical trials are necessary to objectively quantify the efficacy of 'Altering the Mental State' strategies in improving gait performance in PD. In conjunction, measuring the effect of applying these strategies on physiological markers of arousal (e.g., measured by skin conductance, heart rate, pupil diameter) would help establish the plausibility of our proposed neurobiological framework. Lastly, looking into specific patient characteristics that may be associated with the efficacy of either arousal-reducing (e.g., high levels of trait anxiety) or arousal-increasing strategies (e.g., high

levels of apathy or anhedonia) will be essential to eventually work towards a more personalized approach to the use of these non-pharmacological strategies in clinical practice.[73] Indeed, a subgroup characterization of the present cohort revealed that women less frequently reported to have used strategies to increase arousal, which may be a reflection of the higher prevalence of anxiety among women with PD.[74]

Figure 2. How modulating arousal may contribute to optimal gait performance in Parkinson's disease.



A. Healthy persons. In healthy persons, the primary automatic mode of motor control is intact. Different brain networks are largely segregated, as there is (usually) no need for compensatory input to achieve optimal gait control. **B. Parkinson's disease – Suboptimal arousal.** Impaired function of the corticostriatal motor network cannot be optimally compensated for by complementary input from other brain networks, as these networks remain largely segregated in this suboptimal state of arousal. **C. Parkinson's disease – Optimal arousal.** Impaired function of the corticostriatal motor network can be optimally compensated for by complementary input from other brain networks, as these networks are optimally integrated in this optimal state of arousal. **D. Parkinson's disease – Supraoptimal arousal.** Impaired function of the corticostriatal motor network cannot be optimally compensated for by complementary - but now competing - input from other brain networks, as these networks are engaged in dysfunctionally increased 'cross-talk' in this supraoptimal state of arousal.

Green circle: intact corticostriatal motor network; Dashed green circle: impaired corticostriatal motor network; Yellow circle: sensory network; Purple circle: limbic network; Blue circle; cognitive network. Black double-sided triangle arrows represent a simplified schematic illustration of the functional integration between the different brain regions (which is presumably much more complex than depicted); Dashed arrows indicate the impaired function of the primary motor circuitry in Parkinson's disease; Thickness of the dark-grey equilateral barb arrows represents the neuromodulatory activity of the locus coeruleus (depicted here in the rostral pons as a small dark-grey ellipse). PD: Parkinson's disease. *Figure inspired by Gilat et al. (2021).*[47]

Conclusion

Our theoretical framework proposing a central role for the locus coeruleus in facilitating optimal compensation to address gait impairments provides future opportunities to investigate the control of gait, as well as guiding both targeted pharmacological (e.g. tailored use of noradrenergic agents as an add-on to dopaminergic medication in selected PD patients) and non-pharmacological therapies (e.g. a training program on 'Altering the Mental State' strategies for persons with PD). It is also possible that the impaired modulation of arousal arising from the dysfunction of the locus coeruleus may have consequences that extend beyond gait and could play a critical role in PD tremor, 'wearing off' periods, or other key symptoms that have been demonstrated to be significantly affected by one's level of arousal (particularly in the context of stress or anxiety).[6] Future work is necessary to validate this conceptual framework, quantify the efficacy of 'Altering the Mental State' strategies, and further crystallize the potential involvement of the noradrenergic system in optimizing motor performance in PD.

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Part IV

Towards personalized gait rehabilitation in Parkinson's disease

Video vignette IV

The search for suitable compensation strategies is a personal endeavor. It requires creative thinking, and is truly a collaboration between patient and therapist. Identifying the optimal strategies should ultimately facilitate patients in continuing their usual and/or favorite activities. Video vignette IV shows how the application of compensation strategies allowed an avid swimmer to pursue his hobby. The video was published as part of: *Tosserams, A., Nijkrake, M.J., Voet, N.B.M., Bloem, B.R. and Nonnekes, J. (2020), Why People With Parkinson's Disease Experience Near-Drowning—and How to Prevent It. Mov Disord Clin Pract, 7: 573-574.*

9

A practical guide to the evaluation of compensation strategies for gait impairment in Parkinson's disease

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Introduction

Gait impairments are among the most common and disabling symptoms of Parkinson's disease (PD). Management consist of complementary pharmacological and non-pharmacological treatment options.[1] Physiotherapy is a cornerstone of the non-pharmacological pillar, and the application of compensation strategies is one of the elements of physiotherapy. These strategies comprise a wide range of 'detours' to improve walking capacity (Table 1).[2] The application of compensation strategies is believed to improve gait by facilitating a shift from automated to goal-directed gait control,[2] as persons with PD generally experience more difficulties when walking in an automated manner due to a greater loss of dopaminergic innervation in the posterior putamen.[3,4] While the efficacy of gait compensation strategies is generally very high, the effects of specific strategies vary greatly between patients: what works spectacularly well in one patient, has no effect – or even aggravates gait impairment – in the next.[5] Therefore, a personalized approach to gait rehabilitation is imperative to find a suitable strategy for every person with PD and gait impairment. Ideally, every person with PD and gait impairment should be informed about compensation strategies by a healthcare provider (for example, by a skilled PD physiotherapist), who can also provide expert guidance during their search for the most appropriate strategies. To this end, a variety of strategies should be systematically evaluated in a trial-and-error manner, to identify which suit the patient's unique situation and needs best. However, a study in 320 Dutch physiotherapists and other PD healthcare professionals revealed that 87% did not use such systematic approach, reportedly due to limited knowledge and skills on the topic.[6]

Here, we present a straightforward, practical guide specifically focused on the evaluation of compensation strategies for gait impairment in PD, in support of complementary pharmacological treatments and other elements of physiotherapy.[7] Using this stepwise approach - based on scientific evidence as well as our personal clinical expertise on the topic - we aim to provide healthcare professionals with the tools to evaluate the broad variety of compensation strategies in a systematic, tailored and achievable manner.

1. What element of gait is the primary target?

First, determine your primary gait target – of course, there may be multiple targets within one patient in order to optimize functional mobility. Different strategies likely affect different spatiotemporal gait parameters. For example, due to the nature of

the cues, auditory cueing (e.g. using a metronome) likely targets stride time, whereas visual cueing (e.g. stepping over lines) targets stride length.[8] Therefore, depending on the primary gait target you and your patient wish to improve (e.g. alleviating episodes of freezing or festination, improving gait rhythmicity, increasing step length, increasing gait speed, improving posture, improving gait initiation) the choice of the most appropriate strategies varies. With progressing disease, the primary target(s) may shift due to increased disability or cognitive decline, which is why - ideally - strategies should be re-evaluated periodically.

2. In what context will the strategy be applied in daily life?

Next, evaluate a strategy's efficacy in the context in which it will most likely be applied in daily life. This is important because the efficacy of the strategies tends to vary depending on the context in which they are used.[4] The context could entail a certain environment (e.g. what works in the consulting room does not necessarily translate to a crowded marketplace), or a specific situation (e.g. involving an element of time-pressure, or during dual-tasks such as talking while walking). To this end, if possible, it is especially helpful to arrange a home visit to make an inventory of problems that need to be addressed. Perhaps a specifically problematic turn in the kitchen could be tackled by taping down lines on the floor to prevent the occurrence of freezing.[9] If home visits are unfeasible, you could ask your patient to bring a videotape of their home environment to the consultation, or even videotape themselves in the specific areas or situations in which they experience most difficulties.

3. Does your patient have any specific personal preferences?

Lastly, it is important to consider your patient's personal preferences. While wearing laser shoes, or adopting a new walking pattern may be highly effective, some patients will prefer strategies that are not noticeable to bystanders, avoiding stigmatization or feelings of embarrassment.[10] In these cases, the search for appropriate strategies could be narrowed down to strategies like internal cueing, altering the mental state, action observation and motor imagery. Persons who like to walk alone will probably not be helped by applying action observation, and people who are hesitant to wear headphones in public (e.g. in traffic) will probably not want to use a metronome when walking outdoors. Importantly, you should consider your patient's cognitive status

and learnability, which may largely influence the feasibility of certain compensation strategies. In other words, besides being effective, a strategy should also be usable in daily life according to the intended user: your patient.

Another way to incorporate your patient's preferences is by making use of their skills or hobbies. If they love music, try walking to their favorite tune over using a metronome. If they are - or used to be - an avid ice skater, have them try making skating motions instead of adopting their usual walking pattern. The search for appropriate strategies is truly a collaborative effort between you and your patient.

Table 1. Compensation strategies for gait impairment in Parkinson's disease

Category	Suspected principal mechanism	Examples of strategies
External cueing	Introduction of goal-directed behavior by introducing a movement reference or target; Assist in filtering and prioritizing tasks, especially during response selection under conflict.	• Walking to the rhythm of music; • Stepping over lines on the floor; • Bouncing a ball.
Internal cueing	Helps to achieve focused attention toward specific components of gait, to shift from automatic to goal-directed motor control.	• Counting; • Focusing on a specific component of the gait cycle (e.g. making a heel strike).
Changing the balance requirements	Facilitates the ability to make lateral weight shifts, thereby easing the swing phase of the unloaded leg, particularly in gait initiation or turning.	• Using walking aids; • Making a volitional weight shift before gait initiation; • Making wider turns.
Altering the mental state	Enhancing general alertness and arousal. This may help shift from automatic to goal-directed motor control.	• Reducing anxiety (e.g. mindfulness); • Increasing motivation (e.g. encouraging oneself).
Action observation and motor imagery	Activation of the mirror neuron system may facilitate cortically generated movement.	• Mimicking the gait pattern of another person.
Adopting a new walking pattern	Using alternate motor programs that may be less overlearned and less dependent on the automatic mode of motor control.	• Skipping; • Walking backwards or sideways; • Running; • Making skating movements.
Alternatives to walking*	Walking difficulty may be a task-specific problem.	• Riding a bicycle; • Skateboarding; • Riding a scooter; • Roller skating.

Adapted from: *Nonnekes J, Ruzicka E, Nieuwboer A, et al. Compensation strategies for gait impairments in Parkinson's disease: a review. JAMA Neurology 2019.*[2]

*The use of these alternatives to walking should generally only be explored in patients that already have prior experience in using that mode of transportation, to avoid dangerous situations.

How to educate yourself and your patients on compensation strategies

Compensation strategies are often spontaneously 'invented' by persons with PD themselves. Consequently, many new strategies do not reach healthcare professionals or other patients, even though additional resources on the available strategies are in high demand. To meet this demand, we have developed a dedicated online platform (www.walkingwithparkinson.com) with information on compensation strategies, where patients and professionals can also inspire and learn from each other by sharing videos of their own strategies. The platform is currently available in English and Dutch.

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10

Summary and general discussion

Summary

The aim of this thesis was to generate a deeper understanding of compensation strategies for gait impairment in Parkinson's Disease (PD), in order to pave the way towards a more personalized approach to gait rehabilitation for persons with PD. In **Part I** of this thesis, the prerequisites for personalized care were explored, with a specific focus on adequate representation of men and women in PD clinical trials. In **Part II**, the knowledge and use of compensation strategies among persons with PD and PD healthcare providers was systematically investigated, and the efficacy of a variety of strategies was evaluated in persons with PD and gait impairment. In **Part III**, the neural underpinnings of gait compensation strategies in PD were explored. In **Part IV**, the outcomes presented in this thesis are translated into a practical guide for PD healthcare providers, to using a tailored, personalized approach when applying compensation strategies in daily clinical practice. Here, the main findings of this thesis are summarized. In the General Discussion section, I place the results of this work into a broader context and offer directions for future research.

Part I: Prerequisites for personalized care: representation matters

Underrepresentation of women in Parkinson's disease trials

There is growing recognition that women are underrepresented in clinical trials.[1, 2] In PD, this could have important clinical implications, in light of the role played by biological sex in the pathophysiology, natural history, and management of the disease. In **Chapter 2**, I analysed the male-to-female ratio of study participants in PD randomized clinical trials (RCTs) published between 2010-2016 and compared those to existing prevalence data from a meta-analysis of population-based studies,[3] to explore whether women are adequately represented in PD research. In total, 122 trials met our inclusion criteria (i.e. >50 subjects; both sexes included) comprising of 32,607 participants. The overall prevalence of male PD patients was estimated at 53.1%. In RCTs, men were consistently overrepresented. The overall skew towards more men was almost 7%, ranging from 6% in pharmacological trials to 15% in neurosurgical trials. Of all RCTs, 55.7% of the studies included >59% men. PD patients in RCTs are globally younger than those in prevalence studies. Consequently, it cannot be ruled out that some of the observed differences reflect the male predominance in younger age groups.[3] However, there was no association between mean participant age and percentage of men included in trials. Moreover, prevalence is an underestimate of lifetime risk, which is particularly relevant in this case as women tend to live longer than men. Therefore, the male-to-female difference between RCTs and "true" lifetime

risk is conceivably considerably larger than 7%. These findings suggest that some caution is warranted when extrapolating results from PD trials to women.

In **Chapter 3**, I applied a similar approach to establish the sex-specific prevalence of freezing of gait (FOG) among persons with PD, and explore whether intervention trials targeting FOG are accurately representing men and women. In total, 5702 persons from 16 studies (observational cohort- or cross-sectional design, ambulatory, outpatient or community-based setting; >100 participants with PD and FOG; both sexes included) were included in the final meta-analysis of epidemiological studies. The pooled estimate of overall FOG prevalence was 43%, with no significant difference between prevalence among men and women with PD. In the 51 intervention studies (>10 participants with PD and FOG; intervention targeting both sexes; published between 2014-2019) that were included in the comparative analysis, women were markedly underrepresented. The average proportion of women in trial populations was 29.6%. Overall, just 9 of 51 intervention trials (18%) included a population that was representative in terms of sex. This study demonstrates that sex is not a predictor of FOG and that women are underrepresented in FOG intervention trials. Future studies should establish the exact impact of this sex data gap, by investigating whether sex differences may affect the efficacy of FOG interventions.

Women are markedly underrepresented in clinical trials in Parkinson's disease. Therefore, some caution is warranted when extrapolating results from trials to women. A global effort must be undertaken to include a more representative proportion of women in future studies.

Part II: Systematic evaluation of compensation strategies

Perception and use of gait compensation strategies among Parkinson's disease patients and professionals

Compensation strategies are an essential part in the non-pharmacological management of gait impairment in people with PD. In **Chapter 4**, I evaluated the perception and use of these strategies among healthcare professionals who regularly treat PD patients (>1 monthly) in an online survey study. In the survey, each category of compensation strategies (i.e. external cueing, internal cueing, changing the balance requirements, altering the mental state, action observation and motor imagery, adopting a new walking pattern, and alternatives to normal walking[4]) was briefly

explained, and illustrated by several practical examples. Participants were then queried whether they were previously aware of the existence of said category of strategies, and whether they had ever applied it in their daily practice. The included sample of 320 healthcare professionals consisted of physiotherapists (71%), general nurses (9%), occupational therapists (8%), movement disorders specialists (4%), specialized PD nurses (4%) and other (allied) healthcare professionals (e.g. general practitioners, 3%). Notably, 70% of respondents was affiliated with ParkinsonNet, a nation-wide network of healthcare professionals specifically trained in the management of PD.[5] The study revealed an important knowledge and skills gap. Only 35% of professionals was aware of all categories of compensation strategies. Importantly, just 23% actually applied all seven available categories of strategies when treating people with PD in clinical practice. External and internal cueing were best known among professionals, and were also applied in practice by most respondents. Action observation and motor imagery was the least known category among professionals. Most respondents indicated that a lack of knowledge and skills concerning certain strategies was the main reason why they did not apply all categories in practice, and that they would like to receive additional training on the topic.

In **Chapter 5**, I focused on the experiences of persons with PD. The three aims of this study were (1) to evaluate patients' awareness and actual use of compensation strategies for gait impairments in PD; (2) to investigate the patient-rated efficacy of the various strategies, and whether this efficacy depends on the context in which the strategies are applied; and (3) to explore differences in the efficacy between subgroups based on sex, age, disease duration, freezing status, and ability to perform a dual task. An online survey study was conducted among 4,324 persons with PD and self-reported disabling gait impairments within the Fox Insight cohort (Michael J. Fox Foundation, USA) and ParkinsonNEXT (NL). In the survey, participants were queried on the seven categories of compensation strategies: whether they were aware of the category, whether they had ever applied a strategy from that category in daily life, and how the application had affected their gait in a variety of contexts (e.g. gait initiation, passing a doorway, turning, walking outdoors, and in time-pressure situations). Compensation strategies were commonly used by persons with PD and gait impairments, but their awareness of the full spectrum of strategies was limited. The median number of known categories was 3 of 7, and a striking 1 in 5 patients had no prior awareness of any of the available strategies. Moreover, only 1% of patients had tried strategies from all seven categories. The overall patient-rated efficacy of the strategies was high, but varied per person, and also depended on the context in which the strategy was applied. Exploratory subgroup analyses, however, did not demonstrate truly remarkable differences in the patient-rated efficacy of the different

strategies. The outcomes of this study support the application of compensation strategies for gait impairments in PD, but emphasize that a one-size-fits-all approach to gait rehabilitation is inappropriate.

Persons with Parkinson's disease and healthcare professionals should be – and wish to be – more thoroughly informed about the range of available compensation strategies for gait impairments. The choice of strategies should be tailored to the individual patient and to the context in which the strategy needs to be applied.

Evaluation of gait compensation strategies in patients with Parkinson's disease

Besides external cueing, compensation strategies for gait impairment in PD have rarely been investigated in a systematic manner. In **Chapter 6**, I report on a prospective, lab-based, within-subject design intervention study aimed to: (1) establish the patients' perspective on the efficacy and usability of five different compensation strategies; (2) quantify the effects of these strategies on spatiotemporal gait parameters; and (3) explore associations between the efficacy of specific strategies and patient characteristics. A total of 101 participants with PD and self-reported disabling gait impairments were included. Clinimetrics involved: questionnaires (New Freezing of Gait Questionnaire,[6] Vividness of Motor Imagery Questionnaire,[7] Goldsmiths Musical Sophistication Index[8]), cognitive assessments (Attentional Network Test,[9] Montreal Cognitive Assessment,[10] Brixton spatial anticipation test[11]), and physical examinations (Movement Disorders Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS III][12], Mini-Balance Evaluation Systems Test,[12] tandem gait,[12] and rapid turns test[13]). Gait assessment consisted of six three-minute trials of continuous walking around a six-meter walkway. Trials comprised the following: baseline gait (without strategies), external cueing (metronome), internal cueing (counting), action observation, motor imagery, and adopting a new walking pattern (exaggerated arm swing). Spatiotemporal gait parameters were acquired using 3D motion capture analysis to evaluate strategy efficacy as determined by the change in gait variability compared with baseline gait. Associated patient characteristics were explored using regression analyses. The effects of the different strategies on spatiotemporal gait parameters varied greatly among participants. A similar interindividual variation was noted for patient-rated efficacy and usability of the specific strategies. While participants with higher baseline variability showed larger improvements using compensation strategies, participants without FOG,

with lower MDS-UPDRS III scores, higher balance capacity, and better performance in orienting attention also showed greater improvements in gait variability. The findings of this study highlight the importance of a personalized approach, and provide some insight into the possible underlying mechanisms of compensation.

Even patients with significant gait impairment are able to improve through the application of compensation strategies, but certain levels of cognitive and functional reserve seem necessary to optimally benefit from them.

Part III: Underlying mechanisms of compensation strategies

Cortical correlates of gait compensation strategies in Parkinson's disease.
Not much is known about the potential underlying mechanisms of compensation strategies for gait impairment in PD. In **Chapter 7**, I explored the cortical correlates of external cueing, internal cueing, and action observation using electroencephalography (EEG). Eighteen participants with PD and gait impairment were included. 126-channel EEG was recorded during both stance and gait on a treadmill under four conditions: uncued (without strategies); external cueing (listening to a metronome); internal cueing (silent rhythmic counting); and action observation (observing a video of another person walking). To control for the effects of sensory processing of the cues, relative power changes were computed as the difference in power spectral density between walking and standing for each condition. The application of compensation strategies resulted in changed cortical activity compared to uncued gait, which could not be solely attributed to sensory processing of the cueing modality. Relative to uncued gait, the use of all three compensation strategies induced a decrease of beta band activity in sensorimotor areas, indicative of increased cortical activation. Parieto-occipital alpha band activity decreased with external and internal cueing, and increased with action observation. Only internal cueing induced a change in frontal cortical activation, showing a decrease of beta band activity compared to uncued gait. These findings suggest there are multiple routes to control gait, and different compensation strategies seem to rely on different cortical mechanisms to achieve enhanced central motor activation in persons with PD.

The potential role of the noradrenergic system in facilitating optimal compensation for gait impairment

In **Chapter 8**, I focused on the potential underlying mechanisms of an interesting category of compensation strategies, named: 'Altering the mental state'.[4] Anecdotally, it has been reported that people with PD employ compensation strategies that seem to optimize or alter their arousal state in an effort to improve their gait. Most persons with PD experience a general increase in motor symptoms, including gait impairments, in stressful or anxiety-inducing situations.[14] They therefore often apply strategies to facilitate general relaxation.[14] In contrast, a proportion of patients reports to actually benefit from experiencing – and even inducing – stressful, high-arousal situations.[15] Using data from the survey study presented in **Chapter 5**,[16] I demonstrate that individuals with PD indeed deploy an array of such strategies that differ along an axis of arousal – some act to heighten, whereas others diminish, overall sympathetic tone. I propose a novel theoretical, neurobiological framework to explain why heightened arousal has detrimental effects on the occurrence and severity of gait impairments in some, while resolving them in others. Specifically, I postulate that this seemingly contradicting phenomenon is caused by the inherent features of the ascending arousal system: namely, that arousal is related to task performance in the shape of an inverted u-shaped curve (the so-called Yerkes and Dodson relationship).[17] This hypothesis thus implicates the noradrenergic locus coeruleus - which plays an important part in modulating arousal, as well as mediating network-level functional integration across the brain - in the modulation of PD symptom severity and expression.[18] The ability of the locus coeruleus to facilitate dynamic 'cross-talk' between distinct, otherwise largely segregated brain regions may in fact facilitate the necessary cerebral compensation for gait impairments in PD. In the presence of suboptimal arousal, compensatory networks may be too segregated to allow for adequate compensation, whereas in the presence of supraoptimal arousal, dysfunctionally increased cross-talk between competing inputs of these complementary networks may emerge.[19] Together, these strategies suggest that the noradrenergic system may act as a double-edged sword in gait control in PD.

Gait control when applying a compensatory gait strategy presumably relies on alternative locomotor pathways that provide compensatory input from cognitive, sensory and limbic systems, eliciting increased central motor activation. The noradrenergic locus coeruleus may facilitate optimal compensation of impairments through mediating the strength of functional interactions between these otherwise largely segregated brain regions.

Part IV: Towards personalized gait rehabilitation in Parkinson's disease

A practical guide to the evaluation of compensation strategies for gait impairment in Parkinson's disease

In **Chapter 9**, I present a straightforward, practical guide specifically focused on the evaluation of compensation strategies for gait impairment in PD, in support of complementary pharmacological treatments and other elements of physiotherapy. While the efficacy of compensation strategies is generally very high, the effects of specific strategies vary greatly between patients (**Chapter 5**; **Chapter 6**).[16, 20] Therefore, a personalized approach to gait rehabilitation is imperative to find identify appropriate strategies for every person with PD and gait impairment. Ideally, every person with PD and gait impairment should be informed about compensation strategies by a healthcare provider, who can provide expert guidance in the search for suitable strategies. To this end, a variety of strategies should be systematically evaluated in a trial-and-error manner, to establish which fit the patient's unique situation and needs best. Using a stepwise approach, this can be done in a tailored, achievable manner. First, determine the primary gait target – there may be multiple targets within one patient in order to optimize functional mobility. Depending on the primary gait target, the choice of the most appropriate strategies varies.[21] Second, the efficacy of a strategy should be evaluated in the context in which it will most likely be applied in daily life. It is especially helpful to arrange a home visit to make an inventory of problems that need to be addressed. This is important, as the efficacy of strategies tends to vary depending on the context in which they are used (**Chapter 5**).[16] Finally, the patient's personal preferences should be considered. Besides being effective, a strategy should also be usable in daily life. Notably, the patient's cognitive status and learnability should be kept in mind, which may largely influence the feasibility of certain compensation strategies. Making use of a patient's specific hobbies or skills is another way to incorporate your patient in the decision-making process.

Ideally, a variety of compensation strategies should be explored to facilitate finding appropriate strategies for every person with Parkinson's disease and gait impairment. The personalized search for suitable strategies is truly a collaborative effort between therapist and patient.

General Discussion

I will next discuss these findings in a broader clinical context by covering three important general themes that have been addressed in the four parts of this thesis: 1) Diversity, equity and inclusion in PD research; 2) Unraveling the mechanisms underlying gait compensation strategies; and 3) Translating science into daily clinical practice.

Diversity, equity and inclusion in Parkinson's disease research

Diversity, equity and inclusion in scientific research and clinical practice are important prerequisites to achieve truly personalized care for all persons with PD. It is about welcoming, recognizing and accommodating people's differences, to ensure that every individual gets access to the tools and care they need to thrive. Even though the factors driving healthcare disparities are complex, and include broader societal challenges, we as PD researchers and healthcare providers have a responsibility to implement strategies that will advance treatment for everyone with PD.

Underrepresented populations in biomedical research

This thesis has placed specific emphasis on the inclusion of women in PD trials (**Chapter 2**; **Chapter 3**), as increasing evidence supports that biological 'sex' is a significant factor in the development and expression of PD. [22, 23] Understanding how PD pathology affects the two sexes differently may enable the development of interventions that are specifically tailored to meet the distinct needs of men and women. Furthermore, 'gender' impacts PD multidisciplinary care through its influence on how one copes with the disease and complies to therapy. [24] Following our findings presented in **Part I** of this thesis, demonstrating that women are markedly underrepresented in PD clinical trials, we have adopted sex-specific recruitment targets to ensure appropriate representation of men and women in our own studies. Although the prevalence of PD is estimated to be about 1.5 times higher in men, [25] the equal distribution of men and women among our study participants allowed us to explore potential sex differences in the (perceived) efficacy and usability of compensation strategies for gait impairment. Such subgroup analyses should ideally become a standard practice in future PD intervention trials, especially considering the accumulating evidence on the differences in treatment response to pharmacological therapies and deep brain stimulation (DBS) between men and women. [26, 27]

Although a significant 'gender gap' is still present in PD research and the field of medical science as a whole, considerable efforts have been made in the past decade

to make the inclusion of women in trials a priority. However, besides gender, other important (social) determinants of health have received relatively little attention. Indeed, in our own studies we encountered difficulties to include a diverse population of participants in terms of ethnicity, socioeconomic status and level of education. Almost without exception, our study participants were highly educated, Caucasian individuals. PD trials performed at our center between 2003-2021 show a similar pattern in participant enrollment.[28] Like us, the majority of PD investigators struggles to include an adequately diverse sample of study participants.[29, 30] In fact, in 2016 a staggering 81% of all research that focused on the genetic basis of PD had been carried out in European ancestry populations,[31] even though some evidence suggests that PD incidence and prevalence might vary by race/ethnicity.[32, 33] It is imperative that we gain more insight into the characteristics, risk factors and genetic underpinnings of PD in historically marginalized populations to overcome persisting health inequity.[34] Of course, this problem is not limited to the field of PD research. Less than 2% all cancer clinical trials funded by the National Cancer Institute between 1993-2015 included adequate minority enrollment, despite significant racial and ethnic disparities in incidence and mortality.[35-37] A similarly striking discrepancy between disease burden and representation in clinical trials exists for cardiovascular diseases and diabetes.[38, 39]

Overcoming barriers in recruiting marginalized populations

Research recruitment is generally performed ad-hoc, focusing on an existing pool of previously recruited participants that usually fails to capture the full diversity of the affected population. Efforts to improve the inclusion of underrepresented populations in clinical trials may be hampered by several barriers. These populations - particularly those identifying as a racial or ethnic minority, those with low socioeconomic status, or those living in rural areas - often face unique challenges that may hinder research participation, including: low health and research literacy (an estimated 4.4 million adults in the Netherlands[40]), the presence of a language barrier, distrust of the medical community and the biomedical research enterprise, cultural beliefs surrounding illness and medical procedures, or the lack of a strong social support network facilitating research participation.[41-44] Furthermore, some evidence suggests that women, ethnic minorities, and persons with lower levels of education are also underrepresented in specialized clinics, where clinical trials are typically initiated.[45] Research conducted in the Netherlands found that utilization of specialized health care services is lower among immigrant and lower socioeconomic groups, whereas their use of general practitioner care is higher compared to the rest of the Dutch population.[46]

Ongoing and reinforced initiatives from all parties involved in medical research (i.e. funders, academic institutions, researchers) are imperative to establish a diverse and inclusive research practice.[47, 48] In order to engage underrepresented communities in research, researchers must invest in building long-lasting partnerships with community members.[49] Previous studies on the enrollment of marginalized populations in cancer and diabetes trials found that this can be achieved by accessing the community through trusted and respected 'gatekeepers' (e.g. the imam at a local mosque),[50-52] or enlisting and training community-based primary care providers (e.g. general practitioners, physical therapists) to bring relevant ongoing research projects to the attention of their – often more diverse – patient population.[53, 54] Furthermore, traditional recruitment strategies could be improved by tailoring research information to target a broader patient population. For example, by checking the readability of participant information in terms of language and complexity, and expanding recruitment strategies to include digital outreach (e.g. study promotion through social media).[55, 56] The investment in terms of time and financial resources to achieve community engagement (e.g. to hire or train dedicated personnel) is generally not included in research budgets, and presents a significant hurdle for researchers. Funding agencies should therefore take responsibility to provide the necessary incentives supporting diversity and inclusion in research to inspire maximal public health impact. This may entail: increasing funds for innovative health equity and community-engaged research, and requiring grant applicants to demonstrate their advancement of diversity and inclusion goals as a prerequisite for funding initiation and continuation.[47] Positive examples of such funding initiatives in the field of PD include the recent grant call by the Michael J. Fox Foundation ('*Promoting Diversity, Equity and Inclusion in Parkinson's Disease Research*') and the Parkinson's Foundation '*Community Grants*' (supporting local programs, with particular focus on underserved communities).

Expanding on our current understanding of compensation strategies for gait impairment

As previously discussed, gait partly depends on a basic 'locomotor network', involving spinal central pattern generators, brainstem mesencephalic- and cerebellar locomotor regions, along with striatal input to the primary motor cortex.[57, 58] Moreover, distributed cortical areas, particularly the frontoparietal and supplementary motor areas, are involved in fine-tuning gait.[59] During walking in an automated manner (i.e. without consciously paying attention to it), persons with PD typically have difficulties recruiting these cortical motor areas.[60] The prevailing notion is that adopting a more goal-directed mode of gait control – e.g. through applying a compensatory gait strategy – enables persons with PD to 'bypass' the

posterior putamen (involved in automatic habitual behavior) that is subject to greater loss of dopaminergic innervation compared to the relatively preserved rostromedial striatum (involved in goal-directed behavior). [61, 62] Following our findings presented in **Chapter 7**, we now know that this bypass presumably relies on alternative locomotor pathways, eliciting increased cortical activation and providing compensatory input from cognitive, sensory and limbic systems (Figure 1A-C). [63-65] I hypothesize that one important 'gateway' to these alternative pathways may be the noradrenergic locus coeruleus, mediating the strength of functional interactions between otherwise largely segregated brain regions and thereby facilitating optimal compensation of impairments (**Chapter 8**). Conceivably, subcortical structures such as the cerebellum may also play a vital role within these alternative locomotor pathways. Yet, the exact interconnections or 'routes' that produce gait improvements in PD remain to be unraveled.

In order to obtain a more complete picture of the underlying mechanisms of compensation strategies, future studies should aim to combine the advantages of different methodologies. While EEG has excellent temporal resolution and offers opportunities to record brain activity during actual movement, its spatial resolution is limited. MRI techniques, such as fMRI and diffusion tensor imaging (DTI), provide higher spatial resolution and offer the ability to investigate (sub)cortical structures from a network perspective. However, in addition to poor temporal resolution, it presents with the added limitation of subjects having to lie still inside of a scanner in order to avoid movement artefacts. Historically, this was tackled by having subjects perform a motor imagery task, in which a particular movement (e.g. gait) is imagined but not executed. [66] While motor imagery relies on similar neural processes as the actual performance and planning of movement, [67] it is likely to engage only a portion of the cerebral circuits that control gait. Innovative solutions, such as gait-like foot pedaling paradigms to simulate the stepping motion while lying inside of a scanner, [68] are alternatives to motor imagery that may represent a more accurate surrogate to actual gait. The important element of postural control, however, remains absent. Besides MRI, other inventive techniques, such as measuring cortical excitability (i.e. brain reactivity in response to stimulation) using EEG with concurrently delivered transcranial magnetic stimulation (TMS) [69] may add to this approach and help piece together the puzzle regarding the mechanisms underlying gait compensation strategies. Supported by a grant from the EU Joint Programme – Neurodegenerative Disease Research (JPND), we are now preparing the start of an international, collaborative project involving such multi-modal approach to address some of the major unresolved questions regarding the working mechanisms of compensation strategies for gait impairments in people with PD (specifically: internal and external

cueing strategies). I will now elaborate on three knowledge gaps that I believe to be the most pressing.

First, gaining a deeper understanding of the neural underpinnings driving inter-individual differences in compensation strategy efficacy (**Chapter 5**; **Chapter 6**) is crucial to ultimately work towards a tailored, personalized approach to gait rehabilitation in PD. The pivotal question remains how responders to a certain compensation strategy (i.e., those who benefit from it) differ from non-responders (i.e., those who do not benefit from that same strategy). I hypothesize that non-responders to a specific strategy have difficulties in engaging the alternative locomotor pathway associated with that strategy, resulting in suboptimal recruitment of the cortical motor areas and – with that – suboptimal gait performance (**Chapter 7**). I postulate that the efficacy of a certain strategy will correlate with specific neuroimaging outcomes, including: beta-band power of the sensorimotor areas, the extend of (compensatory) activation of other cortical areas, functional connectivity within compensatory networks, and white matter integrity between these compensatory networks and cortical motor areas.

Second, as explored in **Chapter 5** and **Chapter 6**, the presence of certain patient characteristics may co-determine whether a person is a responder or a non-responder to a certain strategy. The preliminary characteristics identified in this thesis merit further investigation in future trials. Efforts should be undertaken to include a broadly inclusive study population of persons with PD and gait impairment, including patients that are more severely affected. Individuals with cognitive impairment or dementia are often excluded from research studies. [70] However, the inclusion of participants with more outspoken cognitive deficits would be of particular interest here, as cognitive dysfunction may potentially hamper efficient switching from automated to goal-directed gait control, [71] and may also mediate a person's ability to successfully apply gait compensation strategies over a prolonged period of time. For example, over time, patients with cognitive impairment may simply forget to use the strategies when gait impairments arise in every-day life situations. Besides the presence of cognitive impairment, I hypothesize that other patient characteristics, including apathy, depression and the absence of a caretaker, will negatively impact a person's 'compliance' or ability to optimally use compensation strategies in daily life as the disease progresses.

Third, in addition to looking into patient characteristics that may mediate the continued successful application of a specific gait compensation strategy in daily life, the JPND project will also focus on the potential temporal changes within

compensatory networks after long-term use. Although robust evidence is lacking (**Chapter 5**), there are concerns that the efficacy of a strategy may taper off (or 'habituate') over time, necessitating a switch to alternative strategies. Based on anecdotal clinical observations, it is believed that a strategy may become less effective due to overuse, which may make it more vulnerable to underlying disease processes. However, rather than the strategy becoming too 'automatized', I postulate that a possible decrease in strategy efficacy over time is actually related to disease progression, eventually affecting the alternative locomotor pathways subserving compensation, or the neuromodulatory function of the locus coeruleus as well (Figure 1D-E). This could be assessed in a longitudinal study in which behavioral measures (i.e. the effect of the strategy on gait performance, and disease severity scores) are combined with (dynamic) neuroimaging (i.e. following up on the neural fingerprint of the strategy over time).

On a final note, the JPND project will focus primarily on cueing strategies, but it deserves mention that at present, other categories of compensation strategies remain relatively underexposed. Especially considering that each of the main categories of compensation may have its own distinct underpinnings (**Chapter 7**),[4, 72] future investigations should aim to address the full spectrum of compensation strategies. The emphasis on cueing in clinical research, however, is unsurprising. To date, the efficacy of cueing to improve gait in PD is well-established,[73-75] in contrast to other categories of compensation strategies currently lacking studies demonstrating robust evidence (i.e., Class I or II) in support of their usefulness in PD gait rehabilitation. Furthermore, compared to most other compensation strategies, the delivery of external and (audible) internal cues is relatively easy to control in a lab-setting. Considering 'Altering the Mental State' strategies for example, one can imagine that the mere act of being a study subject in an unfamiliar, often clinical, (lab) environment can already significantly affect one's mental state, level of arousal, and behavior. The bias introduced by this well-known 'Hawthorne effect'[76] may be of particular relevance in this category of strategies, complicating the study of its underlying mechanisms as well as its objective efficacy to ameliorate gait in persons with PD. The study of compensation strategies for gait impairment in PD beyond cueing may therefore require the development of more creative, out-of-the-box experimental designs. One of the major challenges remains to develop paradigms and algorithms that not only reliably measure gait in a laboratory setting, but also in home-based or community settings, for example through the use of sensors worn on the body or incorporated into homes.[77]

Translating science into daily clinical practice

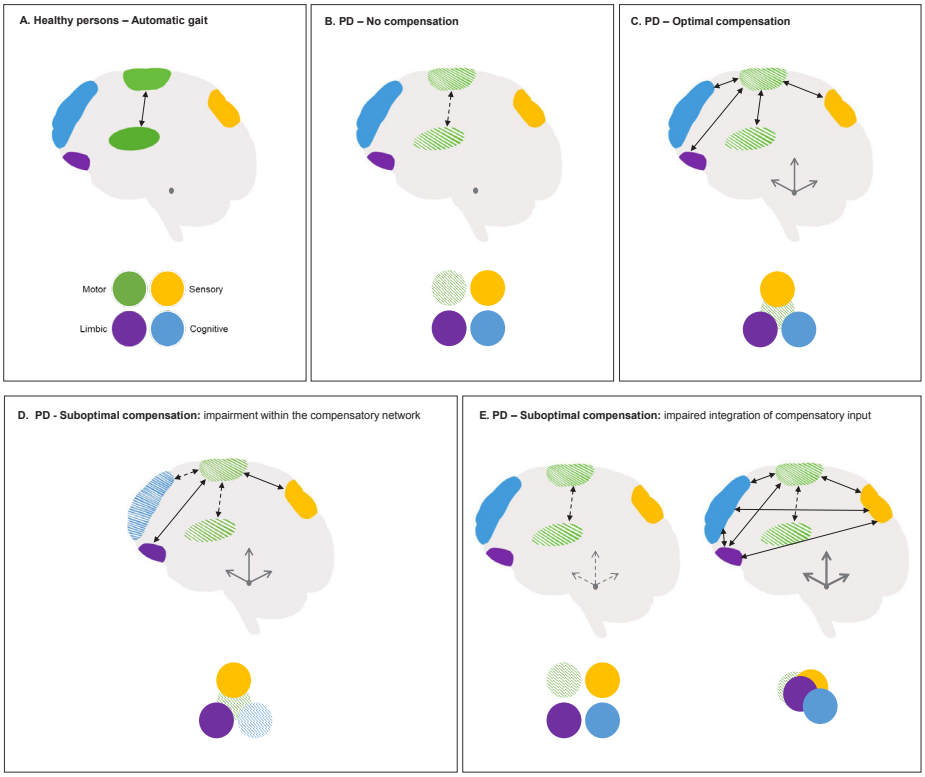
Lastly, I will elaborate on how we could translate our basic scientific understanding of compensation strategies for gait impairment to daily clinical practice, and ultimately work towards optimal access to specialized gait rehabilitation (resources) for all persons with PD. I will touch upon how this may be achieved in the Netherlands, and provide some suggestions for approaches that could be implemented in countries where access to specialized (allied) healthcare services is limited.

Empowering professionals to provide specialized care in a primary practice setting

In the Netherlands, PD care is primarily organized into regional networks of selected and highly trained PD (allied) healthcare professionals. Together these networks form 'ParkinsonNet'.[5] ParkinsonNet was initially focused on setting up a dedicated training program for physiotherapists,[78] but was later expanded to include among others neurologists, rehabilitation experts, PD nurses, speech therapists, dieticians, and psychologists involved in the multidisciplinary management of PD.[79] All affiliated professionals receive specific training to treat patients with PD, based on evidence-based guidelines. Statistics from 2021 show that the majority of Dutch PD patients receiving allied healthcare services are now supported by specialized ParkinsonNet-affiliated therapists rather than generalists for the following disciplines: physiotherapy (59%), speech-language therapy (82%) and occupational therapy (72%).[80] Through this ongoing treatment of large numbers of patients, the expertise of the dedicated networks continues to expand.[5] The added benefit of the (multidisciplinary) ParkinsonNet approach has been cemented by a recent investigation, demonstrating a marked reduction in complications for patients who were treated by specialized ParkinsonNet physiotherapists, compared to those who received generic allied health therapy.[81]

The ParkinsonNet infrastructure offers the opportunity to provide high-quality care from local practices close to the patient's home, rather than university hospitals spread across the country. However, in a highly complex and heterogenous disease such as PD, primary care therapists sometimes wish to receive additional support from experts in secondary or tertiary centers. The survey study among Dutch PD healthcare professionals presented in **Chapter 4** revealed thatspecific knowledge on compensation strategies for gait impairment in PD is suboptimal among physiotherapists – regardless of their affiliation with ParkinsonNet. Therapists indicate that they lack a comprehensive oversight, that they do not use a systematic approach, and that they would ideally like to have the ability to consult an expert on the topic when needed.To this end, the practical guide presented in **Chapter 9** was permanently included in the basic and annual ParkinsonNet training program in 2021.

Figure 1. Hypothetical model of cerebral compensation for gait impairments in Parkinson's disease.



A. Healthy persons. In healthy persons, the primary automatic mode of motor control is intact. Different brain networks are largely segregated, as there is (usually) no need for compensatory input to achieve optimal gait control. **B. Parkinson's disease – No compensation.** Impaired function of the corticostriatal motor network. No compensatory input from other – largely segregated - brain networks. Patients are relying on the affected primary automatic mode of gait control (via the posterior putamen) **C. Parkinson's disease – Optimal compensation.** Impaired function of the corticostriatal motor network can be optimally compensated for by complementary input from other brain networks. This network integration is mediated by locus coeruleus activity. Patients are now relying on the relatively spared goal-directed mode of gait control (via the rostromedial striatum) **D. PD - Suboptimal compensation: impairment within the compensatory network.** Impaired function of the corticostriatal motor network cannot be optimally compensated for, as the associated compensatory network (e.g. cognitive network with internal cueing) is also affected by the disease. As a result, the individual is non-responsive to the strategy that relies on this particular alternative motor pathway. However, other compensation strategies may still succeed in improving gait, as they might rely on different pathways that are still intact (e.g. sensory network with external cueing). **E. PD - Suboptimal compensation: suboptimal integration of compensatory input.** Impaired function of the corticostriatal motor network cannot be optimally compensated for by complementary input from other brain networks, as (1) these networks remain largely segregated due to suboptimal activity of the locus coeruleus; or (2) these networks are engaged in dysfunctionally increased 'cross-talk', due to supraoptimal activity of the locus coeruleus.

< Green circle: intact corticostriatal motor network; Dashed green circle: impaired corticostriatal motor network; Yellow circle: sensory network; Purple circle: limbic network; Blue circle; cognitive network. Dashed blue circle: impaired cognitive network Black double-sided triangle arrows represent a simplified schematic illustration of the functional integration between the different brain regions (which is presumably much more complex than depicted); Dashed arrows indicate the impaired circuitry; Thickness of the dark-grey equilateral barb arrows represents the neuromodulatory activity of the locus coeruleus (depicted here in the rostral pons as a small dark-grey ellipse). PD = Parkinson's disease. Figure inspired by *Gilat et al. (2021)*.[64]

To further address these barriers, healthcare innovations bridging highly sub-specialized (often university-based) PD care with primary care practices should be explored in the future. One idea is to empower primary care physiotherapists in using a systematic, personalized approach to the evaluation of compensation strategies by providing them with the ability to digitally consult a remote expert for on-demand support. One could envision a 'hub-and-spokes' healthcare model, in which a center of expertise (e.g. an academic hospital) would act as a service 'hub' to local primary care practices (the 'spokes') to facilitate the provision of specialized healthcare close to the patients' homes. The hub expert may be digitally consulted when necessary, through the use of existing and secure infrastructure such as the widely-used Siilo application (a messenger that allows for secure communication and sharing of patient videos between medical professionals). To investigate the potential impact of such approach (i.e. its feasibility and usefulness) I would suggest to set up two separate - but closely related - studies. First, a mixed-methods study focused on assessing the feasibility and efficacy of the approach could be conducted in a group of primary care physiotherapists. Qualitative measures could be used to make an inventory of the primary care therapists' experiences with this hub-and-spokes model (e.g. through interviews). Furthermore, (semi-)quantitative measures could be added to investigate whether this approach supports therapists in making the best decisions ('decision support'), and increasing their skills ('continuous learning') regarding the evaluation of compensation strategies for gait impairment in the primary care practice. Potential outcome measures include: the therapists' perceived mastery level regarding the personalized evaluation of compensation strategies pre- vs. post-introduction of the hub-and-spokes approach (0-10), the number of times the hub expert was consulted, and the therapist-expert agreement about the personalized treatment plan (yes/no). Once the feasibility of the approach is established and the digital consultation process has been optimized based on the experiences from this first study, a second study could commence. This second study, a cluster-randomized clinical trial, would now focus specifically on people with PD. The aim of the trial is to investigate whether the systematic evaluation of compensation strategies from the primary care practices embedded in the hub-and-spokes model will also lead to increased mobility and well-being among persons with PD - through a larger reduction of the impact of gait

impairments on daily life activities compared to usual care. The primary outcome could be the change in the Canadian Occupational Performance Measure (patients' rating of their performance on their daily activity of choice that is hindered by gait impairment; 0-10) from pre- to post-intervention. This outcome measure has been successfully applied before, in an earlier randomized controlled trial on the efficacy of occupational therapy for persons with PD.[82] Secondary outcomes may also include: quality of life, fear of falling and self-esteem.

The need for on-demand support on the topic of compensation strategies for gait impairment in people with PD is conceivably considerably higher in other areas of the world that do not have access to an integrated healthcare network like ParkinsonNet. If the hub-and-spokes model is proven to be feasible and useful, it could serve as a template for a similar approach to connect experts in institutions to primary care therapists close(r) to the patients' homes in loosely populated areas (e.g. rural populations in the United States). Furthermore, the approach could potentially be extrapolated to other complex symptoms in PD (e.g. respiratory symptoms or postural deformities), other (allied) healthcare disciplines (e.g. specialized speech therapy), and even to other complex and heterogeneous patient populations (e.g. people with a neuromuscular disease). Of course, the implementation of large-scale healthcare innovations like this warrants appropriate funding.

Facilitating education and (self-)management through the use of technology

Besides this focus on empowering and supporting primary care providers, we should directly target people with PD as well. The findings of the survey study among persons with PD, presented in **Chapter 5**, highlight the great need for patient education on the topic of compensation strategies for gait impairment in PD. Importantly, while the study results show that awareness of compensation strategies is far from optimal in a readily accessible PD population who participate in online surveys, it is likely to be even more scarce in populations with limited access to allied healthcare services.

Particularly since the COVID-19 pandemic, the global desire for technology to facilitate health education and self-management has grown exponentially. To address this need, we have initiated the development of an online platform dedicated to compensation strategies for gait impairment in PD: www.walkingwithparkinson.com. This platform contains background information on PD gait impairment in lay language, and focuses on the framework of seven distinct categories of compensation strategies to overcome these gait impairments: external cueing, internal cueing, changing the balance requirements, altering the mental state, action observation and motor imagery, adopting a new walking pattern and alternatives to walking.[4]

For each of the seven categories a myriad of ready-to-use examples and illustrative patient videos of strategies are available for reference. The platform also includes a printable step-by-step tutorial on how to systematically approach the search for suitable compensation strategies, based on the practical guide provided in **Chapter 9**. The online platform is specifically aimed at persons with PD, their caregivers, and PD healthcare professionals. Since new compensation strategies are typically spontaneously 'invented' by people with PD, an important function of the online platform is to enable persons with PD from all around the world to inspire others by sharing their personal videos of their own creative compensation strategies.

Supported by a Parkinson's Foundation grant, we are now exploring the potential health benefits of the online platform in persons with PD who have limited to no access to specialized (allied) healthcare services. In this study, we assess whether the use of the online platform could elicit a reduction in the perceived impact of gait impairments on daily life activities in a cohort of Brazilian patients who have never received physiotherapy dedicated to improving their walking ability. In Brazil, less than 5% of persons with PD have access to allied healthcare services (based on pilot data from the University of Sao Paolo), but 82.2% of the population has access to the internet.[83] If the use of this online platform aimed at learning about compensation strategies can aid in the management of gait impairments among persons with PD in Brazil, the online approach could potentially be applied elsewhere across the globe to facilitate gait rehabilitation for persons with PD with similarly limited access to specialized healthcare services. This includes persons living in developing countries, where PD prevalence is rapidly growing,[84] as well as persons lacking health insurance or financial resources, and persons living in remote or rural areas with limited means of transportation.[85]

Concluding remarks

Through the study of compensation strategies for gait impairment in PD, we do not solely work towards improved rehabilitation strategies, but also gain a deeper understanding of human motor control in a broader sense. The studies presented in this thesis suggest that there is more than one 'route' to control gait. It is likely that humans in general use multiple routes to control gait (e.g. in the context of urgent situations, or when playing tennis), but that the presence of such alternative routes to motor control only becomes apparent in persons with PD when the primary automatic motor pathway fails. As illustrated by the clinical vignette accompanying **Part IV** of this thesis, this may not only apply to gait control, but to the control of other (complex) movements as well (e.g. swimming, writing), which have anecdotally been reported to improve through the use of compensation strategies in persons with PD.

I hope that this thesis may serve as a preface for a new journey of discovery regarding the potential of compensation strategies to improve gait in persons with PD. Raising awareness about the full spectrum of available strategies among people with PD and healthcare professionals, and gaining more insight into the determinants of inter-individual differences in response to these strategies, as well as their exact underlying mechanisms, will ultimately pave the way towards the development of targeted interventions and a more personalized approach to PD gait rehabilitation.

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11

Nederlandse samenvatting

Nederlandse samenvatting

Dit hoofdstuk geeft een Nederlandse samenvatting van dit proefschrift, en is vooral gericht op lezers zonder uitgebreide achtergrondkennis. De resultaten worden gedetailleerder samengevat en bediscussieerd in **Hoofdstuk 10**.

De ziekte van Parkinson (Box 1 Ziekte van Parkinson) is een hersenaandoening die steeds vaker voorkomt. Elke persoon met parkinson krijgt in de loop van de ziekte in meer of mindere mate te maken met loopproblemen. Stappen worden kleiner, trager, en soms treedt 'bevriezen' van het lopen op (waarbij men het gevoel heeft dat de voeten aan de vloer geplakt staan). Deze problemen leiden regelmatig tot valpartijen en blessures, en hebben een enorme impact op de kwaliteit van leven van mensen met parkinson en hun naasten. Helaas werkt medicatie doorgaans niet voldoende om de hinderlijke loopproblemen te verbeteren.

Box 1 Ziekte van Parkinson

De ziekte van Parkinson is een veelvoorkomende hersenziekte waarbij hersencellen die dopamine maken langzaam afsterven. Door het tekort aan dopamine wat hierdoor ontstaat kan er een brede verscheidenheid aan symptomen optreden. Bewegingen worden trager en kleiner, het lichaam wordt stijver, en er kan sprake zijn van trillen. Naast klachten die te maken hebben met het bewegen, kunnen er ook veranderingen optreden op andere vlakken, bijvoorbeeld in het denken, de stemming, of het slapen. De ziekte van parkinson is progressief en neemt dus over de tijd toe in ernst. Naast cellen die dopamine aanmaken worden ook andere hersencellen aangetast. Helaas is er nog geen behandeling die de ziekte kan genezen of afremmen. Wel zijn er medicijnen waardoor mensen met parkinson minder last hebben van de symptomen. Ook kan bij sommige personen diepe hersenstimulatie (een hersenoperatie) worden toegepast om bepaalde klachten te verlichten. De behandeling van de ziekte van Parkinson vindt doorgaans plaats in een team van verschillende zorgverleners met ieder hun eigen expertise: bijvoorbeeld een neuroloog, parkinsonverpleegkundige, huisarts, fysiotherapeut, ergotherapeut en logopedist.

Gelukkig bedenken mensen met parkinson zelf vaak creatieve manieren om tóch vooruit te kunnen komen. Dit worden ook wel 'compensatiestrategieën' genoemd. Voorbeelden van dit soort strategieën zijn: lopen op het ritme van een metronoom, tellen bij het lopen, het looppatroon van een andere persoon nadoen,

of achteruit lopen. In eerder onderzoek werden de tientallen beschikbare strategieën onderverdeeld in zeven hoofdcategorieën van compensatiestrategieën (Tabel 1). In tegenstelling tot behandelingen met parkinsonmedicatie of hersenchirurgie, zijn compensatiestrategieën echter nog maar zeer beperkt op een wetenschappelijke manier onderzocht. Het doel van het onderzoek dat is gepresenteerd in dit proefschrift was dan ook om meer kennis te vergaren over compensatiestrategieën voor loopproblemen bij mensen met parkinson. Want wanneer we de effecten en onderliggende werkingsmechanismen van deze strategieën beter begrijpen, kunnen we toewerken naar loopbehandeling op maat.

Tabel 1. Classificatie van compensatiestrategieën voor loopproblemen bij de ziekte van Parkinson

Categorie	Voorbeelden van strategieën
Gebruik van externe cues	• Lopen op het ritme van een metronoom, of het ritme van muziek; • Stappen over lijnen op de grond; • Stuiteren met een bal.
Gebruik van interne cues	• Mentaal rekenseries maken (1,2,3,4..); • Focussen op specifieke elementen van het lopen, zoals de haklanding.
Veranderen van de balansvoorwaarden	• Een loophulpmiddel gebruiken; • Een gewichtsverplaatsing maken voor het maken van een stap; • Een ruimere draai maken.
Geestelijke gemoedstoestand veranderen	• Angst of stress verminderen, bijvoorbeeld door mindfulness; • Motivatie vergroten, bijvoorbeeld door jezelf aan te sporen.
Motor imagery / Observeren van lopen	• Het looppatroon van een ander observeren en nabootsen; • Het looppatroon visualiseren en nabootsen.
Een nieuw looppatroon aannemen	• Huppelen; • Schaatsbewegingen maken; • Achteruit of zijwaarts lopen; • De knieën hoog optrekken, of overdreven met de armen zwaaien.
Alternatieven voor lopen	• Fietsen; • Steppen; • Skateboarden.

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Dit proefschrift is opgedeeld in drie delen. In **Deel I** werden de voorwaarden voor zorg op maat geschetst, met een specifieke focus op de vertegenwoordiging van vrouwen in wetenschappelijke onderzoek naar de ziekte van Parkinson. In **Deel II** werd de kennis en het gebruik van compensatiestrategieën geïnventariseerd onder mensen met parkinson en parkinsonzorgverleners. Daarnaast werd ook de

werkzaamheid van een verscheidenheid aan strategieën onderzocht. In **Deel III** werden de onderliggende werkingsmechanismen van compensatiestrategieën verkend. Tenslotte werden de resultaten van dit proefschrift in **Deel IV** vertaald naar een praktische handleiding voor parkinsonzorgverleners in het op maat aanbieden van compensatiestrategieën in de dagelijkse praktijk.

Deel I: Voorwaarden voor zorg op maat

Het was al langer bekend dat vooral mannen meedoen aan wetenschappelijk onderzoek naar bepaalde ziekten en behandelingen. Voor de ziekte van Parkinson was dit nog niet eerder onderzocht. Het is belangrijk dat er genoeg vrouwen meedoen aan wetenschappelijk onderzoek naar parkinson, omdat de ziekte op verschillende vlakken verschilt tussen mannen en vrouwen. Behandelingen die geschikt zijn voor mannen werken daarom mogelijk anders of minder goed bij vrouwen, en andersom. In **Hoofdstuk 2** onderzocht ik de verhouding van mannen en vrouwen die in de periode 2010-2016 meededen aan grote wetenschappelijke studies naar de ziekte van Parkinson. Deze man-vrouwverhouding bleek niet goed overeen te komen met de verhouding mannen en vrouwen die in de 'echte wereld' de ziekte van Parkinson hebben: vrouwen waren duidelijk ondervertegenwoordigd in het merendeel van de onderzochte studies.

In **Hoofdstuk 3** gebruikte ik een vergelijkbare aanpak om te onderzoeken hoe vaak bevriezen van lopen ('freezing') voorkomt onder mannen en vrouwen met parkinson, en of deze man-vrouwverhouding correct wordt weerspiegelt in wetenschappelijke onderzoeken naar de behandeling van freezing. Het bleek dat freezing even vaak voorkomt bij mannen en vrouwen met parkinson, maar dat vrouwen opnieuw ondervertegenwoordigd zijn in studies gericht op de behandeling van dit hinderlijke loopprobleem. In de toekomst moet kritisch gekeken worden hoeveel impact deze scheve verdeling daadwerkelijk heeft, door vast te stellen of er verschillen zijn tussen mannen en vrouwen in de werkzaamheid van behandelingen voor freezing.

In wetenschappelijk onderzoek naar de ziekte van Parkinson doen meestal te weinig vrouwen mee. Sommige onderzoeksresultaten kunnen daarom misschien niet direct worden vertaald naar vrouwen met parkinson. Het is belangrijk dat vrouwen in toekomstige studies beter vertegenwoordigd worden.

Deel II: Systematische evaluatie van compensatiestrategieën

In **Hoofdstuk 4** gebruikte ik een vragenlijst om te onderzoeken wat parkinsonzorgverleners in Nederland weten over compensatiestrategieën voor loopproblemen bij parkinson, en of ze deze strategieën ook gebruiken in hun dagelijkse praktijk. In de vragenlijst werden de zeven categorieën van compensatiestrategieën voorgelegd, en geïllustreerd met een aantal praktische voorbeelden. De studie onthulde dat de kennis en het gebruik van de strategieën onder parkinsonzorgverleners nog niet optimaal is, maar dat zij zeer openstaan voor aanvullende training op dit onderwerp.

In **Hoofdstuk 5** inventariseerde ik op een soortgelijke manier de kennis en het gebruik van compensatiestrategieën onder ruim 4000 mensen met parkinson en loopproblemen. Daarnaast vroeg ik deelnemers om aan te geven welk effect de strategieën hadden gehad op hun lopen in verschillende situaties (bijvoorbeeld bij het zetten van de eerste stap, bij lopen buitenshuis, of wanneer zij stress of tijdsdruk ervoeren). Mensen met parkinson bleken regelmatig compensatiestrategieën te gebruiken in hun dagelijks leven, maar hun kennis over het brede scala aan beschikbare strategieën was – net als bij de zorgverleners – beperkt. Over het algemeen vonden de deelnemers dat de compensatiestrategieën een goed effect hadden op hun lopen. De werkzaamheid van specifieke strategieën varieerde echter sterk per persoon, en hing daarnaast ook af van de situatie waarin de strategie gebruikt werd. Ook mensen met parkinson gaven aan graag meer informatie te willen over dit onderwerp.

In **Hoofdstuk 6** bestudeerde ik de werkzaamheid van verschillende compensatiestrategieën in een looplaboratorium. Uit de metingen onder 101 mensen met parkinson en loopproblemen bleek opnieuw dat de strategieën over het algemeen een goed effect hebben op het lopen, maar dat de werkzaamheid van specifieke strategieën erg verschilt per persoon. Wat werkt voor de één, heeft geen effect – of verergert de loopproblemen zelfs – bij een ander. Zelfs mensen met uitgesproken loopproblemen konden het lopen aanzienlijk verbeteren met behulp van de strategieën, maar bepaalde eigenschappen droegen nog extra bij aan het positieve effect van de strategieën, zoals het beter scoren op bepaalde geheugentesten, of het hebben van betere balans. Ook de uitkomsten van deze studie onderstreepten het belang van een gepersonaliseerde aanpak.

Zowel mensen met parkinson als parkinsonzorgverleners moeten – en willen – beter geïnformeerd worden over het brede spectrum aan beschikbare compensatiestrategieën voor loopproblemen. Een brede kennis is belangrijk, omdat de keuze van geschikte strategieën moet worden afgestemd op het individu en de situaties waarin de strategie zal worden gebruikt in diens dagelijks leven.

Deel III: Onderliggende mechanismen van compensatiestrategieën

Om erachter te komen hoe het komt dat compensatiestrategieën zo goed kunnen werken bij mensen met parkinson, onderzocht ik in **Hoofdstuk 7** hoe het gebruik van een strategie de hersenactiviteit beïnvloedt tijdens het lopen. Ik maakte hiervoor gebruik van een electrodenmuts die van buitenaf oppervlakkige hersenactiviteit kan meten. Deze techniek wordt elektro-encefalografie (EEG) genoemd. Tijdens het succesvolle gebruik van een compensatiestrategie konden mensen met parkinson hun motorische hersenschors (die betrokken is bij het aansturen van bewegingen) beter activeren vergeleken met wanneer ze liepen zonder een strategie te gebruiken. Naast toegenomen activatie van de motorische hersenschors waren verschillende andere hersengebieden meer actief tijdens het gebruik van de compensatiestrategieën. Welke gebieden precies actief waren verschilde per specifieke strategie. Elke strategie lijkt dus een iets ander onderliggend werkingsmechanisme te hebben, wat zou kunnen verklaren waarom de ene strategie bij de ene persoon niet werkt, maar bij de ander wel. Deze bevindingen suggereren daarnaast dat er binnen de hersenen meerdere 'routes' bestaan om het lopen aan te sturen. Als de primaire hoofdroute door de ziekte van Parkinson is aangetast, kunnen deze alternatieve routes met behulp van compensatiestrategieën worden aangesproken. In **Hoofdstuk 8** bespreek ik in meer detail hoe een belangrijke hersenkern (de 'locus coeruleus'), hier mijn inziens aan bijdraagt.

Bij het gebruik van compensatiestrategieën worden waarschijnlijk alternatieve 'routes' in de hersenen aangesproken om het lopen aan te sturen. Elke strategie lijkt een uniek onderliggend mechanisme te hebben, wat zou kunnen verklaren waarom een bepaalde strategie bij de ene persoon wel goed werkt, maar bij een ander niet.

Deel IV: Op naar loopbehandeling op maat voor mensen met parkinson

Tot slot vat ik de bevindingen van dit proefschrift in **Hoofdstuk 9** samen tot een praktische handleiding voor parkinsonzorgverleners in het op maat aanbieden van compensatiestrategieën in hun dagelijkse praktijk. In deze systematische aanpak wordt rekening gehouden met de unieke wensen, vereisten en omstandigheden van de individuele patiënt, om zo voor elke persoon met parkinson en loopproblemen tot passende compensatiestrategieën te kunnen komen. Daarnaast wordt www.radboudumc.nl/lopenmetparkinson geïntroduceerd als hulpmiddel bij dit proces.

Dankwoord | Acknowledgements

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Research data management

Donders Graduate School for Cognitive Neuroscience

Dankwoord | Acknowledgements

En dan is het ineens zover. Nu ik dan toch echt begin aan het schrijven van deze laatste pagina's van mijn proefschrift, laat ik de afgelopen vier jaar graag nog eens de revue passeren. Ik heb ontzettend genoten van mijn tijd als promovenda, en altijd met veel enthousiasme en plezier gewerkt aan de realisatie van dit 'boekje'. Dit mede door de steun en inzet van een grote groep mensen, die ik hier onmogelijk allemaal bij naam kan noemen. Een aantal van hen wil ik via deze weg in het speciaal bedanken.

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Jorik, graag wil ik jou als eerste uitlichten. Wat een eer dat ik de uitvoering van jouw VENI-kindje mede heb mogen verzorgen. Het feit dat ik mijn proefschrift binnen de bepaalde tijd heb kunnen afronden heb ik grotendeels aan jou te danken, en daarvan ben ik me maar al te goed bewust. Jouw internationale reputatie als efficiëntiemachine, of Jorik 'Yesterday' Nonnekes, kan ik dan ook alleen maar onderschrijven. Het was mooi om jouw ontwikkeling tot (o)PI van dichtbij te mogen meemaken. Bedankt dat je naast het glansrijk vervullen van je eigen professionele ambities, mij ook altijd op sleeptouw neemt en actief meedenkt over de volgende stappen in mijn onderzoekscarrière. Hoewel ik meermaals gekscherend heb geopperd: 'Knap hoor, hoe je het allemaal doet' – meestal in de context van een niet nader te bespreken smoothie-incident – zit daar stiekem toch een kern van waarheid in. Wat betreft het balanceren van carrière, gezin en vrije tijd ben jij voor mij absoluut een rolmodel. Ik hoop dat ik jouw voorbeeld kan blijven volgen nu voor mij weer een nieuwe fase in de kliniek aanbreekt.

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Curriculum vitae

Anouk Tosserams was born on November 13th 1994 in 's-Hertogenbosch, the Netherlands. After graduating cum laude from secondary school (Scholengemeenschap Lelystad) in 2012, she started her medical training at the Radboud University, Nijmegen. Anouk performed a scientific elective at the Institute of Exercise and Environmental Medicine in Dallas (USA) in 2015, as part of the Radboud University Honours Programme for Medical Sciences. She investigated the association between brain white matter integrity and physical function in persons with mild cognitive impairment under the supervision of Dr. Jurgen Claassen and Prof. Dr. Rong Zhang. In 2016 she performed another scientific elective at the Institut de Myology, Hôpital de la Pitié-Salpêtrière in Paris, under the supervision of Dr. Nicol Voermans and Prof. Dr. Pascal Laforêt, focused on improving diagnostics in mitochondrial myopathies, supported by a personal grant from the Prinses Beatrix Spierfonds. After completing a dedicated year at the department of Neurology at the Radboudumc, Anouk obtained her medical degree in 2019, graduating cum laude. She then started her PhD project at the Radboud Centre of Expertise for Parkinson and Movement Disorders, aimed at gaining a deeper understanding of compensation strategies for gait impairment in Parkinson's disease, under the supervision of Prof. dr. Bastiaan R. Bloem, Prof. dr. Vivian Weerdesteyn and dr. Jorik Nonnekes. The results of that project are presented in this thesis. Anouk implemented her research findings in clinical practice through the co-development of an interactive online platform aimed at informing persons with Parkinson's disease and healthcare providers about the broad spectrum of available gait compensation strategies (EN: www.walkingwithparkinson.com; NL: www.radboudumc.nl/lopenmetparkinson). Her work was highlighted by international media, and awarded with the Klokhuis Wetenschapsprijs 2023. During her time as a PhD candidate, Anouk initiated fruitful collaborations with distinguished international research groups. She received a personal van Leersum grant from the Royal Netherlands Academy of Arts and Sciences, as well as a Christine Mohrmann Stipendium from the Radboud University. Furthermore, she contributed to several successful international grant applications. As of May 2023, Anouk is working as a resident in Neurology at the Radboudumc. As a postdoctoral researcher, she continues to be involved in several projects on gait rehabilitation for people with Parkinson's disease.

List of publications

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** These authors contributed equally.*

Portfolio

Courses and workshops	Organizer	Year	ECTS*
Introduction Day	Radboudumc	2019	0.25
Graduate School Introduction Day	Donders Graduate School	2019	0.25
Graduate School Day 1 & 2	Donders Graduate School	2019-2020	0.5
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	NFU BROK Academie	2019	1.5
The Art of Presenting Science	Radboud University	2019	1.5
Introduction in using R	Radboudumc	2019	0.25
Neuroanatomy	Cognitive Neuroscience, Radboud University	2019	3
Projectmanagement voor promovendi	Radboud University	2019	2
Poster Pitching	Radboud University	2019	1
Workshop Gait & EEG	Carl von Ossietzky Universität Oldenburg	2019	1
Statistics for PhD candidates by using SPSS	Radboud University	2019	2
Design and Illustration	Radboud University	2020	1
MEG/EEG Toolkit	Donders Graduate School	2020	2
Introduction to Matlab	Coursera	2020	1
Scientific Integrity Course	Radboudumc	2021	1
OGEN WIJD OPEN! De kunst van de non-protocollaire diagnose	Radboudumc	2021	1.7
The Art of Finishing Up	Radboud University	2022	0.4

External lectures and conferences	Role	Location	Year	ECTS
Nederlandse Vereniging voor Fysiotherapie in de Geriatrie (NVFG) conference	Invited lecture	Nieuwegein	2019	0.1
ParkinsonNet basic training for physiotherapists	Invited lecture	Nijmegen	2021	0.1
ParkinsonNet conference	Invited lectures	Nieuwegein	2019-2022	0.2
Movement Disorders Society International Virtual Congress (MDS)	Poster presentations	online	2020-2021	0.1
World Congress of the International Society of Posture and Gait Research (ISPGR)	Oral presentations	Montréal, Canada	2022	1

* ECTS (European Credit Transfer System) equals a workload of 28 hours

Research visits	Supervisor	Year	Duration
Brain and Mind Centre, University of Sydney, Australia.	Prof. dr. Simon Lewis	2022	6 weeks
Northumbria University, Newcastle Upon Tyne, UK.	Dr. Sam Stuart	2022	1 week

Project supervision	Title	Year	Duration
Kris Smits (Master)	The individual effect of six different compensation strategies highly varies among patients with Parkinson's disease: a call for a more personalized approach in gait rehabilitation.	2020	3 months
Willanka Kapelle (Master)	Towards personalized gait rehabilitation: Correlations between patient characteristics and the efficacy of compensation strategies on improving gait in patients with Parkinson's disease.	2020	6 months
Lisanne Wit (Bachelor)	Compensation strategies for gait impairments in Parkinson's disease: a survey among 2,440 patients.	2020	6 months
Tijmen Geurts (Master)	Exercise intolerance: exploring patterns and discriminative value in neuromuscular diseases.	2021	6 months
Tess Bal (Master)	Exploring the mechanisms underlying compensation strategies for gait impairment in Parkinson's disease using electroencephalography.	2021	11 months
Marije Asbreuk (Master)	Predictors of future falls in persons with Parkinson's disease.	2022	1 month

Research data management

General information about the data collection

Research projects part of this thesis were performed in adherence to the applicable laws and ethical guidelines. Data were collected and stored at the Radboud university medical center, Nijmegen the Netherlands.

Ethics

This thesis is based on the results of medical-scientific research with human participants. Studies were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). Informed consent was obtained from research participants. Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage). The studies reported in Chapter 4 and Chapter 5 met the requirements for exemption from the medical ethics committee review, as determined by the Institutional Review Board of the Radboud University Medical Center in Nijmegen, the Netherlands (Ref: 2019-5737). Studies reported in Chapter 6 and Chapter 7 were approved by the Institutional Review Board of the Radboud University Medical Center in Nijmegen, the Netherlands, and the local Medical Ethics Committee Arnhem-Nijmegen (ref: 2019-5710). Research presented in the remaining chapters did not involve human data.

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Privacy

The privacy of the study participants has been warranted through the use of unique individual subject codes. The code list was stored separately from the research data and was only accessible to pre-specified project members.

FAIR principles

Findable

Data were stored on the server of the department of Rehabilitation at the Radboud university medical center: Q:\Research\100 PEARL-PD. Part of the data of the experimental gait studies (Chapters 6 and Chapter 7) was also stored in the online data management system Castor EDC. Paper CRF files were stored in the department's archives (M352.-1.337).

Accessible

The anonymous datasets that were used for analysis are available on reasonable request by contacting the staff secretary of the department of Rehabilitation at the Radboud university medical center (secretariaatstaf.reval@radboudumc.nl).

Interoperable

Documentation was added to the data sets to make the data interpretable. The documentation links to publications, references to the location of the data sets and description of the data sets. The data were stored in the following file formats: .sav (SPSS Statistics Data Document), .xlsx (Microsoft Office Excel), and .mat (MATLAB, Mathworks, USA). No existing data standards were used, such as vocabularies, ontologies or thesauri.

Reusable

The data will be stored for at least 15 years after termination of the study concerned and can therefore be reused in this time period. There is no embargo on the accessibility of the data for future research purposes, as long as the proposed research question is in line with the research goal of the approved study protocol.

Donders Graduate School for Cognitive Neuroscience

For a successful research institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognized as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defenses please visit: https://www.ru.nl/donders/graduate-school/phd/.

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