

Mobility, Stability, Adaptability

The challenges of walking for people with Hereditary Spastic Paraplegia



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Lotte van de Venis

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Hereditary Spastic Paraplegia

Lotte van de Venis

The studies presented in this thesis were carried out at the Department of Rehabilitation, Donders institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen, The Netherlands.

The printing and distribution of this thesis was financially supported by:
Radboud University Medical Centre | Donders Institute for Brain, Cognition and Behavior | Scientific College Physical Therapy (WCF) of the Royal Dutch Society for Physical Therapy (KNGF) | Motek Medical | Merz Therapeutics | Ipsen Farmaceutica B.V. | OIM Orthopedie

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 **Koninklijk Nederlands
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Aangesloten bij KNGF

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orthopedie

ISBN

978-94-6284-322-6

Cover design

Anne Thomaes | www.glasatelierthomaes.com

Printed by

Ipskamp Printing | proefschriften.net

Layout and design

Daisy Zunnebeld | persoonlijkproefschrift.nl

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Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

vrijdag 7 juni 2024
om 10.30 uur precies

door

Lotte van de Venis
geboren op 11 mei 1993
te Zwolle

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Chapter 1

General introduction

General introduction

Everyone occasionally stumbles, trips or falls. But what if this starts to occur more frequently? If you start stumbling at work when going for a cup of coffee? Or if you feel as if you trip and fall over the slightest irregularity in the pavement, or it becomes challenging to engage in a conversation while walking. You experience leg stiffness that is becoming more noticeable and fatiguing over time. Even though you value social interactions, at times you decide to skip sports activities, birthdays, and stay inside while groceries and packages are being delivered. Nevertheless, the leg stiffness intensifies, and colleagues start making comments, asking whether you might have an injury, because it looks like you have some trouble walking. In an attempt to describe what you feel, you use the example of walking with a 'potato bag' over your legs. You feel as if you are clumsily waddling around with a heavy bag filled with potatoes, slow, off-balance, and bothersome every step you make. Several members of your family (have) experience(d) similar problems, but nobody has yet sought medical care. When consulting a general practitioner, you are referred to a neurologist. After several investigations, it turns out that the leg stiffness you experience is called 'spasticity', caused by a condition called 'hereditary spastic paraplegia'. You are referred to a rehabilitation physician who explains that the leg problems are slowly progressive, but that it is difficult to predict the rate of progression. You learn that spasticity, including muscle stiffness, muscle cramps and restless legs, can be alleviated with medication and exercises, but that additional muscle weakness and loss of deep sensibility will progressively hamper your balance and gait capacity.

Hereditary Spastic Paraplegia

Hereditary Spastic Paraplegia (HSP) refers to a genetic and clinical heterogeneous group of movement disorders.^{3,4} From a clinical perspective, HSP can be classified into pure or complex forms.⁵ Pure forms of HSP generally present with progressive bilateral spasticity, muscle weakness, and loss of proprioception of the lower extremities.³ In addition, urinary dysfunctions like incontinence or hesitance are common.⁶⁻⁸ In complex forms of HSP, additional neurological deficits may be present, such as ataxia, cognitive impairments, seizures, peripheral neuropathy, or upper extremity involvement.³ The prevalence of HSP is estimated to be about 2-10 of 100.000 individuals in the general population.⁹ The first signs and symptoms are often subtle with the development of leg stiffness, which may present at any age between infancy until late adulthood. Insight in the individual prognosis is limited, but disease progression is generally slow.^{10,11} Yet, a later onset has been associated with a faster disease progression.¹⁰⁻¹²

The common pathological feature of HSP is a retrograde axonal degeneration of the corticospinal tracts, posterior spinal columns, and, to a lesser extent, the spinocerebellar fibers.⁴ This degeneration may be due to e.g. abnormal membrane trafficking, axonal development, or mitochondrial functioning.¹³ To date, up to 87 genetic subtypes associated with HSP have been identified. The different genetic forms are assigned spastic paraplegia loci (SPG) based on sequential numbering in the order of discovery (e.g., SPG4, SPG8). Autosomal dominant, autosomal recessive, X-linked and mitochondrial modes of inheritance have all been reported.¹⁴ Of note, it is estimated that a genetic diagnosis can still not be made in 51-71% of all suspected cases, despite the introduction of whole exome sequencing. This is due to the large number of genes involved in HSP and the regular discovery of new genes.¹⁴

Gait functioning

As illustrated above, the ability to walk is an important part of daily living: it enables us to move around within our home and community, and is, therefore, an important factor promoting independent living, social participation and quality of life.^{15,16} It requires more than just lifting one foot and placing it in front of the other. In contrast, purposeful walking requires a sufficient level of gait functioning that consists of three aspects: stepping, maintaining dynamic balance, and gait adaptability.¹⁷

Stepping

First, people have to generate a basic stepping pattern. This relates to the rhythmic and repetitive movements of the legs in interaction with the trunk in order to generate propulsion (i.e., forward movement of the body).¹⁷ The description of the stepping pattern is commonly based on distance (i.e., spatial) or time (i.e., temporal) spanned between gait events, referred to as spatiotemporal gait parameters (e.g., step length, step width or step time). Furthermore, position and orientation of body segments is often used, referred to as joint kinematics (e.g., knee flexion or extension).

Maintaining dynamic balance

Second, people require dynamic balance control, referring to the ability to remain stable and upright while walking, despite the occurrence of both self-initiated perturbations (e.g., the destabilizing impact of ankle push-off required for forward propulsion) and external perturbations (e.g., bumping into another person or walking over uneven terrain).¹⁷ To recover from such perturbations requires sufficient proactive and reactive balance control, depending on a well-functioning sensory system to adequately register when dynamic balance is jeopardized, and a good motor system to generate a coordinated response. Then, three strategies can be used to maintain balance while walking. Preferred are 1) the foot placement strategy (i.e., people alter foot placement of the swing leg to adjust

the base of support), and 2) ankle strategies (i.e., ankle moments of the stance leg are modulated to make (minor) adjustments to center of mass movements). When both strategies are hindered, 3) hip strategies can be used (i.e., upper body segments are rotated around the center of mass).¹⁸ Several methods then exist to objectify dynamic balance. In clinical practice, this is often done as part of clinical tests that assess balance capacity (e.g., with the Mini Balance Evaluations Systems Test). More recently, there is growing interest in the use of biomechanical measures that assess dynamic balance or 'gait stability'. Gait stability measures often require sophisticated motion capture systems and complex calculations.¹⁹ In this thesis, we refer to the following measures of gait stability: gait variability, margin of stability, foot placement deviation, and Lyapunov exponents (for a detailed description – see box 1).

Gait adaptability

Finally, people require adaptive capabilities during gait, so that the stepping pattern can be altered to meet environmental demands. Nine domains have been identified that necessitate gait adaptability: (1) obstacle negotiation (e.g., alter step length to step over a loose tile), (2) temporal demands (e.g., slowing down in a busy street), (3) cognitive dual-tasking (e.g., engaging in a conversation while walking), (4) terrain demands (e.g., walking over uneven surfaces), (5) ambient demands (e.g., lighting or familiarity with the surroundings), (6) postural transitions (e.g., turning while walking), (7) motor dual-tasking (e.g., manipulating a phone while walking), (8) physical load (e.g., carrying a bag), and (9) maneuvering in traffic.¹⁷ It is evident that gait adaptability is of high importance for safe and independent ambulation in the community.¹⁷ Gait adaptability can be assessed using clinical tests, such as the obstacle subtask of the Emory Functional Assessment Profile (E-FAP)^{20,21}, or the recently developed Walking Adaptability Ladder test for Kids (WAL-K).²²

Box 1. Biomechanical methods to assess dynamic balance

Gait variability

Gait variability is defined as the fluctuation in spatiotemporal characteristics that occur from step to step during walking.¹⁹ Variability is commonly determined for step length, step time, and step width, and expressed in a standard deviation or coefficient of variation (i.e., standard deviation divided by the mean). It is often assumed that a higher spatiotemporal gait variability reflects reduced gait stability.²³⁻²⁵

Margin of Stability

In order to maintain balance during quiet stance, one has to be able to maintain one's center of mass (CoM) within the area encompassed by both feet - the so-called base of support (BoS). In order not to fall in dynamic situations, for example during gait, a similar requirement exists where the so-called "extrapolated center of mass" (XCoM; a variable that takes both position and velocity of the CoM into account) needs to be maintained within the base of support (BoS).²⁶ The distance between the XCoM and the BoS is called the margin of stability (MoS). If the MoS is negative (i.e., the XCoM exceeds the BoS), the person has to make an adjustment – for example take a step – to prevent a fall. A MoS value approaching null, or an increase in the variability of the MoS are therefore considered to reflect gait instability.²⁷

Foot Placement Deviation

The foot placement deviation (FPD) reflects the adherence to the foot placement strategy. This strategy is based on the preposition that CoM position and CoM velocity at midstance can predict the ideal foot placement of the next step.²⁸ To ensure that the actual foot is placed at this predicted ideal location, adjustments in the timing and location of the actual foot placement have to be controlled. The accuracy of the foot placement strategy is reflected in the root mean square error (RMSE) of the actual foot placement compared to the predicted foot placement. A higher RMSE indicates a lower accuracy of the foot placement strategy, which indicates reduced gait stability.²⁹

Local Dynamic Exponents

Local dynamic exponents (LDEs) reflect the ability of a person to attenuate the effects of small perturbations during gait.¹⁹ For example, in an optimal condition, the variability of trunk displacements during consecutive steps is nil. However, due to small perturbations that arise during natural gait (e.g., during heel strike or small differences in floor height), trunk displacements will be somewhat different from one step to the other. If these differences are not attenuated, their impact will increase exponentially with time. A higher LDE implies that a person is less able to attenuate small gait perturbations, indicating less gait stability.³⁰

The impact of HSP on gait

HSP-related signs and symptoms impact on all three requirements of purposeful walking: In general, people with HSP show a reduced gait speed and reduced step length in comparison to healthy controls.^{31,32} From the early stages of HSP, increased trunk movements during gait can be observed. Previous studies have reported on this phenomenon, though it is not completely clear how these enhanced trunk movements should be interpreted. Presumably, the increased trunk movements are generated to improve foot clearance and step length, but there may be additional explanations.^{33,34} Step width can initially be increased as a compensation to aid balance. Yet, when HSP progresses, hip adductor spasticity increases, which often causes a narrowing of step width. This can result in scissoring gait; a gait pattern in which the legs cross each other.^{32,33,35} Furthermore, due to spasticity and progressive shortening of the calf muscles, toe walking can be seen; a gait pattern characterized by the absence of heel-to-floor contact.³⁶

Loss of proprioception results in delayed balance responses, while spasticity of the lower extremities, contractures and subsequent ankle foot deformities (e.g. pes equinovarus) may further hinder adequate balance control. Indeed, both feet-in-place responses during unperturbed standing, and the ability to make effective balance correcting steps following perturbations can be hampered.³⁷ With respect to gait adaptability, progressive spasticity, muscle weakness and balance impairments may hinder the ability to alter the gait pattern to changing environmental demands. It is therefore understandable that HSP-related signs and symptoms result in reduced gait functioning.¹⁶

Impact of HSP on activities and participation in daily life

For people with HSP, balance and gait impairments are among their most disabling symptoms.¹⁶ It challenges a variety of daily activities, like standing still, stepping over objects, walking on uneven terrain, or getting in and out of a car. This hinders personal hygiene, employment, housekeeping and participation in leisure activities.¹⁵ In addition, activities that require standing or walking generally cost people with HSP more effort and energy compared to their peers.^{15,38} In order to compensate, intensity of daily physical activities is often reduced, or certain activities are ceased completely. A higher severity of gait impairments – specifically when an aid is required to walk – is associated with a reduced quality of life.^{35,39}

As the severity of balance and gait impairments progresses, the risk of falls and fall-related injuries increases: 67% of people with HSP report to fall at least once a year, and in 51%, a fall has led to an injury at least once. It is well known that the experience of a fall may trigger a vicious cycle⁴⁰⁻⁴²: due to the fall, people may develop fear-of-falling. Indeed, in the aforementioned study, 73% of people with HSP stated they were moderately to very afraid of falling.¹⁶ A fear of falling can

make people more cautious and make them cease certain activities, even when they are still physically capable of doing them. This can result in physical inactivity and deconditioning, along with a decline in muscle strength and balance capacity, which further increases fall risk.⁴²

To prevent or break this vicious cycle, insight is needed into parameters that can identify people with HSP who are at increased risk of falling in order to tailor fall prevention interventions. Currently, this is a relatively unexplored topic in people with HSP.

Clinical management of balance and gait problems in HSP.

During consultations with their physician and allied health professionals, people with HSP prioritize the rehabilitation of their balance and gait problems.⁴³ As there are currently no therapies available to prevent, delay or reverse the progressive impairments due to HSP, the clinical management of balance and gait problems in people with HSP must be symptomatic. Possible interventions consist of four domains: (1) exercise therapy (e.g. aimed at maintaining muscle length and functional skills), (2) pharmacological interventions (e.g. to reduce troublesome spasticity), (3) walking aids and orthotic devices, including orthopedic footwear (e.g. to support foot clearance and compensate for foot deformities), and (4) surgical interventions (e.g. to reduce disabling spasticity or contractures). In addition, self-management programs (e.g. directed at fatigue management or attaining adequate levels of physical activity) can be indicated. Some people may require psychosocial support to deal with, for instance, emotional or societal consequences.^{43,44}

A few studies have evaluated the efficacy of gait training interventions.⁴⁵ The interventions were mainly task-specific, and consisted of functional gait training in combination with intramuscular botulinum toxin⁴⁶, robotic gait training (e.g., Lokomat® or exoskeleton)^{47,48}, or hydrotherapy⁴⁹. Following these interventions, promising improvements were reported regarding balance capacity, gait capacity, pain relief, and quality of life.⁴⁶⁻⁴⁹

Although these results are promising, most of the studies used an uncontrolled design comparing pre vs post-training assessments, and included a small number of participants. None of the aforementioned gait training interventions included context-specific tasks that targeted gait adaptability required for walking in the community. Therefore, part of this thesis focuses on the effect of a gait adaptability training in ambulatory people with pure HSP. Gait adaptability training was provided on the C-Mill, a treadmill equipped with augmented reality that provides context-specific gait adaptability training exercises (for a detailed description of the C-Mill - see Box 2).

Box 2. C-MILL

The C-Mill^{1,2} (Motek, Amsterdam, The Netherlands) is a treadmill setup with a walking area of 1x3meters, integrated force plates, a projector, and a safety frame. Visual context (e.g., stepping targets or obstacles) can be projected onto the walking surface to create an augmented reality environment. This is done in an interactive manner. Due to online monitoring of the position and timing of foot placement of the user via the integrated force plates, the visual context can be projected in a gait-dependent manner, and real-time feedback of success or failure can be provided.

The C-Mill has specifically been designed to train gait adaptability in a context-specific manner. It offers various tasks, including goal-directed stepping, obstacle negotiation and adaptation to various walking speed. This mimics daily life, as walking in the community requires a person to be able to adapt their gait to meet environmental demands, such as negotiating one's way through a cluttered terrain, increasing walking speed for a green traffic light, or slowing down speed in a crowded area.

The C-Mill provides a safe training environment, given that it has a safety harness for fall protection. As an additional feature, an optional body-weight support system can be installed to unload patients up to 40% of their body weight. Regarding the work presented in this thesis, the body-weight support feature was not used during the gait adaptability training. Training was always supervised by a physical therapist with ample experience in C-Mill training.

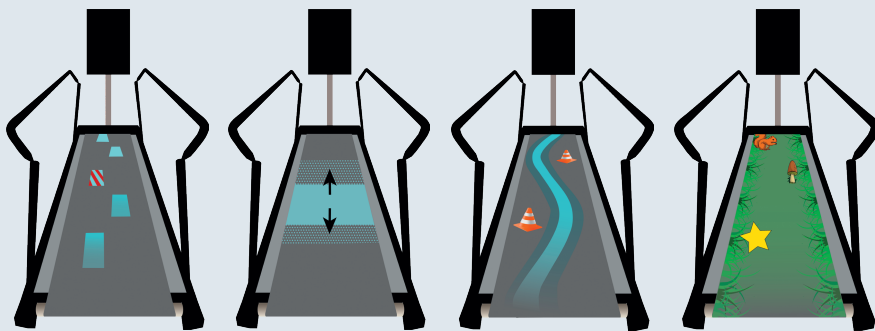


Figure 1: The C-Mill with various exercises projected onto the treadmill belt.

Outline of the thesis

The aim of this thesis is to gain more insight into how balance and gait impairments in people with pure HSP affect their gait capacity. More specifically, we will investigate which factors impact negatively or positively on symptom severity, gait adaptability and fall risk. Furthermore, we will evaluate whether context-specific gait training can improve gait adaptability in people with pure HSP.

Based on clinical experience, it is likely that sufficient levels of daily physical activity have a positive impact on the severity of spasticity-related symptoms, whereas psychological stress may impact negatively. In **Chapter 2**, I investigate this assumption, and report on the results of an online questionnaire that was conducted to evaluate the impact of Covid-19 measures in people with HSP. The Covid-19 measures provided a unique opportunity to evaluate whether changes in levels of physical activity and psychological stress were associated with changes in symptom severity, such as muscle stiffness, pain, or gait impairments.

In **Chapter 3**, I describe the research protocol of a randomized clinical trial with a partial cross-over design that was conducted to evaluate the efficacy of a context-specific gait adaptability training in ambulatory people with HSP. **Chapter 4** presents the results of this randomized clinical trial. I evaluate the efficacy of a five-week gait adaptability training program, added to usual care, to usual care alone on outcome measures related to balance and gait capacity, balance confidence and physical activity. Furthermore, I evaluate potential retention effects of the gait adaptability training after fifteen weeks.

In **Chapter 5**, I take a closer look at increased trunk movements that are observed during gait in people with HSP and investigate whether these trunk movements can (partly) be explained as balance correcting strategies. To this end, I explore whether there is an association between increased trunk movements and reduced balance performance. In **Chapter 6**, I evaluate whether commonly used clinical tests evaluating balance confidence, balance capacity or gait capacity, and novel biomechanical measures of gait stability differ between people with HSP and healthy controls, and whether these tests may have the potential to differentiate fallers from non-fallers among people with HSP. Finally, in **Chapter 7**, the main findings of this thesis are summarized and discussed, and implications for clinical practice and future research are provided.

Reference list

1. Roerdink, M.B., PJ, Device for displaying target indications for foot movements to persons with a walking disorder. 2009.
2. Roerdink, M., et al., Online gait event detection using a large force platform embedded in a treadmill. *J Biomech*, 2008. 41(12): p. 2628-32.
3. Shribman, S., et al., Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*, 2019. 18(12): p. 1136-1146.
4. Salinas, S., et al., Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol*, 2008. 7(12): p. 1127-38.
5. Harding, A.E., Classification of the hereditary ataxias and paraplegias. *Lancet*, 1983. 1(8334): p. 1151-5.
6. Braschinsky, M., et al., Bladder dysfunction in hereditary spastic paraplegia: what to expect? *J Neurol Neurosurg Psychiatry*, 2010. 81(3): p. 263-6.
7. Schneider, S.A., et al., Urinary symptoms, quality of life, and patient satisfaction in genetic and sporadic hereditary spastic paraplegia. *J Neurol*, 2019. 266(1): p. 207-211.
8. Joussain, C., et al., Urological dysfunction in patients with hereditary spastic paraplegia. *Neurourol Urodyn*, 2019. 38(4): p. 1081-1085.
9. Ruano, L., et al., The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology*, 2014. 42(3): p. 174-83.
10. Harding, A.E., Hereditary "pure" spastic paraplegia: a clinical and genetic study of 22 families. *J Neurol Neurosurg Psychiatry*, 1981. 44(10): p. 871-83.
11. McDermott, C., et al., Hereditary spastic paraparesis: a review of new developments. *J Neurol Neurosurg Psychiatry*, 2000. 69(2): p. 150-60.
12. Loureiro, J.L., et al., Autosomal dominant spastic paraplegias: a review of 89 families resulting from a portuguese survey. *JAMA Neurol*, 2013. 70(4): p. 481-7.
13. Blackstone, C., C.J. O'Kane, and E. Reid, Hereditary spastic paraplegias: membrane traffic and the motor pathway. *Nat Rev Neurosci*, 2011. 12(1): p. 31-42.
14. Saputra, L. and K.R. Kumar, Challenges and Controversies in the Genetic Diagnosis of Hereditary Spastic Paraplegia. *Curr Neurol Neurosci Rep*, 2021. 21(4): p. 15.
15. Kerstens, H., et al., Stumbling, struggling, and shame due to spasticity: a qualitative study of adult persons with hereditary spastic paraplegia. *Disabil Rehabil*, 2020. 42(26): p. 3744-3751.
16. van Lith, B.J.H., et al., Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*, 2020. 15(1): p. 64.
17. Balasubramanian, C.K., D.J. Clark, and E.J. Fox, Walking adaptability after a stroke and its assessment in clinical settings. *Stroke Res Treat*, 2014. 2014: p. 591013.
18. Reimann, H.J., JJ, Strategies for the Control of Balance During Locomotion. *Kinesiology Review*, 2017. 7: p. 1.
19. Bruijn, S.M., et al., Assessing the stability of human locomotion: a review of current measures. *J R Soc Interface*, 2013. 10(83): p. 20120999.
20. Fonteyn, E.M., et al., Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration. *Gait Posture*, 2014. 40(1): p. 247-51.

21. Heeren, A., et al., Step by step: a proof of concept study of C-Mill gait adaptability training in the chronic phase after stroke. *J Rehabil Med*, 2013. 45(7): p. 616-22.
22. Kuijpers, R., et al., Reliability and construct validity of the Walking Adaptability Ladder Test for Kids (WAL-K): a new clinical test for measuring walking adaptability in children. *Disabil Rehabil*, 2022. 44(8): p. 1489-1497.
23. Toebes, M.J., et al., Local dynamic stability and variability of gait are associated with fall history in elderly subjects. *Gait Posture*, 2012. 36(3): p. 527-31.
24. Ma, L., et al., Gait variability is sensitive to detect Parkinson's disease patients at high fall risk. *Int J Neurosci*, 2022. 132(9): p. 888-893.
25. Schniepp, R., et al., Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. *J Neurol*, 2014. 261(1): p. 213-23.
26. Hof, A.L., M.G. Gazendam, and W.E. Sinke, The condition for dynamic stability. *J Biomech*, 2005. 38(1): p. 1-8.
27. Fallahtafti, F., et al., Margin of Stability May Be Larger and Less Variable during Treadmill Walking Versus Overground. *Biomechanics (Basel)*, 2021. 1(1): p. 118-130.
28. Wang, Y. and M. Srinivasan, Stepping in the direction of the fall: the next foot placement can be predicted from current upper body state in steady-state walking. *Biol Lett*, 2014. 10(9).
29. Zwiijgers, E., et al., Impaired foot placement strategy during walking in people with incomplete spinal cord injury. *J Neuroeng Rehabil*, 2022. 19(1): p. 134.
30. Mehdizadeh, S., A robust method to estimate the largest Lyapunov exponent of noisy signals: A revision to the Rosenstein's algorithm. *J Biomech*, 2019. 85: p. 84-91.
31. Serrao, M., et al., Dataset on gait patterns in degenerative neurological diseases. *Data Brief*, 2018. 16: p. 806-816.
32. Klebe, S., et al., Gait analysis of sporadic and hereditary spastic paraplegia. *J Neurol*, 2004. 251(5): p. 571-8.
33. Serrao, M., et al., Gait Patterns in Patients with Hereditary Spastic Paraparesis. *PLoS One*, 2016. 11(10): p. e0164623.
34. Adair, B., et al., Kinematic gait deficits at the trunk and pelvis: characteristic features in children with hereditary spastic paraplegia. *Dev Med Child Neuro*, 2016. 58(8): p. 829-35.
35. Gaßner, H., et al., Functional gait measures correlate to fear of falling, and quality of life in patients with Hereditary Spastic Paraplegia: A cross-sectional study. *Clin Neurol Neurosurg*, 2021. 209: p. 106888.
36. Nonnekes, J., et al., Improved Gait Capacity after Bilateral Achilles Tendon Lengthening for Irreducible Pes Equinus Due to Hereditary Spastic Paraplegia: a Case Report. *J Rehabil Med Clin Commun*, 2021. 4: p. 1000059.
37. Nonnekes, J., et al., Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia. *J Rehabil Med*, 2017. 49(5): p. 369-377.
38. Rinaldi, M., et al., Increased lower limb muscle coactivation reduces gait performance and increases metabolic cost in patients with hereditary spastic paraparesis. *Clin Biomech (Bristol, Avon)*, 2017. 48: p. 63-72.
39. Klimpe, S., et al., Disease severity affects quality of life of hereditary spastic paraplegia patients. *Eur J Neurol*, 2012. 19(1): p. 168-71.

40. Yardley, L. and H. Smith, A prospective study of the relationship between feared consequences of falling and avoidance of activity in community-living older people. *Gerontologist*, 2002. 42(1): p. 17-23.
41. Delbaere, K., et al., Fear-related avoidance of activities, falls and physical frailty. A prospective community-based cohort study. *Age Ageing*, 2004. 33(4): p. 368-73.
42. Scholz, M., et al., Fear of falling and falls in people with multiple sclerosis: A literature review. *Mult Scler Relat Disord*, 2021. 47: p. 102609.
43. Kerstens, H., et al., Healthcare needs, expectations, utilization, and experienced treatment effects in patients with hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*, 2021. 16(1): p. 283.
44. Veenhuizen, Y., et al., Self-management program improves participation in patients with neuromuscular disease: A randomized controlled trial. *Neurology*, 2019. 93(18): p. e1720-e1731.
45. Bellofatto, M., et al., Management of Hereditary Spastic Paraplegia: A Systematic Review of the Literature. *Front Neurol*, 2019. 10: p. 3.
46. Paparella, G., et al., Efficacy of a Combined Treatment of Botulinum Toxin and Intensive Physiotherapy in Hereditary Spastic Paraplegia. *Front Neurosci*, 2020. 14: p. 111.
47. Bertolucci, F., et al., Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. *NeuroRehabilitation*, 2015. 36(1): p. 93-9.
48. Seo, H.G., B.M. Oh, and K. Kim, Robot-assisted gait training in a patient with hereditary spastic paraplegia. *Pm r*, 2015. 7(2): p. 210-3.
49. Zhang, Y., et al., The effect of hydrotherapy treatment on gait characteristics of hereditary spastic paraparesis patients. *Gait Posture*, 2014. 39(4): p. 1074-9.



Chapter 2

Covid-19 reveals influence of physical activity on symptom severity in Hereditary Spastic Paraplegia

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Published: Journal of Neurology. 2020 Dec;267(12):3462-3464.

Abstract

Objective

Hereditary spastic paraplegia (HSP) is characterized by progressive spasticity of both lower extremities. Spasticity-related symptoms are common, and thought to be positively influenced by physical activity, and negatively by psychological stress. The lockdown due to the COVID-19 pandemic created an opportunity to explore its impact on symptom severity in HSP.

Methods

During the fifth week of the partial lockdown in the Netherlands, fifty-eight pure HSP patients rated possible changes in levels of physical activity, psychological stress and symptom severity via a web-based questionnaire.

Results

The partial lock-down reduced the physical activity in 74% of patients with HSP, whereas 43% reported an increase in psychological stress. Reduced physical activity was associated with increased muscle stiffness, pain, physical fatigue and gait impairments, whereas increase psychological stress was independently associated with increased mental fatigue.

Conclusions

Our results underscore the potential impact of physical activity on symptom severity in people with HSP.

Introduction

Hereditary spastic paraplegia (HSP) is a neurodegenerative disorder, characterized by progressive spasticity and muscle weakness of both lower extremities.¹ Spasticity-related symptoms such as muscle stiffness and gait impairments are common and disabling in HSP.² Moreover, patients experience a substantial burden from both physical and mental fatigue.² Our clinical experience is that physical activity positively impacts on these symptoms, whereas psychological stress may impact negatively. This has, however, not been formally investigated. The (partial) lockdown due to the COVID-19 pandemic has profoundly changed people's normal routine, assumably reducing levels of physical activity and increasing psychological stress,³ thereby creating an opportunity to explore the influence of these changes on symptom severity in HSP.

Methods

We conducted a web-based survey among people with pure HSP² in the Netherlands. An invitation was sent to participants from our previous survey (n=109), which was approved by our regional medical-ethics committee. Participants were asked to rate possible changes in levels of physical activity, psychological stress, and symptom severity on a 5-point Likert scale. They were invited and completed the questionnaire during the fifth week of the partial lockdown in the Netherlands. Descriptive statistics were used to analyze the primary data. Additionally, chi-square tests (or Fisher-exact-tests if appropriate) were used to test whether changes in physical activity and psychological stress were associated with changes in symptom severity ($p < 0.05$). When both physical activity and psychological stress were associated with a specific change in symptom severity, multivariate logistic forward regression analysis was applied to correct for collinearity of these independent determinants.

Results

Fifty-eight participants returned a completed survey. Their average age was 57 years (range: 30-77) and 47% was male. A reduction of physical activities was reported by 74% (33% strong decrease, 41% mild decrease), whereas 19% reported no change and 7% mild increase. An increase in psychological stress was reported by 43% (3% strong increase, 40% mild increase), 50% reported no change, and 7% decrease (2% strong, 5% mild). The majority reported a general increase in symptom severity (figure 1).

Participants with reduced physical activity more often experienced increased muscle stiffness ($p=0.001$), pain ($p=0.004$), physical fatigue ($\chi^2(1)=4.680$, $p=0.031$), and gait impairments ($\chi^2(1)=5.129$, $p=0.024$) compared to those with no change or an increase

in physical activity (figure 2). The same trend was seen for balance impairments ($\chi^2(1)=3.291$, $p=0.070$). Those who reported increased levels of psychological stress more often reported an increase in muscle stiffness ($\chi^2(1)=4.612$, $p=0.032$), pain ($\chi^2(1)=3.943$, $p=0.047$), and mental fatigue ($\chi^2(1)=6.234$, $p=0.013$). Forward regression analysis of muscle stiffness and pain revealed that only decreased physical activity was independently associated with an increase in muscle stiffness ($R^2=0.222$ ($p<0.001$) and pain ($R^2=0.193$ ($p=0.003$)).

Six participants were treated with intramuscular botulinum toxin injections to reduce spasticity-related symptoms. During the lockdown, treatment continued in five participants.

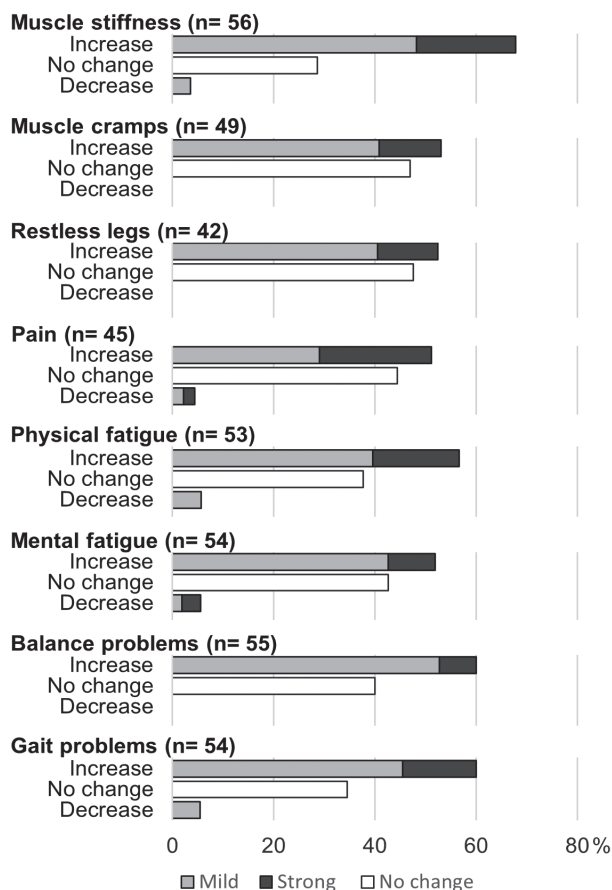


Figure 1. The impact of the COVID-19 partial lockdown measures on spasticity-related symptoms in people with pure HSP. Participants reported whether the experienced symptom severity increased (mild or strong), decreased (mild or strong) or did not change. Only participants who experienced a specific symptom (either before or after the lockdown) are included in the figure.

Discussion

The partial lock-down in the Netherlands due to the COVID-19 pandemic resulted in a reduction of physical activity in the majority of participants with HSP, which proved to be associated with increased muscle stiffness, pain, physical fatigue and gait impairments. This result is coherent with findings in other chronic (neurodegenerative) conditions⁴ and underscores the potential impact of physical activity on symptom severity in people with HSP. Future studies may investigate whether the present findings can be extended to other conditions resulting in spastic paraparesis (e.g. multiple sclerosis and primary lateral sclerosis). Future studies may also evaluate the effect of interventions targeting daily physical activity in this population, preferably including objective outcomes, which were lacking in the present study. Another limitation is the lack of comparison between current and previous clinical status, which was not possible due to the lockdown restrictions. An additional limitation is the risk of selection bias, which may have resulted in an overestimation of changes in physical activity, psychological stress, and/or symptom severity. The question remains whether people with HSP are able to return to 'baseline' levels of functioning after release of the lockdown and expected increase in physical activity.

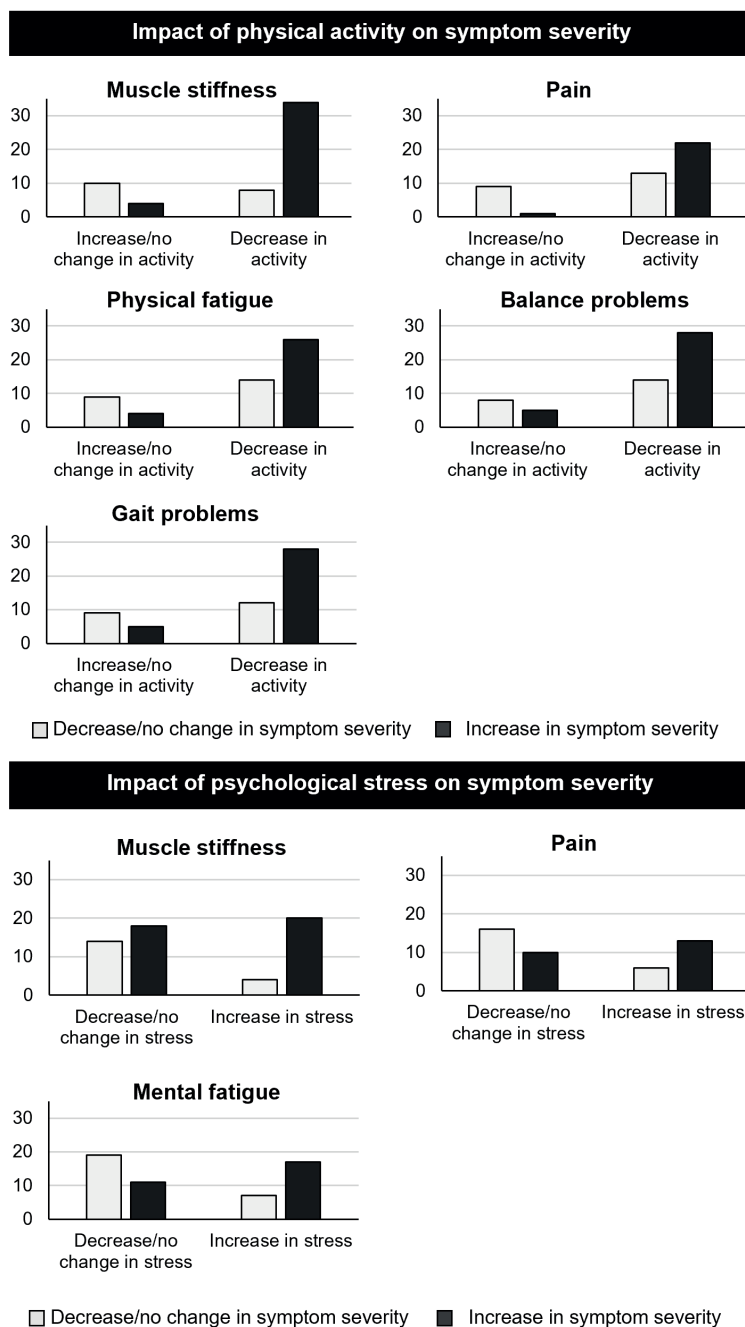
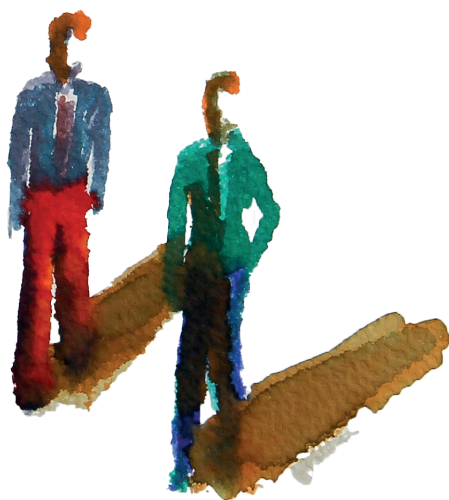


Figure 2. The impact of physical activity and psychological stress on symptom severity in people with pure HSP. Y-axis represents number of people with HSP who experienced the symptom.

Reference list

1. Shribman S, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *The Lancet Neurology*. 2019.
2. van Lith BJH, Kerstens H, van den Bemd LAC, et al. Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*. 2020;15(1):64.
3. Helmich RC, Bloem BR. The Impact of the COVID-19 Pandemic on Parkinson's Disease: Hidden Sorrows and Emerging Opportunities. *J Parkinsons Dis*. 2020;10(2):351-354.
4. van der Kolk NM, de Vries NM, Kessels RPC, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol*. 2019;18(11):998-1008.



Chapter 3

Improving gait adaptability in patients with Hereditary Spastic Paraplegia (Move-HSP): Study protocol for a randomized clinical trial

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Published: Trials. 2021 Jan 7;22(1):32

Abstract

Background

People with hereditary spastic paraplegia (HSP) experience difficulties adapting their gait to meet environmental demands, a skill required for safe and independent ambulation. Gait adaptability training is possible on the C-Mill, a treadmill equipped with augmented reality, enabling visual projections to serve as stepping targets or obstacles. It is unknown whether gait adaptability can be trained in people with HSP. The aim of Move-HSP is to study the effects of ten 1-hour sessions of C-Mill training, compared with usual care, on gait adaptability in people with pure HSP. In addition, this study aims to identify key determinants of C-Mill training efficacy in people with pure HSP.

Method

Move-HSP is a five-week, two-armed, open-label randomized controlled trial with a cross-over design for the control group. Thirty-six participants with pure HSP will be included. After signing informed consent, participants are randomized (1:1) to intervention or control group. All participants register (near) falls for fifteen weeks, followed by the first assessment (week 16), and, thereafter, wear an Activ8 activity monitor for seven days (week 16). The intervention group receives 10 sessions of C-Mill training (twice per week, 1-hour sessions; week 17-21), whereas control group continues with usual care (week 17-21). Afterwards, both groups are re-assessed (week 22). Subsequently, the intervention group enter follow-up, whereas control group receives 10 sessions of C-Mill training (week 23-27), is re-assessed (week 28) and enters follow-up. During follow-up, both groups wear Activ8 activity monitors for seven days (intervention group: week 23, control group: week 29) and register (near) falls for fifteen weeks (intervention group: week 23-37, control group: week 29-43), before the final assessment (intervention group: week 38, control group: week 44). The primary outcome is the obstacle subtask of the Emory Functional Ambulation Profile. Secondary outcomes consist of clinical tests assessing balance and walking capacity, physical activity and fall monitoring.

Discussion

Move-HSP will be the first RCT to assess the effects of C-Mill gait adaptability training in people with pure HSP. It will provide proof-of-concept for the efficacy of gait adaptability training in people with pure HSP.

Background

Hereditary spastic paraplegia (HSP) is a heterogeneous group of neurodegenerative disorders, caused by retrograde axonal degeneration of the corticospinal tracts, fasciculus gracilis fibers and, to a lesser extent, the spinocerebellar fibers.¹⁻³ Pure forms of HSP are clinically characterized by progressive spasticity, muscle weakness and reduced proprioception in the lower extremities, as well as difficulties in making rapid (alternating) leg movements.⁴⁻⁶ Additional symptoms are present in complex forms of HSP, including mental retardation, epilepsy, ataxia, peripheral neuropathy or optic atrophy.^{1, 4, 7} For people with pure HSP, gait and balance impairments are among the most disabling symptoms. They especially experience difficulties when forced to adapt their gait to meet environmental demands, hampering the ability to walk safely and independently in the community.^{4, 8-11} A recent study reported that 57% of pure HSP patients fell at least twice a year, and 73% experience fear of falling.¹¹ Incorporating gait adaptability training in rehabilitation programs for people with pure HSP seems, therefore, logical and potentially beneficial.^{4, 11, 12}

A limited number of task-specific gait interventions has shown to improve walking capacity in people with pure HSP. Twenty-five sessions of robot-assisted exoskeleton and overground walking improved walking velocity and balance capacity.¹³ In addition, eighteen sessions of robotic Lokomat® training increased walking speed, balance capacity and quality of life.⁹ Even though these results are promising, the interventions lacked tasks that promote gait adaptability. As a consequence, it remains unknown whether people with pure HSP will benefit from gait adaptability training.⁴ Furthermore, it is unclear how to tailor gait rehabilitation programs to the individual patient with HSP as it is currently unknown which determinants can predict training efficacy.

To fill this gap, Move-HSP is the first randomized controlled trial to provide proof of concept for the efficacy of gait adaptability training in people with pure HSP. The training takes place in a safe environment on the C-Mill, a treadmill providing augmented reality via visual projections onto the treadmill. Participants will train obstacle negotiation, precision stepping, and unexpected accelerations and decelerations. Its feasibility and efficacy have been described in multiple neurological populations, including patients with stroke,¹⁴ cerebellar ataxia¹⁵ and multiple sclerosis.¹⁶

Currently, the clinical experience with gait adaptability C-Mill training for people with pure HSP is positive, but the scientific evidence is lacking.⁴

Objectives

This study aims to provide an essential step towards evidence-based and individually tailored gait rehabilitation in people with HSP. The objectives are twofold:

1. To study the effect of ten 1-hour sessions of C-Mill training on gait adaptability in people with pure HSP.
2. To identify key determinants of C-Mill training efficacy in people with pure HSP.

Methods

Regulation statement

Move-HSP will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the Medical Research Involving Human Subjects Act. The protocol is written in accordance with the SPIRIT 2013 checklist.

Study design and setting

Move-HSP is a five-week, single-center, two-armed, open-label, randomized controlled trial (RCT), with a cross-over design for the control group, as they receive the intervention after a waiting list period. The study is conducted at the Radboud University Medical Centre (Radboudumc) within the Centre of Expertise for Parkinson & Movement Disorders; Nijmegen, The Netherlands. C-Mill training can be given at the Radboudumc (Nijmegen, The Netherlands), Paramedisch centrum Rembrandt (Veenendaal, The Netherlands), Stichting Tante Louise (Bergen op Zoom, The Netherlands) and Fysiotherapiepraktijk De Lindehoeve (Voorschoten, The Netherlands). Other training locations may be added while the study is ongoing, depending on the success of participant inclusion.

Recruitment and selection

Participants will be recruited at the Center of Expertise for Parkinson & Movement Disorders of the Radboudumc (part of the European Reference Network for Rare Neurological Diseases (ERN-RND)). The treating physician informs the patient about Move-HSP and asks for permission whether the investigator (LV) may contact the patient. In addition, a request to participate will be sent to members of the HSP working group of the patient organization "Spierziekte Nederland". Those who are interested can contact the investigator and will receive an information letter. After two weeks, the investigator (LV) will contact those who expressed their interest and ask for their final decision. If patients agree to participate, eligibility is checked. After inclusion, participants can leave the study at any time without consequences.

Eligibility

For inclusion, participants will have to meet the following inclusion criteria:

- Diagnosis of pure HSP by a neurologist specialized in inherited movement disorders. Diagnosis is based on inheritance pattern and clinical examination, and when available, molecular diagnosis,
- age between 18-70 years old,
- ability to walk barefoot on a level ground for 50 meters without a walking aid (use of orthotic devices or orthopedic shoes is allowed).

Participants will be excluded if they suffer from other neurological, orthopedic or psychiatric conditions, or if patients underwent an HSP-related surgical procedure of the lower extremities.

Group allocation and blinding

Participants will be allocated at random to the intervention group or to the (waiting list) control group following a 1:1 ratio. Randomization will be stratified based on disease duration (2 categories: 0-15 years; >15 years) in blocks with a variable size (n=4 or n=6) to prevent an uneven distribution between groups. To determine disease duration, participants are asked for the year of symptom onset. Randomization will be performed in CastorEDC, a web-based data management system for academic studies (www.castoredc.com). Blinding of participants is not possible, as participants will know whether they receive C-Mill training or continue with usual care. The primary investigator (LV) takes part in the training sessions as a physical therapist and, therefore, cannot be blinded either.

Participant timeline

The outline of this study is shown in Figure 1. Following inclusion, participants are randomly allocated to either the intervention group or the control group (waiting list). During the first fifteen weeks, all participants register (near) falls in a digital fall calendar. Thereafter, participants will have the first assessment at the movement laboratory (Radboudumc; week 16). Following this assessment, participants wear an Activ8 activity monitor for seven consecutive days (week 16). Thereafter, the *control group* enters a waiting period of five weeks (week 17-21), whereas the *intervention group* starts with five weeks of gait adaptability training on the C-Mill (Week 17-21). Each session lasts one hour and takes place twice per week. Subsequently, both groups are re-assessed (week 22). Following this second assessment, the intervention group enters the follow-up period, whereas the control group wears the Activ8 activity monitors for seven days (week 22), starts five weeks of gait adaptability training (week 23-27), has the third assessment (week 28), and, thereafter, enters the follow-up period. During follow-up, both groups wear Activ8 activity monitors during the first week (intervention group: week 23, control group: week 29) and,

additionally, register (near) falls for fifteen weeks (intervention group: week 23-37, control group: week 29-43). After follow-up, participants have a final assessment in the movement laboratory (intervention group: week 38, control group: week 44).

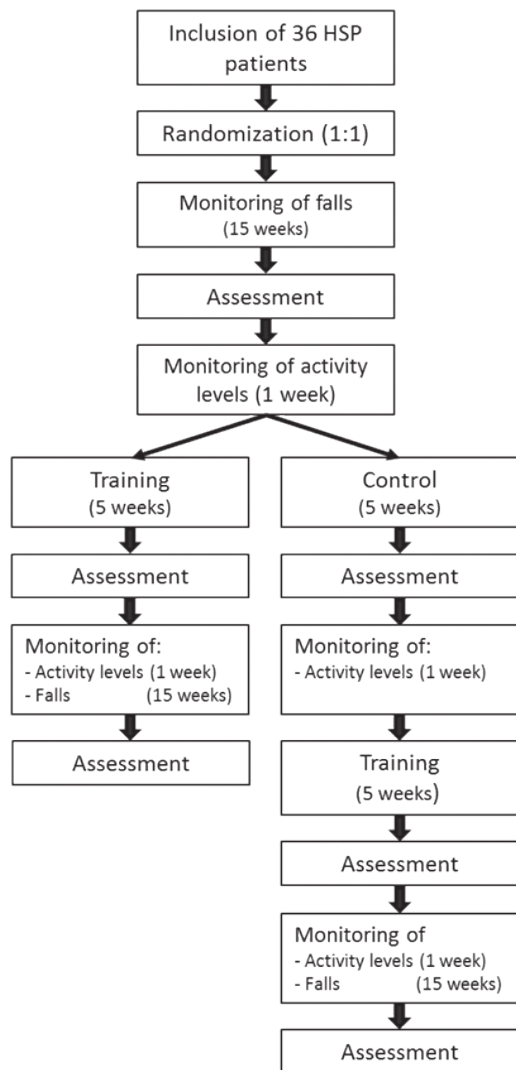


Figure 1. Flowchart of the study protocol

During Move-HSP, all participants can continue their usual care. For some participants, this may include local intramuscular injections of botulinum toxin (BTX). To limit the influence of BTX injections on the outcomes, the scheduling of the

assessments will consider the date of the BTX injections. BTX injections induce an effect on muscle spasticity approximately two weeks post-injection. The maximum effect is reached around 6-8 weeks, after which it gradually subsides.^{17, 18} Participants who receive BTX injections in the lower extremities will have the pre-intervention assessment four weeks post-injection, and the post-intervention assessment ten weeks post-injection. In addition, it will be monitored whether the dosage of oral antispasmodic change during the trial.

Control group

The eighteen participants attributed to the control group are asked to continue with their daily routine and usual care during the five weeks on the waiting list. If therapy is part of the usual care, participants are requested to continue with the same frequency and composition during the waiting period.

Intervention: C-Mill training

Gait adaptability training takes place on the C-Mill (Motek Medical, Culemborg, The Netherlands). The C-Mill is a treadmill, providing augmented reality via visual cues projected onto the treadmill. The projections are either stepping targets or obstacles that challenge the participants to adjust their steps accordingly. The training sessions take place during five consecutive weeks, twice per week during 60-minute sessions. In total, participants will train gait adaptability on the C-Mill for 10 hours.

The C-Mill protocol is based on clinical experience and finalized after a focus group discussion with expert physical therapists. The training sessions are logged to ensure compatibility and a consistent progression. Each session starts with a ten-minute warming-up, followed by five training blocks (figure 2, video). Each training block lasts approximately eight minutes. Block A targets precision stepping by practicing accurate foot placement on the projected stepping tiles. Block B targets obstacle negotiation by avoiding the projected obstacles. Block C elicits changes in the direction of progression by using a variety of slalom trajectories. Block D targets precision acceleration and deceleration, as the participants must walk within a projected square that moves forward and backward on the treadmill. Block E challenges walking at different walking speeds. Block F is the endgame, a five-minute track that combines several gait adaptability components in an interactive way. All sessions end with a cooling-down. To further promote the level of variability, each training block consists of small components (i.e. for block A: Stepping Tiles: belt speed will momentarily increase; width between the stepping stones will momentarily decrease). In addition, different walking speeds are used: 100% is the participant's comfortable walking speed on the treadmill. This will be determined during the first training session. The belt speed will be manually increased until the participant experiences it as comfortable. The therapist will then increase the belt

speed with 0.3 m/s and slowly decrease the belt speed until the participant again experiences it as comfortable. The average of both speeds will be used to set the comfortable walking speed. Other percentages (e.g. 40%, 70%, 120%) are derived from this reference speed. The C-Mill training will be carried out by a physiotherapist with C-Mill certification. Progression over the training period is initiated and controlled by this therapist and based on the patient's capacity and performance. It comprises of increasing the level of task variability, increasing obstacle size, and the addition of a dual task, for example the use of the auditory Stroop task. During the Stroop task, participants listen to an audiotape presenting a random sequence of the words "high" or "low", expressed in either a low-pitched voice or a high-pitched voice. They are asked to respond aloud indicating the pitch of the word ("high" or "low"), while ignoring the (randomly conflicting) semantic meaning of the word.

Procedure and assessments

All outcome measurements will be collected during the assessments at the movement laboratory (table 1). The intervention group is evaluated three times: pre C-Mill training (week 16), post C-Mill training (week 22), and at the end of the follow-up (week 38). The control group is evaluated four times: pre waiting-list (week 16), post waiting-list (week 22), post C-Mill training (week 28), and at the end of the follow-up (week 44). The assessments will follow a standardized protocol and are conducted by the primary investigator (LV) who is trained to perform the outcome measurements. As the primary investigator takes part in the training sessions, outcome assessment cannot be blinded. During all assessments, the use of orthotic devices and/or orthopedic footwear is allowed depending on the task. No other (walking) aids are allowed. If participants use any orthotic or orthopedic device during a task, this will be registered and kept constant throughout the consecutive assessments.

		Training Blocks	Variation within training	Progression over training
60 minutes	10 min	Warming-Up		
	8 minutes	A	Precision stepping • Velocity [40%; 120%] • Step length • Step width	• Increase variation in step width • Decrease available reaction time • Add auditory task (double task)
	8 minutes	B	Obstacle negotiation • Velocity [100%; 120%] • Obstacle width	• Increase obstacle size • Decrease available reaction time • Add auditory task (double task)
	8 minutes	C	Direction of progression • Velocity [40%; 70%] • Slalom trajectory	• Increase variation in slalom trajectory
	8 minutes	D	Precision acceleration • Degree of acceleration	• Increase degree of acceleration • Increase the required precision of acceleration
	8 minutes	E	Walking velocity • Range of gait speeds	• Increase range of gait speeds
	5 min	F	End Game • Combination of all components	
5 min	Cooling Down			

Figure 2. Overview of the C-Mill training

Demographic and clinical assessments

The demographic and clinical assessments are collected during the first assessment in the movement laboratory. The demographic characteristics consist of age; sex; height; weight; presence (or absence) of a genetic diagnosis and inheritance pattern; disease duration (i.e. the number of years since symptom onset); regular use of medication, orthopedic shoes or orthotic devices, or other walking aids; presence and severity of visual deficits; and number of falls in the preceding year.

Clinical assessments consist of the Spastic Paraplegia Rating Scale (SPRS) to determine disease severity.¹⁹ Bilateral muscle strength is scored with the Medical Research Council (MRC) scale for hip adduction, abduction, flexion and extension; knee flexion and extension; and ankle plantar and dorsiflexion.^{4, 20, 21} Bilateral muscle tone is scored with the Modified Ashworth Scale (MAS) for the hip adductors

(hip 70° flexed); knee flexion and extension; ankle plantar and dorsiflexion with knee extended (gastrocnemius) and knee flexed (soleus).²² Vibration sense is evaluated using a tuning fork on bilateral patella, lateral malleolus, and at the first metatarsophalangeal joint. Trunk control is assessed using the Trunk Control Measurement Scale (TCMS).²³ Lastly, coordination is examined via (i) heel-to-knee test, (ii) toe tapping and (iii) leg agility.²⁴

Primary outcome

The primary outcome is gait adaptability as measured with the obstacle subtask of the Emory Functional Ambulation Profile (E-FAP). Participants are asked to negotiate a 10-meter course in which two wooden blocks (100(l) x 10(w) x 5(h) cm) and a bin are placed along the walkway. The instruction given is to complete the task as fast as possible but keep your own safety in mind. The number of seconds needed to complete the task is registered. A faster time score indicates better gait adaptability. The obstacle subtask of the E-FAP has previously been used as an outcome measure for gait adaptability in several neurological populations.^{14, 15} The full protocol is available online and via Wolf et. al.²⁵

Secondary outcomes

Secondary outcome measures comprise of the following clinical tests:

10-Meter Walk Test (10MWT)

The *10MWT* is a standardized and recommended measurement of walking velocity. Participants walk thirteen meters in a straight line; first three times at comfortable speed and then three times as fast as possible. Participants have three meters to accelerate to the requested speed. When the first foot crosses the 3-meter line, the timer starts. The timer stops when the first foot crosses the 13-meter line. Like this, the number of seconds it takes to walk ten meters is recorded.²⁶ The test has been found reliable, valid and sensitive in neurological populations,²⁶ and has been used in people with HSP.^{9, 13, 27, 28}

Mini Balance Evaluation Systems Test (miniBEST)

The *mini-BEST* test is a 14-item, 3 points ordinal rating scale (0-2 points) to evaluate balance capacity in 4 subcategories: anticipatory postural control, reactive postural control, sensory orientation, and gait stability. The attainable sum scores range from 0-28 points, a higher score indicating better balance capacity. Participants perform the test barefoot. The full protocol is available online and has been described by Franchignoni et.al.²⁹ The mini-BEST is often used in neurological populations, has been found valid, reliable and responsive,³⁰⁻³² and has been recommended for use in people with HSP.⁴

Physical activity levels during daily life

Physical activity during daily life will be registered via the Activ8 Physical Activity Monitor (Activ8, Remedy Distribution Ltd., Valkenswaard, The Netherlands). The Activ8 monitor is a small (30x32x10mm) and lightweight device with three axial accelerometers. It registers body positions (non-wear of the Activ8/lying, sitting and standing) and activities (walking, running, cycling).³³ The Activ8 is placed by the primary researcher using Tegaderm™ tape on the right upper thigh of the participants. Interval for data sampling will be set to one measurement per fifteen seconds. Collected measures consist of total time spent walking (minutes) and total time spent active (i.e. minutes classified as walking, running or cycling).

Activities-specific Balance Confidence scale (ABC)

Balance confidence will be measured using the ABC. The questionnaire describes sixteen indoor and outdoor situations. Participants are asked to express their confidence in safely executing the proposed situations without falling. Scores range from 0-100, a higher score indicating more confidence. The ABC has been used to assess balance confidence in people with HSP.^{27, 34} The full questionnaire is available via Powell et al.³⁵

Fall calendar

The *fall calendar* is used to monitor falls and near falls and is self-reported by the participants during a fifteen-week period. The World Health Organization defined a fall as “an event which results in a person coming to rest inadvertently on the ground or other lower level.” A near fall is defined as “a stumble event or loss of balance that would result in a fall if sufficient recovery mechanisms were not activated”.³⁶ In addition, participants register incidents where a fall was likely to happen, but was averted through the action of another person. When a (near) fall occurs, the participant is asked to report a short description of the event, the environment (indoor/outdoor, illuminated/dark space, and surface (e.g. tiles, carpet, forest)) and lastly, whether the (near) fall resulted in any injuries. To meet participants preference, calendars can be filled in digitally or on paper. Every other week, participants are reminded of the fall calendar via a phone call from the primary investigator (LV).

Walking Adaptability Ladder Test (WALT)

The *walking adaptability ladder test (WALT)* is a test to measure step precision. A standardized ladder is placed on the floor. It consists of 17 rectangular stepping targets that gradually decrease two centimeters in length (range: 64cm – 32cm). Participants start stepping in the largest target and walk as fast as possible to the other side, turn and hit the targets in reverse order whilst avoiding the ladder rungs. The instructions are to perform the test as fast as possible, but try to prevent foot placement errors. The test is timed: a faster time is indicative of better stepping

precision. Participants perform the test four times; first twice with one foot per target and, thereafter, twice with both feet in one target. A time penalty of 0.5s is added each time a participant makes a foot placement mistake.

Spatiotemporal gait parameters

Spatiotemporal gait parameters are collected with a 3D full body gait analysis using Vicon (Vicon© Motion systems Ltd.) at the movement laboratory of the Radboudumc, Nijmegen. Retroreflective markers are placed on anatomical landmarks according to the standard Plug-in Gait marker model for upper and lower body. In addition, participants will wear accelerometers on their lateral heels, as the higher measuring frequency will enable a more accurate gait event detection. Participants will walk two bouts of three minutes over an eight-meter walkway. The following spatio-temporal parameters will be retrieved: step length (cm), step width (cm), step time (s), walking speed (m/s), stride time (s), stride length (cm) and cadence (steps/min).

Assessment of therapy adherence and co-interventions

To support adherence to the protocol, participants will be in direct contact with the primary investigator (LV) by telephone every other week. This enables the investigator to verbally confirm assessments and training dates, check adherence to the fall calendar, and quickly address and resolve questions and possible problems that may interfere with continuation of the protocol. In addition, participants are offered flexible time slots for the assessments and training sessions. Assessment of adherence to the C-Mill protocol is possible as therapists will log the performed C-Mill trainings. In case of an unexpected cancellation, the reason will be registered, and the missed training can be compensated in the next week. When multiple consecutive training sessions cannot proceed, a pragmatic solution is sought so that the participant is able to complete the protocol. In addition, assessment of co-intervention will take place during the assessments. Participants are asked to self-report in a survey what type of co-intervention they received (e.g. physical therapy, occupation therapy).

Sample size

Sample size calculation is based on previous studies assessing effectiveness of C-Mill training on the obstacle subtask of the E-FAP scores in neurological populations.^{14, 15} A total of 32 participants is sufficient to demonstrate an improvement on the E-FAP score of 1.75 seconds (SD = 2.0s, $\alpha = 0.05$, $\beta = 0.2$). Considering a 10% attrition rate, 36 participants will be included.

Statistical analysis

The effect of gait adaptability training on primary and secondary outcomes will be tested using ANCOVA. Post-intervention measurements will be used as dependent variables with pre-intervention measurements as the covariate. Group (C-Mill versus

waiting list) is used as an independent between-subjects factors. The retention of gait adaptability training will be tested by merging both groups and using a repeated measures ANOVA with Time as a within-subjects factor (C-Mill group: assessment 1, 2 and 3; waiting list: assessment (2, 3 and 4). Post-hoc tests will be performed in the case of significant main or interaction effects, using paired t-tests. Fall rates will be processed descriptively. Depending on the distribution of the data, the rate of near falls may be analyzed using Wilcoxon signed rank test. In addition, to determine key determinants of C-Mill training efficacy, a stepwise linear regression analysis will be performed with training-induced change in gait adaptability (relative change of the obstacle subtask of the E-FAP) as the dependent variable. Univariate analyses will be performed to select the best factors from the available demographic and clinical characteristics.

Discussion

Limitations in walking capacity are among the most disabling symptoms in people with hereditary spastic paraplegia (HSP). A handful of studies aimed to improve walking capacity in people with HSP,^{9, 13, 37} but these studies did not include context-specific exercises aimed at gait adaptability. Gait adaptability has been successfully trained in several neurological populations using augmented reality on the C-Mill^{14, 15} but, so far, this has never been done in people with HSP.

Move-HSP is a two-armed, open-label randomized controlled trial that will be the first study to assess the effects of gait adaptability training in people with pure HSP. Participants in the intervention group receive ten hours (one-hour sessions; twice per week) of protocolled C-Mill training, whereas the control group continues with treatment as usual (waiting list). After five weeks on the waiting list, the control group will cross over and follow gait-adaptability training. The primary outcome is gait adaptability assessed with the obstacle subtask of the E-FAP. Secondary outcomes focus on several aspects of balance and gait capacity. Mildly to moderately affected people with pure HSP that fit the a-priori established eligibility criteria will be included.

There are no restrictions regarding sex, symptom duration, or use of orthotic/orthopedic devices in order to represent the clinical heterogeneity characteristic of people with pure HSP. Yet, to provide proof of principle and limit the influence of impaired cognitive capacity, people with complex forms of HSP are excluded.

Move-HSP aims to make a step towards evidence-based and individually tailored gait rehabilitation programs for people with HSP. It will reveal whether context-specific training is an effective tool for improving gait adaptability in people with pure HSP. If the C-Mill intervention results in improved walking adaptability, it may be beneficial

to implement this type of training on a regular basis in the rehabilitation of people with HSP. In addition, knowledge of the key determinants of training efficacy will help to optimize the selection of subjects with HSP that are most responsive to gait adaptability training.

Supplementary materials

Supplementary material accompanies this paper at
<https://doi.org/10.1186/s13063-020-04932-9>.

Additional file 1: Video file demonstrating C-Mill training.

Additional table 1

Table 1: Standard protocol items: Recommendations for interventional trials (SPIRIT) figure.						
	Enrollment	Allocation	Post-allocation		Follow-up	
TIMEPOINTS in weeks (intervention / usual care)	-T ₁	T ₀ = (0/0)	T ₁ = (16/16)	T ₂ = (22/22)	T _s (NA/28)	T ₃ = (38/44)
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTION:						
Intervention program			X	X		X
Usual care			X	X	X	X
ASSESSMENT						
Primary outcome						
Emory functional ambulation profile – obstacle subtask			X	X	X	X
Secondary outcome						
10 meter walk test						
Mini balance evaluation test			X	X	X	X
Daily levels of physical activity			X	X	X	X
Activities-specific balance confidence scale			X	X	X	X
Walking adaptability ladder test			X	X	X	X
Spatio-temporal gait parameters						

Table 1: (continued)

	Enrollment	Allocation	Post-allocation	Follow-up
TIMEPOINTS in weeks (intervention / usual care)	-T ₁	T ₀ = (0/0)	T ₁ = (16/16) T ₂ = (22/22)	T ₃ = (38/44)
Other parameters				
Age	X			
Presence (or absence) or genetic diagnosis	X			
Medical history				
Demographics:				
(height, weight, use of medication, use of orthopedic devices or walking aids, visual deficits, number of falls in preceding year)	X		X	
Spastic Paraplegia Rating Scale			X	
Muscle strength			X	
Muscle tone			X	
Vibration sense			X	
Trunk control measurement scale			X	
Coordination			X	
Co-interventions		X	X	X
Adverse events		X	X	X
Overview of enrollment, interventions and assessments during the study protocol. Timepoints T ₁ , T ₂ and T ₃ are applicable for participants in the intervention group and usual care group. Timepoint T ₃ is only applicable for participants in the usual care group. Abbreviations: NA: not applicable.				

Reference list

1. Salinas, S., et al., Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol*, 2008. 7(12): p. 1127-38.
2. Harding, A.E., Classification of the hereditary ataxias and paraplegias. *Lancet*, 1983. 1(8334): p. 1151-5.
3. McDermott, C., et al., Hereditary spastic paraparesis: a review of new developments. *J Neurol Neurosurg Psychiatry*, 2000. 69(2): p. 150-60.
4. Nonnekes, J., et al., Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia. *J Rehabil Med*, 2017. 49(5): p. 369-377.
5. Harding, A.E., Hereditary spastic paraplegias. *Semin Neurol*, 1993. 13(4): p. 333-6.
6. Marsden, J., et al., Muscle paresis and passive stiffness: key determinants in limiting function in Hereditary and Sporadic Spastic Paraparesis. *Gait Posture*, 2012. 35(2): p. 266-71.
7. Shribman, S., et al., Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*, 2019.
8. Klimpe, S., et al., Disease severity affects quality of life of hereditary spastic paraplegia patients. *Eur J Neurol*, 2012. 19(1): p. 168-71.
9. Bertolucci, F., et al., Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. *NeuroRehabilitation*, 2015. 36(1): p. 93-9.
10. Nonnekes, J., et al., Mechanisms of postural instability in hereditary spastic paraplegia. *J Neurol*, 2013. 260(9): p. 2387-95.
11. van Lith, B.J.H., et al., Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*, 2020. 15(1): p. 64.
12. Kerstens, H., et al., Stumbling, struggling, and shame due to spasticity: a qualitative study of adult persons with hereditary spastic paraplegia. *Disabil Rehabil*, 2019: p. 1-8.
13. Seo, H.G., B.M. Oh, and K. Kim, Robot-assisted gait training in a patient with hereditary spastic paraplegia. *Pm r*, 2015. 7(2): p. 210-3.
14. Heeren, A., et al., Step by step: a proof of concept study of C-Mill gait adaptability training in the chronic phase after stroke. *J Rehabil Med*, 2013. 45(7): p. 616-22.
15. Fonteyn, E.M., et al., Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration. *Gait Posture*, 2014. 40(1): p. 247-51.
16. Peruzzi, A., et al., An innovative training program based on virtual reality and treadmill: effects on gait of persons with multiple sclerosis. *Disabil Rehabil*, 2017. 39(15): p. 1557-1563.
17. Kaji, R., et al., Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. *J Neurol*, 2010. 257(8): p. 1330-7.
18. Wissel, J., et al., European consensus table on the use of botulinum toxin type A in adult spasticity. *J Rehabil Med*, 2009. 41(1): p. 13-25.
19. Schule, R., et al., The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. *Neurology*, 2006. 67(3): p. 430-4.

20. Counsil, M.R., Aids to the investigation of the peripheral nervous system. Her Majesty's Stationary Office, 1943.
21. Dyck, P.J., et al., History of standard scoring, notation, and summation of neuromuscular signs. A current survey and recommendation. *J Peripher Nerv Syst*, 2005. 10(2): p. 158-73.
22. Bohannon, R.W. and M.B. Smith, Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*, 1987. 67(2): p. 206-7.
23. Heyrman, L., et al., A clinical tool to measure trunk control in children with cerebral palsy: the Trunk Control Measurement Scale. *Res Dev Disabil*, 2011. 32(6): p. 2624-35.
24. Martinez-Martin, P., et al., Expanded and independent validation of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). *J Neurol*, 2013. 260(1): p. 228-36.
25. Wolf, S.L., et al., Establishing the reliability and validity of measurements of walking time using the Emory Functional Ambulation Profile. *Phys Ther*, 1999. 79(12): p. 1122-33.
26. Graham, J.E., et al., Assessing walking speed in clinical research: a systematic review. *J Eval Clin Pract*, 2008. 14(4): p. 552-62.
27. van Lith, B.J.H., et al., Functional effects of botulinum toxin type A in the hip adductors and subsequent stretching in patients with hereditary spastic paraplegia. *J Rehabil Med*, 2019. 51(6): p. 434-441.
28. Denton, A.L., et al., Effects of superficial heating and insulation on walking speed in people with hereditary and spontaneous spastic paraparesis: A randomised crossover study. *Ann Phys Rehabil Med*, 2018. 61(2): p. 72-77.
29. Franchignoni, F., et al., Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med*, 2010. 42(4): p. 323-31.
30. Leddy, A.L., B.E. Crouner, and G.M. Earhart, Functional gait assessment and balance evaluation system test: reliability, validity, sensitivity, and specificity for identifying individuals with Parkinson disease who fall. *Phys Ther*, 2011. 91(1): p. 102-13.
31. Ross, E., et al., Cohort Study Comparing the Berg Balance Scale and the Mini-BESTest in People Who Have Multiple Sclerosis and Are Ambulatory. *Phys Ther*, 2016. 96(9): p. 1448-55.
32. Tsang, C.S., et al., Psychometric properties of the Mini-Balance Evaluation Systems Test (Mini-BESTest) in community-dwelling individuals with chronic stroke. *Phys Ther*, 2013. 93(8): p. 1102-15.
33. Valkenet, K. and C. Veenhof, Validity of three accelerometers to investigate lying, sitting, standing and walking. *PLoS One*, 2019. 14(5): p. e0217545.
34. de Niet, M., et al., Functional effects of botulinum toxin type-A treatment and subsequent stretching of spastic calf muscles: a study in patients with hereditary spastic paraplegia. *J Rehabil Med*, 2015. 47(2): p. 147-53.
35. Powell, L.E. and A.M. Myers, The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci*, 1995. 50a(1): p. M28-34.
36. Faber, I., et al., SPG11-related parkinsonism: Clinical profile, molecular imaging and l-dopa response. *Mov Disord*, 2018. 33(10): p. 1650-1656.
37. Zhang, Y., et al., The effect of hydrotherapy treatment on gait characteristics of hereditary spastic paraparesis patients. *Gait Posture*, 2014. 39(4): p. 1074-9.



Chapter 4

Gait-adaptability training in Hereditary Spastic Paraplegia: a randomized clinical trial

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Published: Neurorehabilitation and Neural Repair, 2023 jan; 37(1): 27-36

Abstract

Background and objectives

In people with hereditary spastic paraplegia (HSP), reduced gait adaptability is common and disabling. Gait impairments result from lower extremity spasticity, muscle weakness, and impaired proprioception. The aim of this study was to assess the efficacy of a five-week gait-adaptability training in people with pure HSP.

Method

We conducted a randomized clinical trial with a cross-over design for the control group, and a fifteen-week follow-up period after training. Thirty-six people with pure HSP were randomized to five weeks of i) gait-adaptability training (ten hours of C-Mill training - treadmill equipped with augmented reality) or ii) waiting-list control period followed by five weeks gait-adaptability training. Both groups continued to receive usual care. The primary outcome was the obstacle subtask of the Emory Functional Ambulation Profile. Secondary outcome measures consisted of clinical balance and gait assessments, fall rates, and spatiotemporal gait parameters assessed via 3D motion analysis.

Results

The gait-adaptability training group (n=18) did not significantly decrease the time required to perform the obstacle subtask compared to the waiting-list control group (n=18) after adjusting for baseline differences (mean: -0.33 seconds, 95%CI: -1.3;0.6). Similar, non-significant results were found for most secondary outcomes. After merging both groups (n=36), the required time to perform the obstacle subtask significantly decreased by 1.3 seconds (95%CI: -2.1;-0.4) directly following five weeks of gait-adaptability training, and this effect was retained at the fifteen-week follow-up.

Conclusions

We found insufficient evidence to conclude that five weeks of gait-adaptability training leads to greater improvement of gait adaptability in people with pure HSP.

Introduction

Hereditary spastic paraplegia (HSP) is a heterogeneous group of neurodegenerative disorders. It is caused by retrograde axonal degeneration of the corticospinal tract, posterior spinal columns, and spinocerebellar fibres.^{1,2} Pure forms of HSP are clinically characterized by progressive bilateral spasticity, muscle weakness, and a reduced proprioception of the lower extremities.^{1,2} These symptoms result in disabling gait and balance impairments, including difficulties adapting the walking pattern to meet environmental demands (e.g. stepping over an obstacle or speeding up walking to cross the street). This hinders safe and independent ambulation in the community.^{3,4}

Previous uncontrolled studies with pre-post assessments reported beneficial effects on balance and/or gait performance following task-specific gait training in people with HSP. The interventions consisted of 18 sessions of robotic Lokomat training (n=13),⁵ a combined intervention of botulinum toxin type-A injections followed by 10 sessions of physical therapy (n=18),⁶ 25 sessions of robot-assisted exoskeleton and overground walking exercises (n=1),⁷ or a low-intensity 12-week physical therapy program (n=1).⁸ Although the results of these studies are promising, none of these studies included outcome measures aimed at evaluating gait adaptability, nor did the applied gait training interventions include context-specific tasks that specifically targeted gait adaptability. Context-specific gait-adaptability training can be provided on the C-Mill, a treadmill equipped with augmented reality. Via visual projections on the treadmill, participants can train several domains of gait adaptability (e.g., obstacle negotiation and precision stepping) in a safe environment. Previous studies have demonstrated feasibility and efficacy of gait-adaptability training on the C-Mill in chronic stroke patients,⁹⁻¹¹ people with cerebellar degeneration,¹² and persons with Parkinson's disease.¹³

So far, the potential effectiveness of gait-adaptability training has not been studied in people with HSP. Therefore, we designed and conducted the Move-HSP trial¹⁴: a randomized clinical trial to compare the effect of gait-adaptability training added to usual care, with usual care alone. We hypothesized that the addition of gait-adaptability training would result in greater improvements of gait-adaptability performance as evaluated with the obstacle subtask of the Emory functional ambulation profile (E-FAP).¹⁵

In addition, clinical balance and gait measures, balance confidence, spatiotemporal gait parameters, and level of physical activities in daily life were evaluated, and hypothesized to improve more by the addition of gait-adaptability training.

Methods

Study design and setting

We conducted a five-week, randomized clinical trial, with a cross-over design for the waiting-list control group, and a fifteen-week follow-up period after the intervention. This mono-center study was conducted at the Centre of Expertise for Rare and Genetic Movement Disorders of the Radboud University Medical Centre (Nijmegen, The Netherlands), which is part of the European Reference Network for Rare Neurological Diseases (ERN-RND). Ethical approval was obtained from the Medical Ethical Committee Oost-Nederland, the Netherlands (2019-5602, NL70295.091.19). The trial was registered on Clinicaltrials.gov (NCT04180098) and the study protocol has previously been published.¹⁴ All participants signed informed consent. Participants were randomized via a web-based randomization system into two groups: i) *gait-adaptability training group*: five weeks of C-Mill training next to usual care; or ii) *waiting-list control group* receiving five weeks of usual care. Randomization was done following a 1:1 ratio with randomly varying blocks ($n=4$ or $n=6$) and stratified by disease duration (2 categories: 0-15 years and >15 years). Participants in the gait-adaptability training group were assessed three times; pre training, post training, and at follow-up. Participants assigned to the waiting-list control group crossed over to five weeks of gait-adaptability training following five weeks of usual care. Therefore, participants in the waiting-list control group were assessed four times: pre waiting list, pre training, post training, and at follow-up. A detailed flowchart of the study design is available in the previously published protocol paper.¹⁴ The assessments took place at the movement laboratory of the Radboud University Medical Centre (Nijmegen, The Netherlands). The gait-adaptability training sessions were executed at four sites: Radboud University Medical Centre (Nijmegen, NL), Paramedisch centrum Rembrandt (Veenendaal, NL), Stichting Tante Louise (Bergen op Zoom, NL), and Fysiotherapie de Lindehoeve (Voorschoten, NL). Participants could not be blinded, as they unavoidably knew whether they received gait-adaptability training or not. The assessor (LV) conducting the measurements at the movement laboratory also provided the training sessions at Radboud University Medical Centre and could, therefore, not be blinded either. During the trial, all participants were allowed to continue with usual care (e.g., physical therapy).

Participants

Participants were recruited via the outpatient clinic of the Centre of Expertise for Rare and Genetic Movement Disorders of the Radboud University Medical Centre and via the Dutch HSP working group of the patient organization “Spierziekte Nederland”. Inclusion criteria were (1) diagnosis of pure HSP by a neurologist specialized in genetic movement disorders, (2) aged between 18-70 years old, and (3) ability to walk barefoot on a level ground without a walking aid (use of

orthopedic devices was allowed). Participants were excluded if they suffered from concomitant neurological, orthopedic or psychiatric conditions that might affect gait performance, or if they had any HSP-related surgical procedure of the lower extremities in their medical history. Participants provided demographic information including age and sex. Clinical characteristics that were recorded consisted of leg muscle tone assessed with the modified Ashworth Scale (MAS; range 0-5),¹⁶ leg muscle strength assessed with the Medical Research Council scale (MRC; range 0-5),¹⁷ vibration sense at the ankles and feet assessed with a semiquantitative tuning fork (Rydel-Seiffer, Neurologicals Poulsbo, Washington) (range 0-8). In addition, we recorded disease duration (years), level of disease severity assessed with the Spastic Paraplegia Rating Scale (SPRS; range 0-52)¹⁸, trunk control assessed with the Trunk Control Measurement Scale (TCMS; range 0-58),¹⁹ and self-reported falls during the previous year.

Intervention

Participants trained their gait adaptability on the C-Mill (Motek Medical, Culemborg, The Netherlands), a treadmill equipped with augmented reality. Visual projections onto the treadmill acted as stepping targets or obstacles to elicit step adjustments. The training sessions were guided by a physical therapist. Sessions lasted 60 minutes and took place twice a week for a period of five weeks, adding up to a total of ten hours of gait-adaptability training. A detailed description of the training has previously been published.¹⁴ In short, training sessions started with a ten-minute warming-up, followed by five exercises of approximately eight minutes. Each exercise focused on a specific gait-adaptability task: (A) precision stepping, (B) obstacle negotiation, (C) direction of progression, (D), precision acceleration, or (E) walking velocity. Sessions ended with a five-minute game that combined several gait-adaptability tasks and a five-minute cooling-down period. During the training sessions, additional short periods of rest were provided as needed. To ensure sufficient challenge for each participant, progression of task complexity was moderated by the therapist based on the participants capacity. A maximum of two therapists per participant were involved in providing gait-adaptability training sessions.

Outcome measures

The primary outcome was gait adaptability assessed with the obstacle subtask of the Emory Functional Ambulation Profile (E-FAP).¹⁵ Secondary outcomes consisted of the Mini Balance Evaluation Test (MiniBEST),²⁰ Activities-specific Balance Confidence scale (ABC), the Walking Adaptability Ladder Test (WALT),²¹ and the 10-meter Walk Test (10mWT).²² In addition, three-dimensional gait analysis (Vicon© Motion systems Ltd.) was performed. To this end, retroreflective markers were placed according to the standard Plug-In-Gait upper and lower body marker model. During the gait analysis, participants walked two bouts of three minutes at comfortable speed

over an eight-meter walkway with their own comfortable shoes. From the gait analysis, average stride length (m), average stride time (s), average step width (m), walking speed (m/s) and cadence (steps/min) were extracted. The assessments were conducted by a trained investigator using a standardized protocol. Details on how the outcome measures were assessed have been published in the study protocol.¹⁴ Use of orthotic devices, including orthopedic footwear, was allowed and kept consistent throughout the different assessments.

Furthermore, levels of physical activity were measured following each assessment during seven consecutive days with activity monitors (Activ8, Remedy Distribution Ltd., Valkenswaard, The Netherlands). Physical activity was expressed as total time spent walking and total time spent active (i.e., minutes classified as walking, running or cycling). Lastly, during 15 weeks prior to the first assessment and during fifteen weeks following gait-adaptability training, all participants self-reported their falls and near-falls in a digital fall diary. Falls that occurred during these fall diary periods were considered to be outcomes. In contrast, falls that were registered during the five weeks gait-adaptability training or during the five weeks on the waiting-list were considered as adverse events.

Sample Size

Sample size calculation is based on previous studies evaluating the effectiveness of C-Mill training on the obstacle subtask of the E-FAP (these studies involved stroke patients⁹ and people with ataxia¹²). To detect an improvement of 1.75 seconds on the E-FAP obstacle subtask (SD: 2.0s) and applying an $\alpha = 0.05$ and $\beta = 0.2$, 16 participants per group would be needed. Allowing a 10% attrition rate, we aimed for a total of 36 participants.¹⁴

Statistical analysis

The effects of gait-adaptability training on the primary and secondary outcome measures were assessed by comparing the post-intervention scores through analysis of covariance (ANCOVA). The baseline score of the corresponding primary and secondary outcomes was entered into the model as a covariate. Analyses were based on the intention-to-treat principle. In second instance, both groups were merged based on their corresponding pre-training, post-training, and follow-up assessments (i.e., assessments 1, 2 and 3 for the gait-adaptability training group and assessments 2, 3 and 4 for the waiting-list control group). Time effects during and after gait-adaptability training were then assessed with a repeated-measures analysis of variance (ANOVA) using time as a within-subjects factor. Post-hoc testing with paired t-tests was done to assess whether outcomes differed between the post- vs. pre-training assessments, and between the follow-up vs. post-training assessments. The fall dairies were processed descriptively.

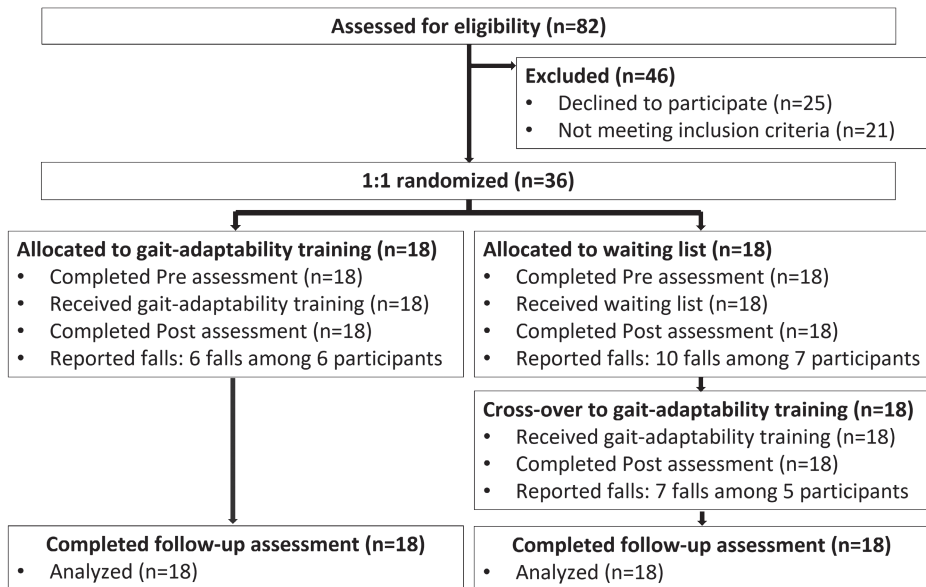


Figure 1. Flowchart of Move-HSP

Results

Patient enrollment, adherence and adverse events

Participants were recruited between November 2019 and June 2021. Out of the 82 eligible people with pure HSP, 36 participants were enrolled and randomized (Figure 1). Eighteen participants were allocated to the gait-adaptability training group and 18 to the waiting-list control group. The overall adherence to the gait-adaptability training was 99.7% (359 out of 360 training sessions completed). There were no drop-outs during the study period. The disease severity of two participants in the gait-adaptability training group prevented them from performing the WALT. As a result, the WALT scores of 34 participants were included in the analysis. The completion rate of fall diaries was 97,2% (70 out of 72 fall diaries were returned). The fall diaries of 2 participants were excluded from the analysis, as one participant did not complete the follow-up fall diary due to lack of motivation, and one participant experienced technical difficulties. As a result, the fall diaries of 34 participants were analyzed.

During the study period, one serious adverse events occurred. One participant touched electric wires when replacing a lamp during work. On advice of his general practitioner, this participant was admitted to hospital for 24 hours observation, after which he was discharged without residual symptoms. During the gait-adaptability training period, a total of 13 falls (range 1-2 per participant) were reported by 11 of

the 34 participants; however, none of these falls occurred during the training itself. Lastly, during the five-week waiting-list period, a total of ten falls (range 1-3 falls per participant) were reported among 7 out of 18 participants.

Participant characteristics and co-interventions

The participants randomized to either the gait-adaptability training group or waiting-list control group did not differ in demographic or clinical characteristics (Table 1). A total of 16 participants received physical therapy as a co-intervention: in the gait-adaptability training group, 10 of the 18 participants received physical therapy for an average of 70 minutes per week (range 20-270); in the waiting-list control group, 6 of the 18 participants received physical therapy for an average of 100 minutes per week (range 20-180). No other co-interventions were reported.

Intervention effects

The time required to perform the EFAP obstacle subtask did not decrease more in the gait-adaptability training group compared to the waiting-list control group after adjustment for baseline differences (mean group differences: -0.33 seconds, 95% CI: -1.3;0.6; $p=0.471$). Similar non-significant results were found for the secondary outcomes, except for the single run of the WALT (mean group differences: -2.14 seconds; 95% CI: -4.1;-0.1; $p=0.037$, see table 2).

Table 1: Clinical characteristics of participants per group.

		Gait-adaptability training group	Waiting-list control group
Number of participants		18	18
Age (years)		47.6 ($\pm$ 8.8)	50.0 ($\pm$ 12.7)
Sex (women)		14	13
Time since first symptom (years)		15.8 ($\pm$ 13.5)	17.1 ($\pm$ 13.9)
Falls past year		3	5
Hip flexors	MRC	4 [3-5]	4 [4-5]
Hip extensors	MRC	4 [3-5]	4 [4-5]
Hip abductors	MRC	5 [2-5]	4 [4-5]
Hip adductors	MRC	5 [2.5-5]	4 [4-5]
Knee extensors	MAS	1 [0-2.5]	1 [0-2.5]
	MRC	4 [4-5]	4 [4-5]
	MAS	1 [0-3]	0 [0-2.5]
Knee flexors	MRC	4 [3-5]	4 [3-5]
	MAS	1.25 [0-3]	1 [0-2.5]
	MRC	5 [4-5]	5 [4-5]
Ankle plantarflexors	MAS – knee extended	1.5 [0-3]	1 [0-2.5]
	MAS – knee flexed	1 [0-3]	1.25 [0-2]
	MRC	5 [3.5-5]	4.5 [3-5]
Ankle dorsiflexors	MAS	0 [0-1]	0 [0-0.5]
Vibration sense – Malleoli laterales		3.8 [0-8]	5.3 [0-8]
Vibration sense – Head of metatarsal I		3.5 [0-8]	5.3 [0-8]
Spastic Paraplegia Rating Scale (range 0-52)		11.4 ($\pm$ 5.2)	10.1 ($\pm$ 3.6)
Trunk Control Measurement Scale (range 0-58)		46.3 ($\pm$ 5.7)	47.6 ($\pm$ 3.3)

Values displayed are means ($\pm$ standard deviation) or median [range]. MRC scores (0-5), MAS scores (0-5) and vibration sense scores (0-8) are averaged values of the left and right body side. Vibration sense was assessed using a semiquantitative tuning fork (Rydel-Seiffer, Neurologicals Poulsbo, Washington).

Time effects

Directly following five weeks of gait-adaptability training, the participants of both groups reduced the required time to perform the obstacle subtask [mean difference: -1.3 seconds; 95% CI: -2.1;-0.4; $p < 0.01$] and retained this gain up to the fifteen-week follow-up assessment (Figure 2). Similar results were found for most secondary outcomes, including the MiniBEST, ABC scale, 10mWT (comfortable and fast gait speed), WALT single and double run, levels of daily activity, and average stride length and walking velocity recorded during gait analysis (Table 3). The scores of all assessments for each group separately are included in the supplementary materials – table 4 (gait-adaptability training group) and table 5 (waiting-list control group).

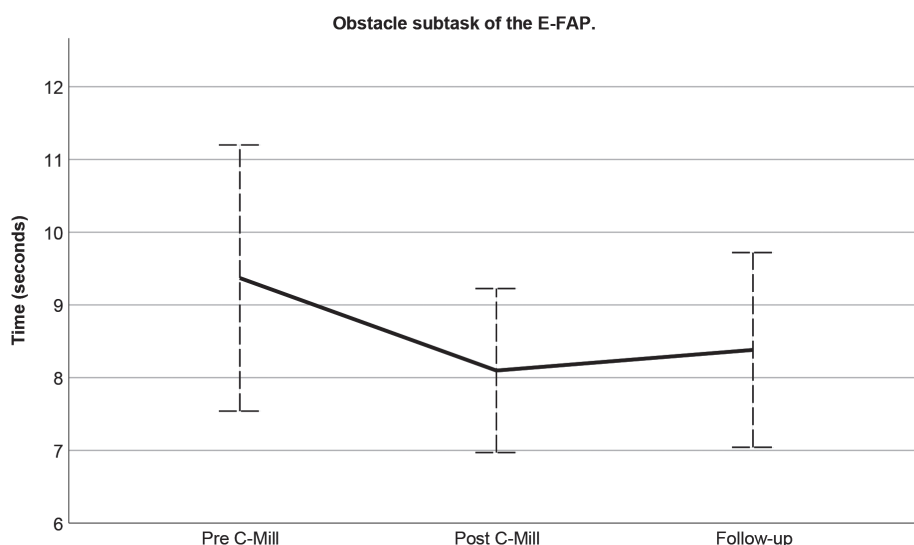


Figure 2. Time effects of C-Mill training on the obstacle subtask for both groups together. Values displayed are unadjusted means. Error bars represent 95% confidence intervals.

Fall Diaries

In the 15 weeks prior to the first assessment, 26 falls were reported by 12 out of 34 participants (35%; 1-4 falls per participant). In the 15-week following the gait-adaptability training, 26 falls were reported by 12 out of 34 participants (35%; 1-5 falls per participant).

In the 15 weeks prior to the first assessment, 291 near-falls were reported by 22 out of 34 participants (65%; 1-75 near-falls per participant). In the 15 weeks following the gait-adaptability training, 200 near-falls were reported by 11 out of 34 participants (32%; 1-63 near-falls per participant). Nineteen participants reported a decrease in their near-falls (56%; 1-42 near-falls per participant), whereas two participants reported an increase of 1 and 33 near-falls, respectively. Additionally, 2 participants reported an identical count of near-falls.

Table 2: group means pre and post intervention period and mean group differences post intervention period (ANCOVA).

	Gait adaptability training group (n=18)			Waiting list control group (n=18)			Gait adaptability training group vs. waiting list control group		
	n	Mean ± SD	Post (week 6)	n	Mean ± SD	Pre (week 0)	Mean group difference post intervention period adjusted for baseline values [95% CI]	P value	
Clinical Assessment									
Obstacle subtask EFAP (s)	18	10.3 ± 6.6	8.6 ± 3.9	18	9.6 ± 4.7	8.5 ± 3.9	-0.33 [-1.3;0.6]	0.471	
MiniBEST	18	18.3 ± 6.0	20.1 ± 5.4	18	19.3 ± 3.8	19.9 ± 3.8	1.09 [-0.4;2.6]	0.172	
Activities-specific Balance Confidence Scale	18	66.5 ± 18.1	72.7 ± 16.2	18	70.9 ± 18.2	72.7 ± 16.6	3.40 [-2.7;9.5]	0.268	
Ten-meter walk test									
– comfortabel (m/s)	18	1.3 ± 0.3	1.3 ± 0.3	18	1.2 ± 0.3	1.3 ± 0.3	0.03 [0.0;0.1]	0.387	
Ten-meter walk test									
– fast (m/s)	18	1.6 ± 0.3	1.7 ± 0.4	18	1.7 ± 0.4	1.7 ± 0.3	0.04 [-0.1;0.1]	0.430	
Walking Adaptability Ladder test – single run (s)	16 ^A	21.9 ± 13.8	18.3 ± 8.6	18	23.0 ± 12.3	21.2 ± 9.9	-2.14 [-4.1;-0.1]	0.037*	
Walking Adaptability Ladder test – double run (s)	16 ^A	38.7 ± 17.9	35.1 ± 14.9	18	38.7 ± 16.8	36.3 ± 14.9	-1.26 [-4.3;1.8]	0.412	
Time spent active (% of day)	17 ^B	9.9 ± 3.4	10.2 ± 2.9	17 ^B	10.6 ± 3.0	9.7 ± 2.9	0.52 [-0.9;1.9]	0.447	
Time spent walking (% of day)	17 ^B	8.1 ± 3.2	8.3 ± 3.0	17 ^B	8.2 ± 2.8	7.5 ± 1.6	0.62 [-0.5;1.8]	0.282	

Table 2: (continued)

Gait adaptability training group (n=18)				Waiting list control group (n=18)				Gait adaptability training group vs. waiting list control group	
Pre (week 0)		Post (week 6)		Pre (week 0)		Post (week 6)		Mean group difference post intervention period adjusted for baseline values [95% CI]	P value
n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD		
Three-dimensional gait analysis									
Average stride length (m)	18	1.19 ± 0.2	1.24 ± 0.2	18	1.17 ± 0.2	1.19 ± 0.2	0.03 [-0.0;0.1]	0.232	
Average stride time (s)	18	1.15 ± 0.16	1.12 ± 0.1	18	1.15 ± 0.2	1.13 ± 0.2	<0.01 [-0.1;0.1]	0.968	
Average step width (m)	18	0.16 ± 0.04	0.16 ± 0.04	18	0.15 ± 0.05	0.15 ± 0.05	0.01 [0.0;0.0]	0.116	
Cadence (steps/min)	18	106.2 ± 12.0	107.8 ± 10.0	18	106.9 ± 15	109.1 ± 16	<0.01 [0.0;0.0]	0.947	
Walking velocity (m/s)	18	1.06 ±0.3	1.11 ± 0.2	18	1.05 ± 0.2	1.09 ± 0.3	0.02 [0.0;0.0]	0.119	

Values displayed: unadjusted means ± standard deviation. Results of a one-way analysis of covariance (ANCOVA) for group differences with pre-intervention assessment (week 0) as covariate; mean differences represent the differences between the estimated means post-intervention (week 6) and estimated means pre-intervention (week 0). * indicates significant differences. Abbreviations: n = number of participants included in the analysis. SD = standard deviation; CI: Confidence Interval. * collected during two trials of 3 minute overground walking. Some participants were excluded from the analysis due to missing data resulting from: ^an inability to perform the test or ^ technical issues.

Table 3: Group means of both groups combined (n=36) pre training, post training and at follow-up and mean differences between assessments.

	Pre training (n=36)		Post training (n=36)		Follow-up (n=36)		Time effect	Mean group difference between post training and pre training assessment [95% CI]	Mean group difference between follow-up and post training assessment [95% CI]
Clinical Assessment									
	Mean ± SD		Mean ± SD		Mean ± SD		P value		
Obstacle subtask (s)	9.4 ± 5.4		8.1 ± 3.3		8.4 ± 4.0		0.006	-1.3 [-2.1;-0.4]**	0.3 [-0.1;0.6]
MiniBEST	19.1 ± 5.0		21.6 ± 4.6		21.2 ± 5.2		< 0.001	2.5 [1.7;3.3]**	-0.4 [-1.0;0.3]
Activities-specific balance confidence scale (%)	69.6 ± 17.4		74.1 ± 16.4		73.1 ± 15.3		0.010	4.5 [1.3;7.7]**	-1.0 [-3.7;1.5]
Ten-meters walk test – Comfortabel (m/s)	1.3 ± 0.3		1.3 ± 0.3		1.3 ± 0.2		0.001	0.1 [0.0;0.1]**	0.0 [-0.1;0.0]
Ten-meters walk test – Fast (m/s)	1.7 ± 0.3		1.7 ± 0.3		1.7 ± 0.3		0.003	0.1 [0.0;0.1]**	0.0 [-0.1;0.0]*
Walking adaptability ladder test – single run (s)	21.5 ± 11.7		18.4 ± 7.9		19.2 ± 10.2		< 0.001	-3.1 [-4.6;1.5]**	0.8 [-3.4;1.7]
Walking adaptability ladder test – double run (s)	37.4 ± 16.2		34.0 ± 14.7		33.9 ± 14.6		< 0.001	-3.4 [-4.9;-1.9]**	-0.1 [-1.7;1.4]
Time spent active (% of day)	9.8 ± 3.1		10.3 ± 3.1		9.9 ± 3.5		0.709	0.2 [-0.4;0.9]	-0.4 [-1.2;0.3]
Time spent walking (% of day)	7.8 ± 2.5		8.3 ± 3.0		7.4 ± 2.9		0.078	0.2 [-0.4;0.9]	-0.9 [-1.6;-0.2]
Three-dimensional gait analysis*									
Average stride length (m)	1.2 ± 0.2		1.3 ± 0.2		1.2 ± 0.2		< 0.001	0.1 [0.0;0.1]**	-0.0 [-0.0;-0.0]*
Average stride time (s)	1.1 ± 0.2		1.1 ± 0.1		1.1 ± 0.1		0.273	0.0 [0.1;0.0]	0.0 [0.0;0.0]
Average step width (m)	0.15 ± 0.0		0.15 ± 0.0		0.16 ± 0.0		0.372	0.0 [0.0;0.0]	0.0 [0.0;0.0]
Walking velocity (m/s)	1.1 ± 0.2		1.1 ± 0.2		1.1 ± 0.2		0.001	0.1 [0.0;0.1]**	-0.0 [-0.1;0.0]*
Cadence (steps/min)	107.6 ± 13.8		109.0 ± 11.8		108.6 ± 11.1		0.417	1.4 [-1.0;3.8]	-0.4 [-2.0;1.3]

Values displayed are unadjusted means ± standard deviation. Presented data includes the pre-training, post-training and follow-up assessment data for the gait-adaptability training group and waiting-list control group (gait-adaptability training group: assessments 1,2,3; waiting-list control group: assessments 2,3,4). * indicates significant differences at $P < 0.05$. ** indicates significant differences at $P < 0.01$. * collected during two trials of 3 minute overground walking.

Discussion

Move-HSP is the first randomized clinical trial investigating the effects of gait-adaptability training in people with pure HSP. Our results showed that, following gait-adaptability training, participants improved on the obstacle subtask of the Emory Functional Ambulation Profile as well as on various secondary outcome measures of balance and gait. However, our results did not confirm the hypothesis that adding gait-adaptability training to usual care would result in greater improvements on these outcome measures.

Previous uncontrolled studies using a pre-post assessment design reported that gait, balance, and/or gait adaptability performance improved following 3.5 to 10 hours of C-Mill training in people with Parkinson's disease¹³, stroke⁹, and cerebellar degeneration¹². In addition, a previous randomized controlled trial in people with chronic stroke reported that the primary outcome walking speed did not show a greater improvement following C-Mill training compared to overground gait adaptability training. Yet, additionally, they reported that the C-Mill training group did show a greater improvement on context-specific walking speed (secondary outcome) directly post intervention, but this effect was not retained after five weeks follow-up. The results of the current study are coherent with the above-mentioned studies, as across both groups, the obstacle subtask of the E-FAP showed a significant improvement of 1.3 seconds directly post intervention, that was retained after 15 weeks follow-up. However, five weeks of gait-adaptability training added to usual care did not lead to a greater improvement of gait adaptability compared to usual care alone. Of note, we did find a greater improvement on the single run of the WALT – a novel test designed to evaluate walking adaptability²¹ – in the gait-adaptability training group compared to the waiting-list control group. The potential utility of the WALT to evaluate gait adaptability should be investigated in future trials.

Surprisingly, during the waiting-list period, participants in the control group improved on the obstacle subtask of the E-FAP as well as on most of the secondary outcomes, including measures of balance, balance confidence, gait speed and gait adaptability. These improvements in the control group may be explained in two ways. First, they may have been influenced by the so-called Hawthorne effect,²³ the potential change in behavior that occurs when people become aware of being observed and examined²⁴⁻²⁷. A second explanation relates to the impact of the Covid-19 pandemic. Unfortunately, we had to postpone the first assessments in all participants until the lockdown related to the Covid-19 restrictions was over. Previous research from our group showed that, during the Covid-19 pandemic, people with HSP were generally less active,²⁸ a phenomenon that has also been reported in other neurological populations.²⁹⁻³⁴ In addition, we found that the relative inactivity during the Covid-19 lockdown negatively impacted on spasticity-related symptoms, including gait

and balance impairments. Because – in the current study – the first assessments took place shortly after a period of generally reduced levels of physical activity, both groups may have increased their levels of activity and exercise in such a way that the added effects of gait-adaptability training were reduced.

This study has several strengths and limitations. Despite a delay of four months due to the Covid-19 pandemic, we were able to conduct the trial according to the previously published protocol.¹⁴ We were able to recruit the required number of participants and had no participant drop-out during the trial. Moreover, the adherence to the gait-adaptability training was very high. The generalizability of our results to the population of ambulatory people with HSP at large is expected to be high as well, as our participants showed large clinical heterogeneity (i.e., disease severity, disease duration and muscle tone), the use of orthotics was allowed, and the level of independent ambulation varied between the ability to walk 50 meters and completion of a marathon (i.e., 42km). We cannot fully rule out a ceiling effect in the E-FAP obstacle subtask results (limiting room for improvement), however comparison of the current HSP data with unpublished control data obtained by us in healthy controls of similar age (N=15; 49.0± 11.5 years) indicated that only 6 of our 36 HSP participants completed the E-FAP obstacle subtask within a normal range (mean + 2SD of healthy controls).

The most important shortcoming of this study was that assessors were not blinded for group allocation. To limit observational bias, a standardized protocol was used for all assessments. In addition, the current protocol implemented a relatively short training period of five weeks. Although this is in line with previous studies^{9, 12}, it remains unknown if people with HSP would benefit from a longer training period, including the use of booster sessions. Furthermore, although we did include the ABC – a self-perceived balance confidence scale – we lack qualitative feedback from our participants on how they perceived the gait-adaptability training. Lastly, we have no details about the content of the usual care (e.g. to what extent aspects of gait adaptability were trained). Hence, it is possible that the contrast between the gait-adaptability training group and the usual care control group was insufficient.

With regard to clinical implications, our study provides insufficient evidence to conclude that five weeks of gait-adaptability training, added to usual care, leads to greater improvement of gait-adaptability performance in people with HSP compared to usual care alone. Our study has several implications for future research. Future studies should focus on the evaluation of long-term gait-adaptability training, including booster sessions. They should also make use of a validated outcome measure that is more sensitive than the E-FAP obstacle subtask to the acquisition of complex gait and dynamic balance skills. Lastly, future studies should include qualitative assessments of the intervention by patients to improve its feasibility, content and attractiveness.

Supplementary materials

Table 4. Group means of the gait-adaptability training group (n=18) pre training, post training and at follow-up.

	Pre training Mean $\pm$ SD	Post training Mean $\pm$ SD	Follow-up Mean $\pm$ SD
Clinical Assessment			
Obstacle subtask (s)	10.3 $\pm$ 6.6	8.6 $\pm$ 3.9	8.8 $\pm$ 4.5
MiniBEST	18.3 $\pm$ 6.0	20.1 $\pm$ 5.4	20.0 $\pm$ 5.9
Activities-specific balance confidence scale (%)	66.5 $\pm$ 18.1	72.7 $\pm$ 16.2	72.2 $\pm$ 13.4
Ten-meters walk test – Comfortabel (m/s)	1.3 $\pm$ 0.3	1.3 $\pm$ 0.3	1.3 $\pm$ 0.2
Ten-meters walk test – Fast (m/s)	1.6 $\pm$ 0.3	1.7 $\pm$ 0.4	1.7 $\pm$ 0.3
Walking adaptability ladder test – single run (s)	21.6 $\pm$ 13.8	18.3 $\pm$ 8.6	19.4 $\pm$ 11.5
Walking adaptability ladder test – double run (s)	38.7 $\pm$ 17.9	35.1 $\pm$ 14.9	33.6 $\pm$ 13.7
Time spent active (% of day)	9.8 $\pm$ 3.4	10.2 $\pm$ 2.9	9.5 $\pm$ 3.7
Time spent walking (% of day)	8.1 $\pm$ 3.0	8.3 $\pm$ 3.0	7.4 $\pm$ 3.6
Three-dimensional gait analysis #			
Average stride length (m)	1.2 $\pm$ 0.2	1.2 $\pm$ 0.2	1.2 $\pm$ 0.1
Average stride time (s)	1.1 $\pm$ 0.2	1.1 $\pm$ 0.1	1.1 $\pm$ 0.1
Average step width (m)	0.2 $\pm$ 0.0	0.2 $\pm$ 0.0	0.2 $\pm$ 0.0
Walking velocity (m/s)	1.1 $\pm$ 0.3	1.1 $\pm$ 0.2	1.1 $\pm$ 0.2
Cadence (steps/min)	106.2 $\pm$ 11.9	107.8 $\pm$ 10.0	107.8 $\pm$ 9.0

Values displayed are means $\pm$ standard deviation. Presented data includes the pre-training, post-training and follow-up assessment data for the gait-adaptability training group. # Collected during two trials of 3 minute overground walking.

Table 5. Group means of the waiting-list control group (n=18) pre waiting-list, pre training, post training and at follow-up

	Pre waiting-list	Pre training	Post training	Follow-up
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Clinical Assessment				
Obstacle subtask (s)	9.5 ± 4.7	8.5 ± 3.8	7.6 ± 2.7	7.9 ± 3.3
MiniBEST	19.3 ± 3.8	19.9 ± 3.8	23.1 ± 3.1	22.5 ± 9.1
Activities-specific balance confidence scale (%)	70.9 ± 18.2	72.7 ± 16.6	75.5 ± 16.8	74.0 ± 17.3
Ten-meters walk test – Comfortabel (m/s)	1.2 ± 0.3	1.3 ± 0.3	1.4 ± 0.3	1.3 ± 0.3
Ten-meters walk test – Fast (m/s)	1.7 ± 0.4	1.7 ± 0.3	1.8 ± 0.3	1.7 ± 0.3
Walking adaptability ladder test – single run (s)	23.0 ± 12.3	21.2 ± 9.9	18.6 ± 7.6	19.0 ± 9.1
Walking adaptability ladder test – double run (s)	38.7 ± 16.8	36.3 ± 14.6	33.1 ± 14.9	34.1 ± 15.3
Time spent active (% of day)	10.6 ± 3.0	9.7 ± 2.8	10.5 ± 3.4	10.3 ± 3.4
Time spent walking (% of day)	8.2 ± 2.8	7.5 ± 1.6	8.2 ± 3.1	7.3 ± 2.0
Three-dimensional gait analysis #				
Average stride length (m)	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2
Average stride time (s)	1.2 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
Average step width (m)	0.2 ± 0.2	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1
Walking velocity (m/s)	1.0 ± 0.2	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.2
Cadence (steps/min)	107.0 ± 15.4	109.1 ± 15.6	110.2 ± 0.3	109.5 ± 13.1

Values displayed are means ± standard deviation. Presented data includes the pre waiting-list, pre training, post training and follow-up assessment data for the waiting-list control group. # Collected during two trials of 3 minute overground walking.

Reference list

1. Shribman, S., et al., Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*, 2019.
2. Salinas, S., et al., Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol*, 2008. 7(12): p. 1127-38.
3. van Lith, B.J.H., et al., Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*, 2020. 15(1): p. 64.
4. Nonnekes, J., et al., Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia. *J Rehabil Med*, 2017. 49(5): p. 369-377.
5. Bertolucci, F., et al., Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. *NeuroRehabilitation*, 2015. 36(1): p. 93-9.
6. Paparella, G., et al., Efficacy of a Combined Treatment of Botulinum Toxin and Intensive Physiotherapy in Hereditary Spastic Paraplegia. *Front Neurosci*, 2020. 14: p. 111.
7. Seo, H.G., B.M. Oh, and K. Kim, Robot-assisted gait training in a patient with hereditary spastic paraplegia. *Pm r*, 2015. 7(2): p. 210-3.
8. Sato, M., et al., Physical therapy intervention with a low frequency of exercise for a patient with a complicated form of hereditary spastic paraplegia: a case report. *J Phys Ther Sci*, 2019. 31(7): p. 545-549.
9. Heeren, A., et al., Step by step: a proof of concept study of C-Mill gait adaptability training in the chronic phase after stroke. *J Rehabil Med*, 2013. 45(7): p. 616-22.
10. van Ooijen, M.W., et al., Improved gait adjustments after gait adaptability training are associated with reduced attentional demands in persons with stroke. *Exp Brain Res*, 2015. 233(3): p. 1007-18.
11. Timmermans, C., et al., Walking-adaptability therapy after stroke: results of a randomized controlled trial. *Trials*, 2021. 22(1): p. 923.
12. Fonteyn, E.M., et al., Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration. *Gait Posture*, 2014. 40(1): p. 247-51.
13. Wang, Y., et al., Efficacy of C-Mill gait training for improving walking adaptability in early and middle stages of Parkinson's disease. *Gait Posture*, 2022. 91: p. 79-85.
14. van de Venis, L., et al., Improving gait adaptability in patients with hereditary spastic paraplegia (Move-HSP): study protocol for a randomized controlled trial. *Trials*, 2021. 22(1): p. 32.
15. Wolf, S.L., et al., Establishing the reliability and validity of measurements of walking time using the Emory Functional Ambulation Profile. *Phys Ther*, 1999. 79(12): p. 1122-33.
16. Bohannon, R.W. and M.B. Smith, Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*, 1987. 67(2): p. 206-7.
17. Counsil, M.R., Aids to the investigation of the peripheral nervous system. Her Majesty's Stationary Office, 1943.
18. Schule, R., et al., The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. *Neurology*, 2006. 67(3): p. 430-4.
19. Heyrman, L., et al., A clinical tool to measure trunk control in children with cerebral palsy: the Trunk Control Measurement Scale. *Res Dev Disabil*, 2011. 32(6): p. 2624-35.

20. Franchignoni, F., et al., Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med*, 2010. 42(4): p. 323-31.
21. Kuijpers, R., et al., Reliability and construct validity of the Walking Adaptability Ladder Test for Kids (WAL-K): a new clinical test for measuring walking adaptability in children. *Disabil Rehabil*, 2022. 44(8): p. 1489-1497.
22. Graham, J.E., et al., Assessing walking speed in clinical research: a systematic review. *J Eval Clin Pract*, 2008. 14(4): p. 552-62.
23. Mayo, E., *The Human Problems of an Industrial Civilization*. 1 ed. 2003, London.
24. Lutjeboer, T., et al., Effect of awareness of being monitored on wearing of orthopaedic footwear. *J Rehabil Med*, 2020. 52(11): p. jrm00127.
25. Gale, E.A., et al., Recruitment to a clinical trial improves glycemic control in patients with diabetes. *Diabetes Care*, 2007. 30(12): p. 2989-92.
26. Pate, A., et al., Study investigating the generalisability of a COPD trial based in primary care (Salford Lung Study) and the presence of a Hawthorne effect. *BMJ Open Respir Res*, 2018. 5(1): p. e000339.
27. Purssell, E., et al., The Hawthorne effect on adherence to hand hygiene in patient care. *J Hosp Infect*, 2020. 106(2): p. 311-317.
28. van de Venis, L., et al., COVID-19 reveals influence of physical activity on symptom severity in hereditary spastic paraplegia. *J Neurol*, 2020. 267(12): p. 3462-3464.
29. Helmich, R.C. and B.R. Bloem, The Impact of the COVID-19 Pandemic on Parkinson's Disease: Hidden Sorrows and Emerging Opportunities. *J Parkinsons Dis*, 2020. 10(2): p. 351-354.
30. Matysiak, M., et al., The influence of COVID-19 pandemic lockdown on the physical activity of people with multiple sclerosis. The role of online training. *Mult Scler Relat Disord*, 2022. 63: p. 103843.
31. Vercellino, M., et al., Impact of COVID-19 lockdown on progressive multiple sclerosis patients. *Neurol Sci*, 2022. 43(5): p. 2943-2946.
32. Held, J.P.O., et al., Changes in Stroke Rehabilitation during the Sars-Cov-2 Shutdown in Switzerland. *J Rehabil Med*, 2022. 54: p. jrm00272.
33. D'Souza, J., et al., Barriers leading to increased disability in neurologically challenged populations during COVID-19 pandemic: a scoping review. *Disabil Rehabil*, 2021: p. 1-14.
34. Nightingale, T.E., et al., Physical Activity and Health-Related Quality of Life in Adults With a Neurologically-Related Mobility Disability During the COVID-19 Pandemic: An Exploratory Analysis. *Front Neurol*, 2021. 12: p. 699884.



Chapter 5

Increased trunk movements in people with hereditary spastic paraplegia: do these involve balance correcting strategies?

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Journal of Neurology. 2022 Aug;269(8):4264-4269

Abstract:

Objective

Hereditary spastic paraplegia (HSP) is characterized by a bilaterally spastic gait pattern. During gait, increased trunk movements are often observed. People with HSP likely generate trunk movements to improve foot clearance and step length, but there may be additional explanations. Here, we investigate whether there is an association between reduced balance performance and increased trunk movements, as an increase in trunk movements may partly reflect balance correcting strategies.

Methods

We analyzed an historic cohort of 86 people with HSP who underwent gait analysis and balance examination. Two researchers reviewed gait analyses videos and classified the observed trunk movement as i) normal, ii) moderately increased, or iii) markedly increased, and categorized participants as 'toe walkers' (yes/no). Balance performance and spatiotemporal gait parameters were collected from the medical files. Parameters were compared between people with normal vs. moderately increased trunk movements, moderately vs. markedly increased trunk movements, and normal vs. markedly increased trunk movements.

Results

Patients with moderately increased trunk movements during gait scored lower on the Berg Balance Scale ($p=0.002$) and/or the Mini Balance Evaluation Test ($p=0.043$) than patients with normal trunk movements. Likewise, patients with markedly increased trunk movements performed worse on the BBS ($p=0.037$) and/or the Mini-BESTest ($p=0.004$) than patients with moderately increased trunk movements. Patients with markedly increased trunk movements were more often toe-walkers than patients with moderately increased (68% vs. 6%; $p<0.001$).

Conclusions

We found an association between increased trunk movements and reduced balance capacity. This may have several – not mutually exclusive – explanations. One of these explanations is that trunk movements, at least partly, reflect balance correcting strategies. With disease progression, ankle strategies and foot placement strategies become impaired and insufficient to restore balance after intrinsic perturbations. Hip strategies are then potentially recruited to maintain balance, resulting in increased trunk movements.

Introduction

Hereditary spastic paraplegia (HSP) is a heterogeneous group of neurodegenerative disorders. Pure forms are clinically characterized by bilateral progressive spasticity. With disease progression, people with HSP often develop muscle weakness and contractures in the lower extremities (e.g., a pes equinovarus deformity).¹⁻³ Together with impaired proprioception, these motor impairments often lead to reduced balance and gait capacities, which are among the most disabling consequences of HSP.^{4,5} In complex forms, additional neurological symptoms are present, such as ataxia, mental retardation, peripheral neuropathy and/or optic atrophy.^{1,2} As the disease progresses, balance and gait problems become gradually more severe, and people with HSP typically develop a bilaterally spastic gait pattern.^{5,6} Increased truncal movements during gait in frontal, sagittal and transversal planes are reported from the early phases of the disease.⁷⁻⁹ In daily clinical practice, the most pronounced trunk movements seem to be present in relatively young patients, and in patients without plantigrade foot contact during gait ('toe walkers'). Muscle weakness and spasticity are rarely found in the trunk of people with HSP. Increased trunk movement during gait therefore likely reflect a secondary phenomenon or compensation strategy.^{8,10}

The clinical determinants underlying increased trunk movements during gait in people with HSP have rarely been studied. Assumingly, trunk movement are partly made in a compensatory effort to improve foot clearance and step length, but there may be additional explanations.^{8,11,12} Here, we explore the hypothesis that increased trunk movements during gait in people with HSP partly reflect balance correcting strategies, specifically, the recruitment of so-called hip strategies. Hip strategies consist of the rotation of upper body segments around the center of mass, for instance, by making trunk or arm movements, and are usually recruited when other balance strategies are unavailable or insufficient.^{13,14} To investigate this hypothesis, we assessed whether the magnitude of truncal movements during gait in people with HSP was associated to a reduced clinical balance capacity. In addition, we explored whether increased trunk movements coincided with a higher percentage of toe walking.

Methods

The Centre of Expertise for Rare and Genetic Movement Disorders at Radboudumc Nijmegen, part of the European Reference Network for Rare Neurological Diseases (ERN-RND), is a primary national referral centre for patients with HSP. In our expertise centre, the diagnosis of HSP is based on clinical physical examination

combined with clinical inheritance pattern and/or proven molecular defect. In the presence of disabling gait impairments, 3D-instrumented gait analysis is performed in our movement laboratory.

For the current study, an historic cohort of patients was included, based on the following inclusion criteria: (i) established diagnosis of HSP, (ii) the availability of a gait analysis performed between October 2013 and May 2021, and (iii) the availability of documented balance scores (Berg Balance Scale (BBS) and/or Mini Balance Evaluation System Test (Mini-BESTest)). As some participants performed multiple gait analyses during the selected time period, the first gait analysis with a documented balance score was included for analysis. If both Berg Balance Scale and Mini-BESTest scores were available, both scores were included for analysis. Exclusion criteria consisted of concomitant neurological or orthopedic conditions, inability to walk eight meters barefoot without walking aids, and age below 18 years.

Prior to the gait analysis, 16 retroreflective markers were placed on the lower extremities according to the standard Plug-In Gait marker model for lower body. Patients then walked barefoot over an eight-meter walkway at a self-selected speed. The gait pattern was recorded with an eight-camera motion analysis system (VICON, Oxford UK) and two video cameras, one capturing the frontal plane and the second the sagittal plane.

Two researchers (LV, JN) reviewed videos from the gait analyses in both the frontal (i.e., trunk lateroflexion) and sagittal plane (i.e. trunk flexion and extension) and classified the observed trunk movement as i) normal, ii) moderately increased, or iii) markedly increased. In addition, patients who walked without plantigrade (heel touching the floor) contact during the stance phase were classified as 'toe-walkers'.

Cohen's kappa coefficients were calculated to determine the inter-rater reliability between the two raters for the classification of trunk movements during gait. Any initial disagreements between the raters were discussed and resolved in consensus. Spatiotemporal gait parameters (walking velocity, cadence, step length, step width) were calculated based on marker data in Vicon Polygon. Data were checked for normality. Independent samples t-tests or Mann-Whitney U tests were used where appropriate to assess differences between groups on balance scores and spatiotemporal parameters.

Comparisons were made between persons with normal vs. moderately increased trunk movements, between persons with moderately vs. markedly increased trunk movements, and between persons with normal vs. markedly increased trunk movements. Differences in the percentage of toe-walkers between the three categories was assessed using Chi-Square Tests.

Results

In total, 147 persons diagnosed with HSP, and with available gait analyses and balance scores were screened for eligibility. Sixty participants were excluded for the following reasons: concomitant neurological or orthopedic conditions ($n=15$), inability to walk eight meters barefoot without the use of walking aids ($n=38$), or age below 18 ($n=8$). As a result, 86 (58 men) participants were included with a mean age of 48 years (range: 19-75 years). A molecular diagnosis was present in 43 participants: SPG4 ($n=26$); SPG7 ($n=5$); SPG30 ($n=3$), SPG31 ($n=3$), SPG11 ($n=2$), SPG10 ($n=1$), SPG17 ($n=1$), SPG3A ($n=1$) and SPG9 ($n=1$)).

The initial absolute interrater agreement in the classification of trunk movements during gait was 83% ($\kappa = 0.74$). After discussion and through consensus, 100% agreement was reached.

Thirty-five participants (41%) were classified as having moderately increased trunk movements, while 13 participants (15%) had markedly increased trunk movements. Thirty-eight participants (44%) were classified as having normal trunk movements. Participants with markedly increased trunk movements were on average younger than participants with moderately increased trunk movements (33.2 ± 13 years vs. 48.2 ± 11 years; $p < 0.001$). Participants with normal trunk movements were 51.8 ± 12 years old, which was significantly different from the group with markedly increased trunk movements ($p < 0.001$), but not from the group with moderately increased trunk movements. Figure 1 shows the balance scores for each category of observed trunk movements for 68 participants (BBS score) and 51 participants (Mini-BESTest score); note that both balance scores were available for 33 participants. Participants with moderately increased trunk movements scored 2.0 points lower on the BBS ($p = 0.002$) and 2.3 points lower on the Mini-BESTest ($p = 0.043$) than those with normal trunk movements. Participants with markedly increased trunk movements scored 4.0 points lower on the BBS ($p = 0.037$) and 4.6 points lower on the Mini-BESTest ($p = 0.004$) than those with moderately increased trunk movements. Participants with markedly increased trunk movements scored 6.0 points lower on the BBS ($p < 0.001$) and 6.9 points on Mini-BESTest ($p < 0.001$) compared to participants with normal trunk movements.

In total, 11 participants (13%) were categorized as toe walkers. They were on average younger than participants without toe walking (37.0 ± 14 vs. 49.1 ± 12 years; $p = 0.003$). The group of participants with markedly increased trunk movements included a higher percentage of toe walkers than the group with moderately increased trunk movements (69% vs 6%; $p < 0.001$). None of the patients with normal trunk movements showed toe walking.

Table 1 shows the spatiotemporal gait parameters for each level of observed trunk movements during gait. Participants with moderately increased trunk movements showed on average 0.07m/s lower gait velocity ($p<0.022$) and 0.05m smaller step length compared to those with normal trunk movements ($p<0.007$). Participants with markedly increased trunk movements had 0.04m smaller step width compared to those with moderately increased trunk movements ($p=0.015$). Participants with markedly increased trunk movements showed on average 0.06m/s lower gait velocity ($p=0.030$), 0.04m smaller step width ($p=0.021$), and 13 steps per minute lower cadence ($p<0.001$), compared to those with normal trunk movements. Other comparisons were non-significant.

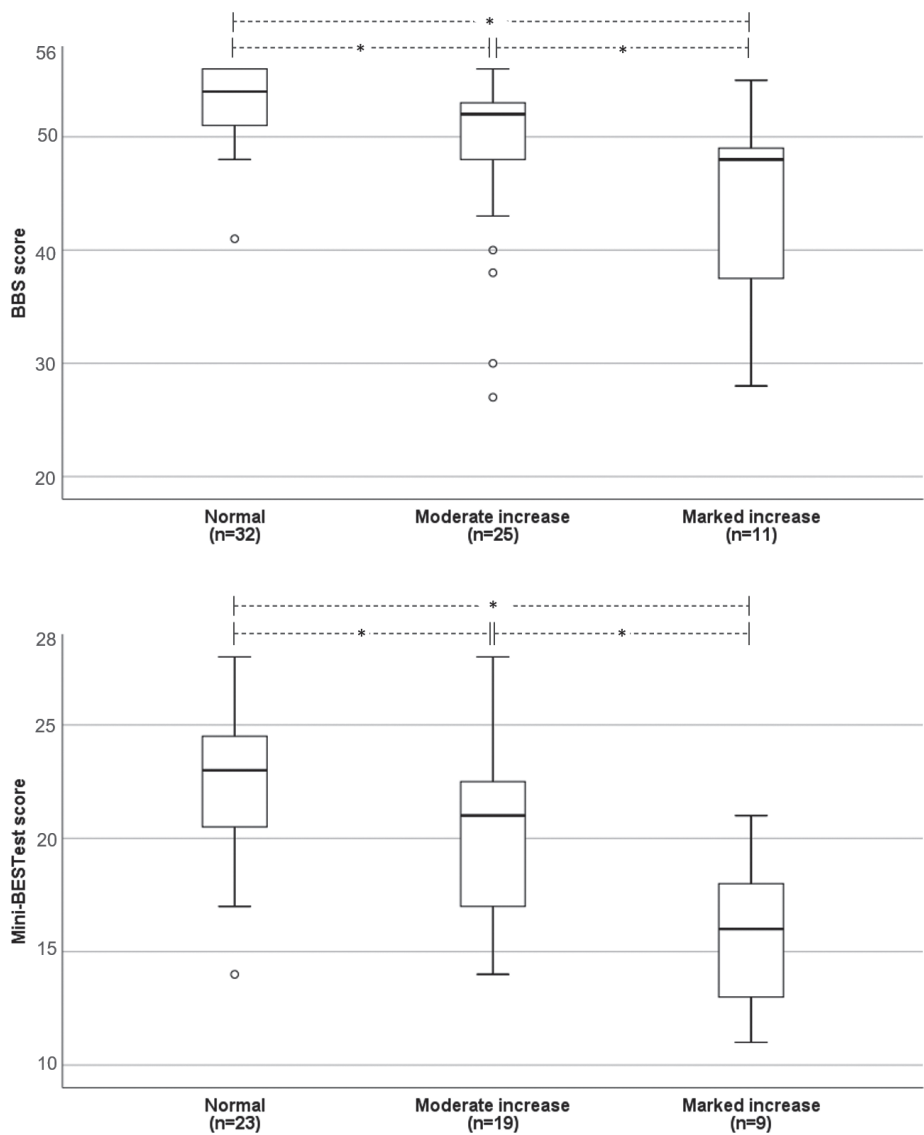


Figure 1. Balance scores for each level of trunk movements during gait in participants with HSP (n=86). Median, interquartile range, and total range of balance scores (o indicating outliers) are shown per level of trunk movements. For a total of 33 participants both Mini-BEST test scores and BBS test scores were available. Abbreviations: BBS: Berg Balance Scale. Mini-BEST: Mini Balance Evaluation Test. * indicates significant differences between categories.

Table 1. Spatiotemporal gait parameters for each level of trunk movements in participants with HSP.

	Trunk movements during gait		
	Normal (n=35)	Moderately increased (n=38)	Markedly increased (n=13)
Walking speed (m/s)	0.93 [0.72 - 1.35]	0.86 [0.26 - 1.26]*	0.87 [0.53 - 1.04]***
Cadence (steps/min)	103.8 ± 10.0	97.9 ± 15.6	90.8 ± 12.3 ***
Step length (m)	0.55 ± 0.07	0.50 ± 0.10*	0.53 ± 0.07
Step width (m)	0.19 [0.13 - 0.38]	0.19 [0.13 - 0.37]**	0.15 [0.09 - 0.42]***
Toe-walkers (% of subgroup)	0%	6%**	69%

Values displayed are means (± standard deviation) or median [range]. * indicates significant differences between patients with normal trunk movements and moderately increased trunk movements.

** indicates significant differences between patients with moderately increased trunk movements and markedly increased trunk movements. *** indicates significant differences between patients with normal trunk movements and markedly increased trunk movements.

Discussion

In this historic cohort study, we investigated whether increased trunk movements during gait in people with HSP were associated with reduced balance capacity. Previous studies already reported increased trunk movements during gait in people with HSP in comparison to healthy controls^{7-9, 15}. The current study has added value by exploring the potential association between increased trunk movements and clinical balance performance. Although our retrospective and cross-sectional study design does not allow inferences about causality, we found an association between increased trunk movements and reduced balance capacity. This association may have several – not mutually exclusive – explanations. One of these explanations is that trunk movements, at least partly, reflect balance correcting strategies.

Balance perturbations can be due to extrinsic factors (such as an icy pavement) or intrinsic factors (such as an impaired anticipatory postural adjustment to self-initiated movement). In people with HSP, intrinsic factors appear to play an important part. For instance, calf muscle spasticity may result in a sudden knee extension during the single-stance phase of gait, or cause retropulsion in a sit-to-stance transfer, jeopardizing postural stability.⁴ Compensatory trunk movements for enlarging step length and foot clearance during gait^{8, 11, 12} may also act as balance perturbations. Following an intrinsic balance perturbation, balance needs to be restored reactively. In general, humans have three strategies to restore balance during gait i): the *foot placement strategy*, where people alter foot placement of the swing leg to adjust the base of support^{13, 14, 16-18}; ii) the *ankle strategy*, where ankle moments of the stance leg are modulated to make (minor) adjustments to center-of-

mass (CoM) movements^{13, 16, 18, 19}; and iii) the *hip strategy*, where upper body segments are rotated around the CoM.^{13, 14} When all three strategies are available for balance recovery, foot placement adjustment strategies and ankle strategies are preferred, while hip strategies are generally recruited when both foot placement and ankle strategies are insufficient; for instance, when walking on a narrow beam¹⁴, when performing under time pressure (i.e., responding to a perturbation that occurs just prior to foot contact, leaving insufficient time to perform an adequate foot placement adjustment²⁰⁻²²), or when affected by a neurological disease¹⁵).

People with HSP may be limited in using the ankle strategy for balance corrections due to lower-extremity spasticity (e.g., of the calf muscles), muscle weakness (e.g. of the ankle dorsiflexors), and/or ankle-foot deformities (e.g., pes equinus or pes equinovarus), or even sensory or cerebellar ataxia.⁴ To compensate, patients become more dependent on the foot placement strategy.¹⁷ When adjustments in the mediolateral direction are needed, for example, step width must be increased. In more severely affected individuals with HSP, adjustments in foot placement themselves may be impaired due to proximal lower-extremity spasticity (e.g. of the hip adductors), ataxia, and/or apparent slowness of postural responses.⁴ In these patients, the recruitment of hip strategies may become particularly important to maintain balance during gait, which would explain the presently reported increased trunk movements. Although less likely, we cannot rule out truncal ataxia as an alternative explanation for increase trunk movements as we did not assess its presence at the time of the instrumented gait analysis.

In support of this line of reasoning, a previous study reported that after restoring the prerequisites for recruitment of ankle strategies and foot placement strategies in a patient with HSP and bilateral structural pes equinus (through bilateral Achilles tendon lengthening), a clear decrease in trunk movements was observed, suggesting less reliance on hip strategies to maintain balance during gait.¹⁵ In addition, studies in other populations have demonstrated increased trunk movements when ankle strategy recruitment was artificially hampered. For example, in nine healthy participants, bilateral foot- and ankle-immobilizing casts were used to limit ankle strategy recruitment. During gait, trunk lateroflexion increased in the cast-condition compared to walking with lightweight sneakers.²³ Comparably, in children with cerebral palsy, rigid ankle-foot orthoses hampering the recruitment of ankle strategies were found to increase lateral trunk movements compared to barefoot walking^{24, 25} and compared to walking with shoes without orthoses.²⁶ As plantigrade foot contact is a prerequisite for effective use of ankle strategies,⁴ the loss of ankle strategies likely explains the large proportion of toe walkers in our patient category with markedly increased trunk movements.

A disadvantage of increased trunk movements during walking is the inevitable rise in mechanical energy costs related to larger CoM excursions, which most likely results in greater metabolic costs as well. A commonly used method to assess the metabolic costs of walking is indirect calorimetry.²⁷ Regrettably, indirect calorimetry is not part of our routine clinical gait analysis and could therefore not be included in the current analyses. In line with our clinical observations, our results indicate that markedly increased trunk movements during gait were predominantly present in relatively young people with HSP. It may be that younger people with HSP are able to walk with markedly increased trunk movements, although energy demanding, whereas this is often too demanding for older people with HSP, who therefore opt for the use of walking aids. Alternatively, we found that the group of toe walkers was on average younger than those without toe walking. It might be that people with an earlier disease onset progressed further (resulting in more severe spasticity and development of contractures resulting in pes equinus), compared to ambulatory older people with HSP. Both suggestions require further investigation.

This study has several limitations that should be taken into account. First, an objective assessment of trunk movements during gait was lacking, as 3D gait analyses were performed using the lower body marker model. A second limitation is the lack of other clinical participant characteristics, such as disease duration, degree of spasticity and muscle weakness of the lower extremities, presence of sensory impairments, or an indicator of disease severity (e.g., the Spastic Paraplegia Rating Scale).²⁸ Hence, we could not test whether disease progression itself was associated with increased trunk movements. In addition, it was not possible to extract item subscores off e.g., the BBS from the medical files to investigate the notion that increased truncal movements while walking – although unlikely – might be associated with truncal instability or ataxia while sitting. Thirdly, we could not make use of the same balance score for all participants. This was due to the fact that this retrospective study spanned an extended period of time, in which we initially used the BBS in clinical practice, and later switched to the Mini-BESTest, as this test shows less ceiling effects.²⁹ Nevertheless, we believe that the current findings may help clinicians and therapists to better relate individual movement patterns to balance and gait capacities and, thus, to select an optimal treatment approach for individual patients with HSP, including ankle-foot surgery (in case of structural ankle-foot deformities) and balance-assistive devices, to reduce the dependence on hip strategies.^{4, 15}

Reference list

1. Salinas, S., et al., Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *Lancet Neurol*, 2008. 7(12): p. 1127-38.
2. Shribman, S., et al., Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*, 2019.
3. Nonnekes, J., et al., StartReact restores reaction time in HSP: evidence for subcortical release of a motor program. *J Neurosci*, 2014. 34(1): p. 275-81.
4. Nonnekes, J., et al., Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia. *J Rehabil Med*, 2017. 49(5): p. 369-377.
5. van Lith, B.J.H., et al., Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*, 2020. 15(1): p. 64.
6. Shribman, S., et al., Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*, 2019. 18(12): p. 1136-1146.
7. Serrao, M., et al., Gait Patterns in Patients with Hereditary Spastic Paraparesis. *PLoS One*, 2016. 11(10): p. e0164623.
8. Adair, B., et al., Kinematic gait deficits at the trunk and pelvis: characteristic features in children with hereditary spastic paraplegia. *Dev Med Child Neurol*, 2016. 58(8): p. 829-35.
9. van Vugt, Y., et al., Postural stability during gait for adults with hereditary spastic paraparesis. *J Biomech*, 2019. 88: p. 12-17.
10. Bonnefoy-Mazure, A., et al., Full body gait analysis may improve diagnostic discrimination between hereditary spastic paraplegia and spastic diplegia: a preliminary study. *Res Dev Disabil*, 2013. 34(1): p. 495-504.
11. Rijken, N.H., et al., Gait propulsion in patients with facioscapulohumeral muscular dystrophy and ankle plantarflexor weakness. *Gait Posture*, 2015. 41(2): p. 476-81.
12. Michel, V. and M.C. Do, Are stance ankle plantar flexor muscles necessary to generate propulsive force during human gait initiation? *Neurosci Lett*, 2002. 325(2): p. 139-43.
13. Reimann, H.F.T., Jeka JJ, Strategies for the Control of Balance During Locomotion. *Kinesiology Review*, 2017. 7(1): p. 18-25.
14. Horak, F.B., Clinical measurement of postural control in adults. *Phys Ther*, 1987. 67(12): p. 1881-5.
15. Nonnekes, J., et al., Improved Gait Capacity after Bilateral Achilles Tendon Lengthening for Irreducible Pes Equinus Due to Hereditary Spastic Paraplegia: a Case Report. *J Rehabil Med Clin Commun*, 2021. 4: p. 1000059.
16. Bruijn, S.M. and J.H. van Dieën, Control of human gait stability through foot placement. *J R Soc Interface*, 2018. 15(143).
17. Hof, A.L., et al., Control of lateral balance in walking. Experimental findings in normal subjects and above-knee amputees. *Gait Posture*, 2007. 25(2): p. 250-8.
18. Fettes, T., et al., Interdependence of balance mechanisms during bipedal locomotion. *PLoS One*, 2019. 14(12): p. e0225902.
19. Reimann, H., et al., Complementary mechanisms for upright balance during walking. *PLoS One*, 2017. 12(2): p. e0172215.

20. Vlutters, M., E.H.F. van Asseldonk, and H. van der Kooij, Reduced center of pressure modulation elicits foot placement adjustments, but no additional trunk motion during anteroposterior-perturbed walking. *J Biomech*, 2018. 68: p. 93-98.
21. Hof, A.L., S.M. Vermerris, and W.A. Gjaltema, Balance responses to lateral perturbations in human treadmill walking. *J Exp Biol*, 2010. 213(Pt 15): p. 2655-64.
22. Oddsson, L.I., et al., Recovery from perturbations during paced walking. *Gait Posture*, 2004. 19(1): p. 24-34.
23. Nepomuceno, A., et al., Effect of foot and ankle immobilization on able-bodied gait as a model to increase understanding about bilateral transtibial amputee gait. *Prosthet Orthot Int*, 2017. 41(6): p. 556-563.
24. Swinnen, E., et al., The influence of the use of ankle-foot orthoses on thorax, spine, and pelvis kinematics during walking in children with cerebral palsy. *Prosthet Orthot Int*, 2018. 42(2): p. 208-213.
25. Degelaen, M., et al., Effect of ankle-foot orthoses on gait in typically developing children: Developmental trend in segmental coordination. *J Pediatr Rehabil Med*, 2010. 3(3): p. 163-70.
26. Meyns, P., et al., Ankle foot orthoses in cerebral palsy: Effects of ankle stiffness on trunk kinematics, gait stability and energy cost of walking. *Eur J Paediatr Neurol*, 2020. 26: p. 68-74.
27. Hills, A.P., N. Mokhtar, and N.M. Byrne, Assessment of physical activity and energy expenditure: an overview of objective measures. *Front Nutr*, 2014. 1: p. 5.
28. Schule, R., et al., The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. *Neurology*, 2006. 67(3): p. 430-4.
29. Godi, M., et al., Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders. *Phys Ther*, 2013. 93(2): p. 158-67.



Chapter 6

Are clinical tests and biomechanical measures of gait stability able to identify fallers in hereditary spastic paraplegia?

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Abstract

Introduction

Balance and gait impairments are common in people with hereditary spastic paraplegia (HSP) and often result in falls. Measures that identify patients at risk of falling are clinically relevant, but relatively unexplored in HSP. Here, we evaluated the potential of different balance and gait constructs to (1) identify differences between healthy controls and people with HSP and (2) discriminate between fallers and non-fallers with HSP.

Methods

We included 33 people with pure-HSP and 15 healthy controls. We assessed balance confidence (six-item Activities-specific Balance Confidence scale), clinical balance capacity (Mini-Balance Evaluation Systems Test) and gait capacity (ten-meter Walk Test). Biomechanical measures included spatiotemporal gait variability, mediolateral Margin of Stability (MoS), Foot Placement Deviation (FPD), and Local Divergence Exponents (LDEs) of trunk and pelvis, derived from treadmill-walking at comfortable and fixed gait speed. People with HSP logged their falls during a fifteen-week period and were categorized as 'faller' (≥ 1 fall) or 'non-faller'.

Results

People with HSP had significantly lower balance confidence, balance capacity, and gait capacity compared to age-matched controls. They also showed reduced gait stability, reflected by increased spatiotemporal gait variability, FPD, and LDEs of trunk and pelvis. Overall, 44% of people with HSP were categorized as 'faller'. Balance confidence (AUC: 0.84) and balance capacity (AUC: 0.75) discriminated fallers from non-fallers, whereas none of the biomechanical measures significantly differed.

Conclusion

Balance confidence, clinical balance and gait capacity, and biomechanical measures are affected in HSP, but clinical measures showed potential to identify people with HSP who exhibit a propensity for falling.

Introduction

Hereditary spastic paraplegia (HSP) comprises a heterogeneous group of neurodegenerative disorders. Pure forms of HSP are clinically characterized by progressive bilateral spasticity, muscle weakness, and loss of proprioception of the lower extremities.¹ Due to these symptoms, balance and gait impairments are common, disabling and often result in fear-of-falling, falls, and fall-related injuries.^{2,3} In order to optimally tailor fall prevention interventions, the clinical field is in need of measures that can identify individuals with HSP who exhibit a propensity for falling, and those who do not. Nonetheless, this is a relatively unexplored topic in HSP.

Fall risk can be assessed using different constructs: balance confidence is used to assess perception of fall risk through patient-reported outcomes (e.g., the Activities-specific Balance Confidence scale (ABC))^{4,5}, whereas objective clinical measures are used to assess general balance capacity (e.g., Mini Balance Evaluations Systems Test (Mini-BEST))^{4,6} or gait capacity (e.g., self-selected gait speed during the ten-meter walk test)⁷. Moreover, biomechanical measures of gait stability (e.g., spatiotemporal gait variability, mediolateral Margin of Stability (MoS), mediolateral Foot Placements Deviation (FPD), and Local Divergence Exponents (LDEs)) can objectify detailed aspects of dynamic balance capacity.⁸ The ability of these measures to differentiate between fallers and non-fallers has been reported in various neurological populations.⁹⁻¹⁴ Even though the aforementioned studies offer important insights, their potential to discriminate between fallers and non-fallers in people with HSP has not been evaluated.

In this study, we evaluated the potential of both clinical and biomechanical balance and gait measures for the fall risk assessment in ambulatory people with pure HSP. To this end, we assessed the different constructs, i.e., subjective balance confidence, objective clinical balance and gait capacity, and biomechanical measures of gait stability. As a first explorative step, we evaluated whether these constructs differed between people with pure HSP and healthy age-matched controls. Second, we divided the HSP cohort into fallers and non-fallers based on their real-life fall incidence and assessed the ability of these constructs to discriminate between fallers and non-fallers among people with HSP.

Methods

Participants and setting

This study was part of the data collection in a randomized clinical trial.^{15,16} Specifically, we obtained fall rates logged by the participants in the fifteen weeks prior to the first assessment. Thirty-three of the 36 participants with pure HSP (age: 48.7±11 years, 73% male) were included in the current study; three participants were excluded

as they were unable to walk on the treadmill. Participants were recruited via the Centre of Expertise for Rare and Genetic Movement Disorders of the Radboudumc - part of the European Reference Network for Rare Neurological Diseases (ERN-RND) - and via the HSP patient organization "Spierziekte Nederland". Participants with HSP were found eligible if they met the following inclusion criteria: (i) diagnosis of pure HSP made by a neurologist specialized in inherited movement disorders, (ii) aged between 18-70 years old, and (iii) being able to walk barefoot on a level ground for 50 meters without a walking aid during the assessment (use of orthotic devices was allowed). Exclusion criteria consisted of (i) any concomitant neurological, orthopedic or psychiatric condition affecting balance or gait performance and (ii), any HSP-related surgical procedure of the lower extremities in the medical history. Additionally, fifteen healthy control participants (i.e., without neurological or orthopedic impairments) of comparable age and sex (age: 49.0 ± 11 years, 73% male) were recruited from the community. The study was approved by the ethical committee Oost-Nederland and all participants provided written informed consent. Participants visited the movement laboratory of the Radboudumc (Nijmegen, The Netherlands) once.

Fall Assessment

Prior to the assessment, participants with HSP logged their falls with a digital fall diary for fifteen weeks. During these fifteen weeks, participants were allowed to use their walking aids and orthotics as usual. For this study, a fall was defined as an event that resulted in a person coming to rest inadvertently on a lower level surface.¹⁷ Falls that occurred while playing sports were excluded. Based on these data, participants with HSP were either classified as 'fallers' (if they had logged one or more falls) or as 'non-fallers' (if they had not logged any falls). Every other week, participants were contacted via a phone call by the primary investigator (LvdV) to remind them of the fall diary.

Clinical assessment

Balance confidence was assessed with the six-item version of the Activities-specific Balance Confidence scale (ABC-6).¹⁸ Balance capacity was evaluated with the Mini Balance Evaluation Systems Test (Mini-BEST)¹⁹, and gait capacity with the 10-meter Walk Test (10mWT) performed at both comfortable gait speed and at maximum gait speed.²⁰ As a clinical descriptor, disease severity in people with HSP was assessed with the Spastic Paraplegia Rating Scale (SPRS), where higher scores indicate greater disease severity (range 0-52).²¹ Furthermore, to gain insight in the amount of time that people with HSP spent walking on a daily basis, an activity monitor was placed on their right upper leg (Activ8, Remedy Distribution Ltd., Valkenswaard, the Netherlands) for seven consecutive days following the assessment.

Biomechanical assessment

In order to obtain the biomechanical measures of gait stability, a gait analysis was performed on an instrumented treadmill. We extracted the following biomechanical measures: i) variability of step length, step time and step width⁸, ii) medio-lateral margin of stability (MoS)²², iii) adherence to the medio-lateral foot placement strategy through foot placement deviations (FPD)²³, and iv) local dynamic stability through maximum local divergence exponents (LDEs).²⁴ All measures are further explained below. To this end, 35 reflective markers were placed on anatomical landmarks according to the standard upper and lower body plug-in-gait model. Thereafter, the individual comfortable treadmill speed was determined: the treadmill speed was gradually increased until the participant stated that it felt comfortable. Then, treadmill speed was increased by 0.3 ms^{-1} before gradually decreasing the speed until participants again stated they walked at their comfortable speed.^{10, 25} The average speed of both assessments was used as the individual comfortable gait speed during the two three-minute walking trials. Participants with HSP performed two additional trials of three-minute treadmill walking at a fixed speed of either 0.6 ms^{-1} or 0.8 ms^{-1} . In contrast, healthy controls were asked to perform two additional three-minute walking trials at both fixed walking speeds. All participants were instructed to walk as comfortable as possible without holding onto the treadmill bars. Participants with HSP wore their own (orthopedic) shoes and orthotic devices if required. Kinematic data were collected using a 10-camera 3-dimensional motion capture system (Vicon Nexus, Oxford, UK) at a sampling rate of 100Hz. The treadmill was equipped with two force plates sampling at a rate of 2000Hz. Details of the kinematic data processing can be found in Supplementary Explanations 1.

Prior to calculating the biomechanical measures, walking trials were checked for events where participants lost balance and needed to hold onto the bars. The steps occurring during these events were removed, in addition to two additional steps prior to and following the event. This was done to ensure that the biomechanical measures reflected the participants' ability to independently recover from small perturbations, without these measures being influenced by the external support that the bars provided. Heel strikes were identified as the moment of heel marker position minima in the vertical direction during a gait cycle. Step length and step time were calculated between two subsequent heel strikes (i.e., from left heel strike to right heel strike, and vice-versa). Step width was calculated as the distance between the left and right heel markers at mid stance. The mean and standard deviation of the spatiotemporal measures were calculated over the valid left and right steps collected during two similar three-minute walking trials.

Spatiotemporal gait variability

Gait variability was expressed in the coefficient of variation (CoV) for step length, step time and step width using the following equation:

$$\text{Coefficient of Variation} = \frac{\text{Standard deviation}}{\text{Mean}} * 100\% \quad (1)$$

Medio-lateral Margin of Stability

MoS was calculated in the mediolateral direction using the following equation²⁶, and defined as its minimum value during single stance:

$$\text{MoS} = \text{BoS} - \text{XCoM} \quad (2)$$

The base of support (BoS) was defined as the position of the mediolateral center of pressure (CoP) using the force plate recordings.²² The extrapolated center of mass (XCOM) was calculated according to Hof et al.²⁶ for which the position of the center of mass (CoM) was extracted from VICON. The mean MoS was calculated over the valid left and right steps collected during the three-minute walking trials, whereas variability of MoS was calculated using standard deviation.

Foot Placement Deviation

A previous study showed that the optimal mediolateral foot placement of the next step can be predicted based on the mediolateral CoM position and CoM velocity at mid stance.²⁷ To evaluate whether people with HSP can adhere to this optimal foot placement strategy, we calculated foot placement deviations using the root mean square error (RMSE) between the predicted and actual foot placements.²³ To this end, we calculated the predicted foot placement in mediolateral direction based on the medio-lateral CoM position and velocity at heel strike using the following equation:²³

$$\text{Predicted foot placement} = \beta_{\text{position}} * \text{CoM} + \beta_{\text{velocity}} * \text{CoM}' + \varepsilon \quad (3)$$

where the β_{position} and β_{velocity} are defined as the regression coefficients, and ε as the model error. The actual foot placement was calculated as the centered medio-lateral distance (i.e., subtracting the general mean from each individual step) between the left and right heel markers at midstance.²³

Local Dynamic Stability

To assess local dynamic stability, the revised Rosenstein algorithm was used to calculate maximum local divergence exponents (LDEs).^{8, 24} LDEs were calculated for the trunk and pelvis over one step (i.e., the so-called short-LDE) in the anterior-posterior, medio-lateral and vertical directions. For this purpose, the trunk was defined as the midpoint between the processus spinosus of the 7th cervical

vertebra (i.e., C7-marker) and the manubrium sterni (i.e., CLAV-marker). The pelvis was defined as the midpoint between the center of the left and right spina iliaca posterior superior and the left and right spina iliaca anterior superior (i.e., LPSI, RPSI, LASI and RASI-markers, respectively). The LDEs of the raw velocity of the spatially filtered trunk and pelvis trajectories were calculated over 65 strides per trial, as this was the maximum available number of strides across all participants. Further details on the calculation of the LDEs can be found in Supplementary Explanation 2.

Statistical Analysis

All analyses were conducted using IBM SPSS statistics (version 25) software. Data were first checked for normality using Shapiro-Wilk Test. Then, a series of independent samples t-tests (or Mann-Whitney U tests when appropriate) were used to assess differences between participants with HSP and healthy controls. To correct for multiple testing, level of significance was set at $p < 0.01$. Group differences were assessed for subjective balance confidence, objective clinical balance and gait capacity tests, and the biomechanical measures of gait stability derived from walking trials at comfortable gait speed.

As most biomechanical measures of gait stability are known to be speed-dependent,^{7, 28, 29} we repeated the analyses for both groups when walking at the same fixed treadmill speed. In these analyses, we only included participants with HSP who were able to perform the additional fixed-speed trials at either 0.6ms^{-1} or 0.8ms^{-1} . We assessed the distribution of 0.6ms^{-1} and 0.8ms^{-1} among these participants with HSP, and pseudo-randomly selected a similar distribution of the 0.6ms^{-1} and 0.8ms^{-1} trials from the healthy controls.

Lastly, differences between fallers and non-fallers among participants with HSP were assessed. First, a series of independent samples t-tests (or Mann-Whitney U tests when appropriate) were used to assess differences between fallers and non-fallers regarding the clinical capacity and gait stability measures extracted from the walking trials at comfortable gait speed. The ability of these measures to discriminate fallers from non-fallers was evaluated using the area under the curve (AUC) of the receiving operating characteristics curve (ROC). An $\text{AUC} \geq 0.9$ was considered outstanding discrimination, ≥ 0.8 to < 0.9 excellent discrimination, ≥ 0.7 to < 0.8 acceptable discrimination, and < 0.7 poor discrimination.³⁰

Results

Participants

A molecular diagnosis was available for 26 of the 33 participants with HSP (SPG4 (n=23); SPG5A (n=1); SPG8 (n=1); NEFL (n=1)). The mean SPRS score of the whole

group was 10.1 ± 3.9 points. The mean time since first symptom onset was 16 ± 13 years. Participants with HSP and healthy controls did not differ in age or sex.

Clinical assessment

Participants with HSP scored significantly worse on the ABC-6, Mini-BEST, and 10mWT compared to healthy controls (Table 1).

Biomechanical assessment at comfortable walking speed

Participants with HSP showed a slower comfortable treadmill speed than the healthy controls ($0.88 \pm 0.26 \text{ ms}^{-1}$ vs. $1.31 \pm 0.11 \text{ ms}^{-1}$; $p < 0.001$). Five participants with HSP used the treadmill bars occasionally to restore balance (one participant one time, one participants two times, two participants five times, and one participant eight times). None of the healthy controls used the treadmill bars. They also showed significantly greater variation of step length and step time (Table 1). In line with these results, the foot placement deviation and the LDE of the trunk in mediolateral direction, and the LDEs of the pelvis in anteroposterior and vertical direction were significantly higher in participants with HSP compared to healthy controls (Table 1). The MoS outcomes did not differ between groups.

Biomechanical assessment at fixed walking speed

A total of 24 participants with HSP were able to perform the additional trials at a slower fixed speed of either 0.6 ms^{-1} ($n=16$) or 0.8 ms^{-1} ($n=8$). Nine participants were unable to perform these additional trials: five participants were too fatigued, and four participants already had a self-selected walking speed below 0.6 ms^{-1} . To provide insight in whether this imposed a selection bias of this subgroup (i.e., only the best ‘walkers’ remained in the analysis), we included the scores of balance confidence, balance capacity and gait capacity test of the selected participants in Table 2.

This shows that the subgroup of 24 participants performed more or less the same on the clinical tests compared to the full cohort of 33 participants (ABC: 59 ± 23 vs. 56 ± 23 points; MiniBEST: 20 ± 4 vs. 20 ± 5 points; 10mWT at comfortable gait speed: 1.3 ± 0.3 vs. $1.3 \pm 0.2 \text{ ms}^{-1}$, respectively). Of the 24 participants included in this analysis, five patients with HSP used the treadmill bars to restore balance (four participants one time, one participant two times). None of the healthy controls used the treadmill bars. To perform the statistical analysis, we individually matched the slow fixed speed trials performed by the HSP participants with trials from the healthy control group: ten at the fixed speed of 0.6 ms^{-1} and five at the fixed speed of 0.8 ms^{-1} . The coefficient of variation of step length and step time remained significantly higher among participants with HSP compared to healthy controls. In addition, participants with HSP showed significantly greater LDE of the trunk in vertical direction and MoS variability (Supplementary Table 1).

Table 1: Differences between participants with HSP and healthy controls regarding clinical and biomechanical measures at comfortable treadmill velocity

	HSP (n=33)	HC (n=15)	P-value
Clinical assessment			
Activities-specific Balance Confidence scale			
– six-item	56 ± 23	92 ± 78	< 0.001
Mini-BEST	19.5 ± 4.5	27.0 ± 1.0	< 0.001
Ten-meter walk test – comfortable (ms ⁻¹)	1.3 ± 0.3	1.6 ± 0.2	< 0.001
Ten-meter walk test – fast (ms ⁻¹)	1.7 ± 0.3	2.4 ± 0.4	< 0.001
Biomechanical assessment			
Step width (mm)	125 ± 44	94 ± 33	0.021
Coefficient of variation			
• Step length (%)	7.3 ± 5	2.4 ± 0.6	< 0.001
• Step time (%)	4.9 ± 3	2.1 ± 0.5	< 0.001
• Step width (%)	27.5 ± 13	27.1 ± 13.4	0.973
Mediolateral Margin of Stability (MoS) (mm)	45.8 ± 17	47.6 ± 10.6	0.696
Variability of MoS (mm)	13.4 ± 8	14.3 ± 6.8	0.368
Mediolateral Foot Placement Deviation (cm)	1.0 ± 0.3	0.7 ± 0.2	< 0.001
Local Divergence Exponents			
• Trunk - mediolateral	1.5 ± 0.3	1.8 ± 0.2	< 0.001
• Trunk - anteroposterior	1.7 ± 0.3	1.6 ± 0.2	0.019
• Trunk - vertical	1.4 ± 0.2	1.3 ± 0.1	0.013
• Pelvis - mediolateral	1.3 ± 0.2	1.1 ± 0.2	0.064
• Pelvis - anteroposterior	1.5 ± 0.3	1.3 ± 0.2	0.008
• Pelvis - vertical	1.3 ± 0.2	1.2 ± 0.1	0.008

Values displayed are means ± standard deviation. Abbreviations: Mini-BEST: Mini Balance Evaluation Systems Test. Mini-BEST ranges between 0-28 points; Activities-specific Balance Confidence scale – six-item ranges between 0-100 points.

Differences between fallers and non-fallers

A total of 32 participants with HSP returned a completed fall-diary over a period of fifteen weeks; one participant experienced technical difficulties. Of these 32 participants, 14 (44%) reported one or more falls and were categorized as ‘fallers’. The reported fall rates ranged between 1-5 falls per participant (1 fall (n=7); 2 falls (n=2); 3 falls (n=1); 4 falls (n=3) and 5 falls (n=1)). The remaining 18 participants did not report any falls and were categorized as ‘non-fallers’. Fallers and non-fallers did not differ in terms of age (50 ± 9 vs. 48 ± 13; p=0.70), sex (71% vs 78% males; p=0.68), time since first symptom onset (19 ± 12 years vs. 12 ± 10 years, p=0.084), SPRS scores (11.2 ± 4.1 vs. 9.1 ± 3.6, p=0.145), or the percentage spent walking on a daily basis (7.4% ± 2.8 vs. 9.0% ± 3.1, p=0.15). Two fallers (14% of fallers) used the treadmill bars to restore balance (one participant two times, one participant eight times), whereas three non-fallers (17% of non-fallers) used the treadmill bars

(one participant one time, two participants five times). Moreover, the comfortable treadmill speed did not significantly differ between fallers and non-fallers ($0.84 \pm 0.31 \text{ ms}^{-1}$ vs. $0.92 \pm 0.22 \text{ ms}^{-1}$; $p=0.39$). Fallers scored significantly worse on the ABC-6 compared to non-fallers ($p=0.001$), and the ABC showed excellent discrimination between fallers and non-fallers ($\text{AUC} = 0.84$). Furthermore, the Mini-BEST showed acceptable discriminatory ability between fallers and non-fallers fallers scored significantly worse on the Mini-BEST compared to non-fallers ($\text{AUC} = 0.75$). The gait capacity and gait stability measures showed poor discriminatory ability between fallers and non-fallers ($\text{AUCs} < 0.70$; Table 2).

Table 2: Differences between fallers and non-fallers regarding clinical and biomechanical measures at comfortable treadmill velocity.

	Fallers (n=14)	Non-Fallers (n=18)	P-value	AUC
Clinical Assessment				
Activities-specific Balance Confidence scale – six-item	44 ± 19	78 ± 14	0.001	0.837
Mini-BEST	17.6 ± 4.1	20.8 ± 4.5	0.046	0.750
Ten-meter walk test – comfortable (ms^{-1})	1.2 ± 0.3	1.4 ± 0.2	0.081	0.659
Ten-meter walk test – fast (ms^{-1})	1.6 ± 0.4	1.8 ± 0.3	0.251	0.615
Biomechanical assessment				
Step width (mm)	135 ± 43	120 ± 44	0.350	0.433
Coefficient of variation				
• Step length (%)	7.4 ± 5.7	7.2 ± 5.3	0.808	0.472
• Step time (%)	5.7 ± 0.4	4.5 ± 2.1	0.587	0.560
• Step width (%)	27.3 ± 14.9	26.8 ± 12.5	0.925	0.488
Mediolateral Margin of Stability (MoS) (mm)	40.3 ± 17.7	51.2 ± 15.2	0.071	0.690
Variability of MoS (mm)	13.3 ± 8.8	13.7 ± 7.7	0.866	0.480
Mediolateral Foot Placement Deviation (cm)	1.0 ± 0.3	1.0 ± 0.3	0.377	0.595
Local Divergence Exponents				
• Trunk - mediolateral	1.8 ± 0.4	1.8 ± 0.3	0.878	0.480
• Trunk - anteroposterior	1.7 ± 0.2	1.8 ± 0.3	0.737	0.500
• Trunk - vertical	1.4 ± 0.2	1.4 ± 0.2	0.764	0.464
• Pelvis - mediolateral	1.3 ± 0.2	1.3 ± 0.2	0.706	0.563
• Pelvis - anteroposterior	1.5 ± 0.2	1.4 ± 0.3	0.574	0.560
• Pelvis - vertical	1.3 ± 0.2	1.3 ± 0.1	0.266	0.611

Values displayed are means ± standard deviation. Abbreviations: Mini-BEST: Mini Balance Evaluation Systems Test. Mini-BEST ranges between 0-28 points; Activities-specific Balance Confidence scale – six-item ranges between 0-100 points.

Discussion

This exploratory cohort study provides insight in the potential of various constructs - i.e., subjective balance confidence, objective clinical balance and gait capacity tests, and several promising biomechanical measures of gait stability - to discriminate between fallers and non-fallers among people with HSP. As a first step, we compared outcomes between people with HSP and healthy age-matched controls. We found that subjective balance confidence (ABC-6), objective clinical balance and gait capacity (Mini-BEST and 10mWT), and multiple biomechanical measures (spatiotemporal variability of step length and step time, FPD, and LDEs of the trunk) were significantly poorer in people with HSP compared to healthy controls. Subsequently, we compared the outcomes between fallers and non-fallers in HSP. Subjective balance confidence (ABC-6) showed excellent discriminative ability and objective clinical balance capacity (Mini-BEST) showed acceptable discriminative ability, whereas none of the biomechanical measures of gait stability were able to differentiate between fallers and non-fallers in HSP.

It is not surprising that people with HSP showed decreased balance confidence (ABC-6), balance capacity (Mini-BEST), and gait capacity (10mWT) compared to healthy controls, as these findings are in line with the literature.^{2, 3, 31-33} The observed greater variability of spatiotemporal gait parameters in people with HSP compared to age-matched controls is also in line with the literature.³⁴ Although no studies have assessed FPD or LDEs in people with HSP, previous studies did report a higher FPD in people with incomplete spinal cord injury²³, and higher LDEs in a mixed neurological cohort³⁵ compared to healthy controls. In contrast, a previous study found reduced medio-lateral MoS at midstance in HSP³⁶, whereas we did not find such differences between both groups. These contrasting results might be due to differences in disease severity of the included participants, but unfortunately this assumption cannot be verified as no measure of disease severity was reported in the study by van Vugt et al.³⁶

It may be argued that differences in biomechanical measures between HSP and controls emerged as a result of differences in gait speed. Indeed, comfortable gait speed was significantly lower in people with HSP, and earlier studies have demonstrated that gait speed affects gait stability.^{28, 29, 37, 38} To make a speed-controlled comparison between HSP and controls, we asked both groups to walk at a similar, fixed gait speed. For these conditions, we still found that people with HSP walked with greater variability of step length and step time. Furthermore, we found greater variability of the mediolateral MoS, and a larger LDE of the trunk in vertical direction) in HSP compared to controls. These findings indicate that the

observed differences in stability measures at comfortable gait speed cannot merely be explained by speed differences, but (at least partly) reflect true differences in gait stability.

Interestingly, our data show that balance confidence (as measured with the ABC-6), had the best potential to discriminate between fallers and non-fallers with HSP. Previous studies also reported that ABC or ABC-6 is able to differentiate fallers from non-fallers in people with multiple sclerosis (AUC: 0.92)⁵, Parkinson's disease (AUC: 0.73)³⁹, stroke (AUC: 0.78)⁴⁰, and dystonia (AUC: 0.72)⁴¹. Our data additionally show that balance capacity as assessed with the Mini-BEST may be a good objective clinical test for fall risk assessment in people with HSP. Its ability to discriminate fallers from non-fallers has previously been reported in people with Parkinson's disease (AUC: 0.75-0.86)^{6, 42, 43}, myotonic dystrophy (AUC: 0.83)⁴⁴, and in the elderly (AUC: 0.72-0.80).^{45, 46} In contrast to the discriminatory ability of the ABC-6 and the Mini-BEST, we did not find similar evidence for any of the gait capacity or biomechanical measures. This is in contrast to recent studies that reported increased LDEs when comparing fallers and non-fallers in the elderly^{47, 48} and in people with multiple sclerosis.^{10, 11} The question remains why the biomechanical measures were unable to discriminate between fallers and non-fallers in HSP. In order not to fall, people have to be able to recover from both small perturbations that occur during every step (e.g. resulting from heel strike), and larger perturbations (e.g. when tripping over an obstacle).⁸ In the current study, the biomechanical measures were derived from unperturbed treadmill walking. Therefore, the biomechanical measures primarily reflect the ability to recover from small perturbations.⁸ In contrast, the Mini-BEST includes tasks that impose greater challenges to both proactive and reactive balance control. These perturbations are more representative of those encountered in daily life, and as such, more representative of those resulting in falls. This difference may partly explain the higher discriminatory ability of the Mini-BEST compared to the treadmill-based biomechanical measures of gait stability in this study. Therefore, future studies could explore whether biomechanical measures have the ability to capture individual deficits contributing to falls when derived from daily life walking.

Apart from the biomechanical considerations above, our study has some methodological limitations. Participants with HSP logged their falls using a fall diary prior to the assessment.¹⁶ As a result, fallers answered the questions of the ABC-6 after they had experienced a fall, which may have affected their confidence. Future research could evaluate the predictive validity of ABC-6 for fall risk assessment in people who have not yet experienced a fall. Furthermore, previous studies have shown that a fall in the preceding year is a strong predictor for future falls.^{49, 50} Unfortunately, we were unable to collect fall data of the year preceding our assessment, as this timespan partly coincided with the fifteen-week fall diary. Moreover, we were unable to maintain a fall diary following the assessment in

order to examine predictive efficacy of the assessed measures. We did not ask about perceived risk of falling to assess whether fallers were conscious of their own susceptibility of falling. Lastly, we did not include a validation cohort to confirm our findings.

Our results show that the ABC-6 and Mini-BEST are useful clinical measures to identify potential fallers among people with HSP. Our findings also provide insight in the potential usefulness of the applied outcome measures for trials investigating the effectiveness of fall-prevention interventions. As a next step, future studies could evaluate the potential of biomechanical measures in a free-living environment that encompasses the challenging circumstances during which falling usually occurs. Recently, it has been reported that stride characteristics in people with HSP can effectively be evaluated by using wearable inertial gait sensors in a controlled clinical environment and that the so-obtained data are associated with disease severity and progression.³⁴ Yet, it remains to be investigated whether real-life gait assessment using inertial gait sensors is able to improve fall risk assessment and select targeted interventions.

Supplementary materials

Supplementary Table 1: Differences between participants with HSP and healthy controls regarding clinical and biomechanical measures at fixed treadmill velocity.

	HSP (n=24)	HC (n=15)	P-value
Clinical Assessment			
Activities-specific Balance Confidence scale			
– six-item	59 ± 23	92 ± 8	< 0.001
Mini-BEST	20.0 ± 3.5	27.0 ± 1.0	< 0.001
Ten-meter walk test – comfortable (ms ⁻¹)	1.3 ± 0.2	1.6 ± 0.2	< 0.001
Ten-meter walk test – fast (ms ⁻¹)	1.8 ± 0.3	2.4 ± 0.2	< 0.001
Biomechanical assessment			
Step width (mm)	127 ± 36	119 ± 30	0.481
Coefficient of variation			
• Step length (%)	7.6 ± 2.5	5.2 ± 1.1	< 0.001
• Step time (%)	6.1 ± 2.4	4.3 ± 1.2	0.003
• Step width (%)	24.4 ± 10	17.0 ± 7.3	0.016
Mediolateral Margin of Stability (MoS) (mm)	39.8 ± 13	35.6 ± 7.8	0.262
Variability of MoS (mm)	11.4 ± 7	6.7 ± 2.3	0.001
Mediolateral Foot Placement Deviation (cm)	1.0 ± 0.2	0.9 ± 0.2	0.172
Local Divergence Exponents			
• Trunk - mediolateral	2.0 ± 0.2	1.8 ± 0.3	0.013
• Trunk - anteroposterior	1.8 ± 0.2	1.8 ± 0.3	0.786
• Trunk - vertical	1.5 ± 0.2	1.2 ± 0.2	0.003
• Pelvis - mediolateral	1.4 ± 0.2	1.5 ± 0.2	0.138
• Pelvis - anteroposterior	1.6 ± 0.2	1.7 ± 0.3	0.128
• Pelvis - vertical	1.4 ± 0.2	1.2 ± 0.2	0.018

Values displayed are means ± standard deviation. Abbreviations: Mini-BEST: Mini Balance Evaluation Systems Test. Mini-BEST ranges between 0-28 points; Activities-specific Balance Confidence scale – six-item ranges between 0-100 points.

Reference list

1. Shribman, S., et al., Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*, 2019. 18(12): p. 1136-1146.
2. van Lith, B.J.H., et al., Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*, 2020. 15(1): p. 64.
3. Nonnekes, J., et al., Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia. *J Rehabil Med*, 2017. 49(5): p. 369-377.
4. Winsor, S.J., et al., Measures of balance and falls risk prediction in people with Parkinson's disease: a systematic review of psychometric properties. *Clin Rehabil*, 2019. 33(12): p. 1949-1962.
5. Tajali, S., et al., Predicting falls among patients with multiple sclerosis: Comparison of patient-reported outcomes and performance-based measures of lower extremity functions. *Mult Scler Relat Disord*, 2017. 17: p. 69-74.
6. Mak, M.K. and M.M. Auyeung, The mini-BESTest can predict parkinsonian recurrent fallers: a 6-month prospective study. *J Rehabil Med*, 2013. 45(6): p. 565-71.
7. Chee, J.N., et al., Influence of Multiple Sclerosis on Spatiotemporal Gait Parameters: A Systematic Review and Meta-Regression. *Arch Phys Med Rehabil*, 2021. 102(9): p. 1801-1815.
8. Bruijn, S.M., et al., Assessing the stability of human locomotion: a review of current measures. *J R Soc Interface*, 2013. 10(83): p. 20120999.
9. Peebles, A.T., et al., Dynamic margin of stability during gait is altered in persons with multiple sclerosis. *J Biomech*, 2016. 49(16): p. 3949-3955.
10. Tajali, S., et al., Impaired local dynamic stability during treadmill walking predicts future falls in patients with multiple sclerosis: A prospective cohort study. *Clin Biomech (Bristol, Avon)*, 2019. 67: p. 197-201.
11. Peebles, A.T., et al., Dynamic balance in persons with multiple sclerosis who have a falls history is altered compared to non-fallers and to healthy controls. *J Biomech*, 2017. 63: p. 158-163.
12. Chini, G., et al., Local Stability of the Trunk in Patients with Degenerative Cerebellar Ataxia During Walking. *Cerebellum*, 2017. 16(1): p. 26-33.
13. Schniepp, R., et al., Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. *J Neurol*, 2014. 261(1): p. 213-23.
14. Ma, L., et al., Gait variability is sensitive to detect Parkinson's disease patients at high fall risk. *Int J Neurosci*, 2022. 132(9): p. 888-893.
15. van de Venis, L., et al., Gait-Adaptability Training in People With Hereditary Spastic Paraplegia: A Randomized Clinical Trial. *Neurorehabil Neural Repair*, 2023. 37(1): p. 27-36.
16. van de Venis, L., et al., Improving gait adaptability in patients with hereditary spastic paraplegia (Move-HSP): study protocol for a randomized controlled trial. *Trials*, 2021. 22(1): p. 32.
17. Buchner, D.M., et al., Development of the common data base for the FICSIT trials. *J Am Geriatr Soc*, 1993. 41(3): p. 297-308.

18. Peretz, C., et al., Assessing fear of falling: Can a short version of the Activities-specific Balance Confidence scale be useful? *Mov Disord*, 2006. 21(12): p. 2101-5.
19. Franchignoni, F., et al., Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med*, 2010. 42(4): p. 323-31.
20. Graham, J.E., et al., Assessing walking speed in clinical research: a systematic review. *J Eval Clin Pract*, 2008. 14(4): p. 552-62.
21. Schüle, R., et al., The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. *Neurology*, 2006. 67(3): p. 430-4.
22. Watson, F., et al., Use of the margin of stability to quantify stability in pathologic gait - a qualitative systematic review. *BMC Musculoskelet Disord*, 2021. 22(1): p. 597.
23. Zwiijgers, E., et al., Impaired foot placement strategy during walking in people with incomplete spinal cord injury. *J Neuroeng Rehabil*, 2022. 19(1): p. 134.
24. Mehdizadeh, S., A robust method to estimate the largest Lyapunov exponent of noisy signals: A revision to the Rosenstein's algorithm. *J Biomech*, 2019. 85: p. 84-91.
25. Mofateh, R., et al., Effects of cognitive versus motor dual-task on spatiotemporal gait parameters in healthy controls and multiple sclerosis patients with and without fall history. *Mult Scler Relat Disord*, 2017. 18: p. 8-14.
26. Hof, A.L., M.G. Gazendam, and W.E. Sinke, The condition for dynamic stability. *J Biomech*, 2005. 38(1): p. 1-8.
27. Wang, Y. and M. Srinivasan, Stepping in the direction of the fall: the next foot placement can be predicted from current upper body state in steady-state walking. *Biol Lett*, 2014. 10(9).
28. England, S.A. and K.P. Granata, The influence of gait speed on local dynamic stability of walking. *Gait Posture*, 2007. 25(2): p. 172-8.
29. Dingwell, J.B. and L.C. Marin, Kinematic variability and local dynamic stability of upper body motions when walking at different speeds. *J Biomech*, 2006. 39(3): p. 444-52.
30. Hosmer, D.W.L., S.; Sturdivant, R.X., *Applied Logistic Regression*. Third edition ed. Wiley Series in Probability and Statistics. 2013, Hoboken, NJ: Wiley.
31. van de Venis, L., et al., Increased trunk movements in people with hereditary spastic paraplegia: do these involve balance correcting strategies? *J Neurol*, 2022. 269(8): p. 4264-4269.
32. Nonnekes, J., et al., Neurological disorders of gait, balance and posture: a sign-based approach. *Nat Rev Neurol*, 2018. 14(3): p. 183-189.
33. Serrao, M., et al., Gait Patterns in Patients with Hereditary Spastic Paraparesis. *PLoS One*, 2016. 11(10): p. e0164623.
34. Regensburger, M., et al., Inertial Gait Sensors to Measure Mobility and Functioning in Hereditary Spastic Paraplegia: A Cross-Sectional Multicenter Clinical Study. *Neurology*, 2022. 99(10): 1079-89.
35. Reynard, F., et al., Could local dynamic stability serve as an early predictor of falls in patients with moderate neurological gait disorders? A reliability and comparison study in healthy individuals and in patients with paresis of the lower extremities. *PLoS One*, 2014. 9(6): p. e100550.
36. van Vugt, Y., et al., Postural stability during gait for adults with hereditary spastic paraparesis. *J Biomech*, 2019. 88: p. 12-17.

37. Raffalt, P.C., et al., Economy, Movement Dynamics, and Muscle Activity of Human Walking at Different Speeds. *Sci Rep*, 2017. 7: p. 43986.
38. Bruijn, S.M., et al., Is slow walking more stable? *J Biomech*, 2009. 42(10): p. 1506-1512.
39. Almeida, L.R., et al., Comparison of Self-report and Performance-Based Balance Measures for Predicting Recurrent Falls in People With Parkinson Disease: Cohort Study. *Phys Ther*, 2016. 96(7): p. 1074-84.
40. An, S., et al., Discriminative and predictive validity of the short-form activities-specific balance confidence scale for predicting fall of stroke survivors. *J Phys Ther Sci*, 2017. 29(4): p. 716-721.
41. Boyce, M.J., et al., Validation of Fear of Falling and Balance Confidence Assessment Scales in Persons With Dystonia. *J Neurol Phys Ther*, 2017. 41(4): p. 239-244.
42. Duncan, R.P., et al., Accuracy of fall prediction in Parkinson disease: six-month and 12-month prospective analyses. *Parkinsons Dis*, 2012. 2012: p. 237673.
43. Leddy, A.L., B.E. Crouner, and G.M. Earhart, Utility of the Mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J Neurol Phys Ther*, 2011. 35(2): p. 90-7.
44. Duchesne, E., et al., Validity of the Mini-BESTest in adults with myotonic dystrophy type 1. *Muscle Nerve*, 2020. 62(1): p. 95-102.
45. Viveiro, L.A.P., et al., Reliability, Validity, and Ability to Identify Fall Status of the Berg Balance Scale, Balance Evaluation Systems Test (BESTest), Mini-BESTest, and Brief-BESTest in Older Adults Who Live in Nursing Homes. *J Geriatr Phys Ther*, 2019. 42(4): p. E45-e54.
46. Magnani, P.E., et al., What is the best clinical assessment tool for identification of adults aged ≥ 80 years at high risk of falls? *Physiotherapy*, 2021. 110: p. 63-69.
47. Toebes, M.J., et al., Local dynamic stability and variability of gait are associated with fall history in elderly subjects. *Gait Posture*, 2012. 36(3): p. 527-31.
48. Bizovska, L., et al., Local dynamic stability during gait for predicting falls in elderly people: A one-year prospective study. *PLoS One*, 2018. 13(5): p. e0197091.
49. Pickering, R.M., et al., A meta-analysis of six prospective studies of falling in Parkinson's disease. *Mov Disord*, 2007. 22(13): p. 1892-900.
50. Jørgensen, V., et al., Falls and fear of falling predict future falls and related injuries in ambulatory individuals with spinal cord injury: a longitudinal observational study. *J Physiother*, 2017. 63(2): p. 108-113.



Chapter 7

Summary and general discussion

Summary

The aim of this thesis was to gain more insight into gait impairments in people with hereditary spastic paraplegia (HSP). More specifically, our aim was to explore factors that impact on the severity of gait impairments and other spasticity-related symptoms, either negatively or positively, and how to evaluate gait impairments and fall risk in clinical practice. Furthermore, we investigated whether context-specific training can improve gait adaptability in people with pure forms of HSP.

Chapter 1 provides the necessary background by introducing the main clinical characteristics of hereditary spastic paraplegia (HSP). This chapter also elaborates on how HSP-related signs and symptoms result in balance and gait impairments, and it provides insight in current clinical management.

Insight in factors that contribute to the level of symptom severity, either negatively or positively, are of great importance for clinical practice. Clinical experience shows that a sufficient level of daily physical activity has a positive impact on the severity of spasticity-related symptoms, whereas psychological stress may impact negatively.

Chapter 2 explores this assumption by assessing the impact of the COVID-19-related ‘lockdown’ in the Netherlands through a web-based survey in 58 people with HSP. In total, 74% of the respondents reported reduced levels of physical activity during the lockdown, which was associated with increased levels of muscle stiffness, pain, physical fatigue, and balance and gait impairments. Moreover, 43% of the respondents experienced increased psychological stress, which was associated with increased levels of muscle stiffness, pain and mental fatigue.

People with HSP often indicate that balance and gait impairments are among their most disabling symptoms. Insight in interventions to ameliorate balance and gait impairments is, therefore, critical to improve their perspective. Previous studies reported beneficial effects of task-specific gait training interventions in people with HSP, but it remained unclear whether context-specific gait adaptability training may improve gait adaptability in people with HSP. **Chapter 3** describes the research protocol of a randomized clinical trial that was conducted to evaluate the efficacy of a five-week gait adaptability training added to usual care, compared to usual care alone, in people with pure HSP. We hypothesized that, compared to usual care alone, five weeks of gait adaptability training would lead to greater improvements in gait adaptability, clinical balance and gait capacity, balance confidence, spatiotemporal gait parameters, and level of daily physical activities. To test this hypothesis, a single-center, two-armed, open-label, randomized controlled trial, with a cross-over design for the waiting-list control group, and a fifteen-week follow-up period was conducted. Gait adaptability training was provided on the C-Mill, a treadmill equipped with augmented reality through projections of visual targets onto the

treadmill belt. Participants trained for five weeks, twice per week, while each session lasted 60 minutes, adding up to a total of ten hours of gait adaptability training. All training sessions were personalized and took place under supervision of a trained physical therapist. The primary outcome was gait adaptability as measured with the obstacle subtask of the Emory Functional Ambulation Profile (E-FAP). Furthermore, the assessment included a complementary set of secondary outcome parameters: gait speed (10-Meter Walk Test), balance capacity (mini-BESTest), balance confidence (ABC-scale), physical activity for 24 hours (Activ8 monitors), fall rates, walking adaptability (Walking Adaptability Ladder Test / WALT), and spatiotemporal gait parameters obtained through 3-D motion analysis (gait speed, step length, step time and step width).

Chapter 4 presents the results of the randomized clinical trial, in which 36 people with pure HSP participated. Despite delays due to Covid-19-related lockdown measures, we were able to conduct the protocol as described in chapter 3. At baseline, both groups did not differ in demographic or clinical characteristics such as age, disease duration or disease severity. All participants adhered to their allocated group and there was no participant drop-out during the study period. Furthermore, adherence to the intervention was high, since 99.7% of the planned training sessions were completed. After adjusting for baseline differences, we found that the gait adaptability training group did not improve more on the obstacle subtask of the E-FAP compared to the waiting-list control group. Similar results were found for most of the secondary outcome parameters. After merging the pre-training, post-training, and follow-up assessments for both groups, we found that participants had improved on the obstacle subtask of the E-FAP directly post-training, which effect was retained at the fifteen-week follow-up. Similar results were found for the 10-meter walk test, the mini-BESTest, the ABC-scale, the WALT, and the spatiotemporal gait parameters: walking velocity and average stride length. We concluded that there was insufficient evidence for adding five weeks of context-specific gait adaptability training to usual care to improve gait adaptability in people with HSP.

When evaluating gait impairments in people with HSP, previous studies have reported increased trunk movements during gait, which was evident even in the early stages of the disease. Yet, it remains ambiguous how these exaggerated trunk movements should be interpreted. It is often assumed that people with HSP generate increased trunk movements as a compensatory mechanism to improve their foot clearance and step length. **Chapter 5** reports that increased trunk movement may (additionally) reflect balance correcting strategies. After reviewing gait analysis videos of 86 people with HSP and classifying their observed trunk movements into three categories ('normal', 'moderately increased', 'markedly increased'), a significant association was found between increased trunk movements and reduced balance capacity as assessed with the Berg Balance Scale or the Mini-BESTest. Generally, in

order to maintain balance during gait, people prefer foot placement strategies and ankle strategies, but people with HSP become limited in recruiting these strategies when disease severity progresses. Hip strategies that require trunk movements may then be recruited to better maintain balance during gait, which is one of several – but not mutually exclusive – explanations for increased trunk movements during gait in people with HSP.

Fear-of-falling, falls and fall-related injuries are often the result of the previously mentioned balance and gait impairments in people with HSP. In order to optimally tailor personalized fall prevention intervention, the clinical field needs measures that can distinguish between people who are at risk of falling, and those who are not. **Chapter 6** evaluates the potential of different constructs to identify differences between healthy controls and people with HSP. We found that subjective balance confidence, objective balance and gait capacity, and multiple biomechanical measures of gait stability were significantly worse in people with HSP compared to healthy controls. Within the HSP cohort, 14 out of the 32 people were identified as fallers (≥ 1 fall during a fifteen-week period). We found that subjective balance confidence (ABC-Scale) and clinical balance capacity (Mini-BESTest) are promising parameters in clinical practice to identify fallers in HSP, and outperform biomechanical gait stability measures derived from unperturbed treadmill walking. For future studies, it may be of interest to evaluate these gait stability measures in a free-living environment, as this includes the more challenging circumstances during which falling usually occurs in daily life.

General discussion

Here, I will discuss the main insights obtained from the work presented in this thesis on gait problems in people with hereditary spastic paraplegia (HSP). I will elaborate on two gait-related themes: assessment and intervention. In addition, I will reflect on methodological considerations and future perspectives for clinical practice and research.

Assessment

A valid and diligent assessment of gait is required to establish a tailored clinical management plan for the individual with HSP. This is a complex process as, for example, evaluating kinematics obtained from a 3D gait analysis on a level floor will not detect that anxiety while walking outdoors is causing the experienced gait problems. Also, the translational value of clinical research is influenced by proper outcome assessment. Therefore, clinical practice and research require valid, reliable, and responsive measures that can objectify the impact of gait problems in daily life.

To understand the consequences of a health condition on a person's daily life, the International Classification of Functioning, disability, and health (ICF) is a helpful tool.¹ It classifies the functional consequences of a health condition into three domains: bodily functions and structures, activities, and participation. In addition, the framework illustrates the interactions of the health condition and its functional consequences with environmental and personal factors. Within the ICF, functional gait is reflected in the domains activities (i.e., the range of individual tasks performed) and participation (i.e., the variety of societal roles one is engaged in).¹ The ICF aids in the selection of adequate outcome measures and interventions that align with the needs and wishes of patients.

Inspired by the ICF, functional gait comprises three qualifiers: gait capacity, gait performance, and gait perception.² *Gait capacity* refers to what people are able to do in a standardized environment, for example, during a lab-based gait assessment. *Gait performance* refers to what people habitually do in their own environment (i.e., daily functioning outside formal settings). Both gait capacity and gait performance are recognized qualifiers of functional gait within the ICF. In line with the previous work of Maetzler and colleagues, we here add the qualifier *gait perception*, which refers to the subjective evaluation of gait by the individual (e.g., gait satisfaction).² For these gait qualifiers, three requirements for purposeful walking have been identified by Balasubramanian and colleagues: the coordination of leg and trunk movements for propulsion (stepping), maintaining balance (dynamic balance), and adapting gait to meet environmental demands (adaptability)³ - see figure 1.

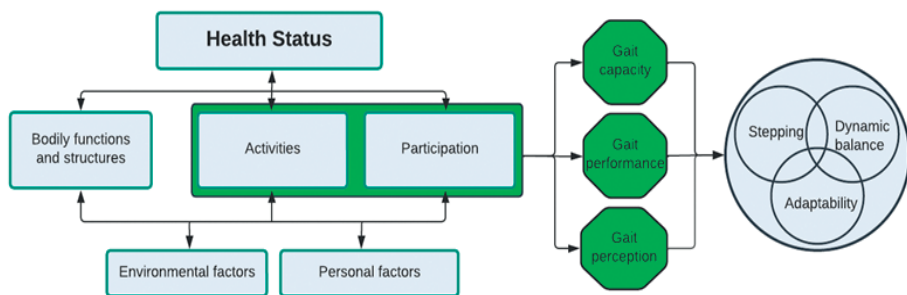


Figure 1. Functional gait is reflected by the domains 'activities' and 'participation' in the International Classification of Functioning, disability, and health (ICF). It comprises three qualifiers: gait capacity, gait performance, and gait perception. For these qualifiers, three requirements have been identified. Inspired by Maetzler et. al.² and Balasubramanian et. al.³

Gait capacity

Comfortable gait speed, six-minute walk test, maximum knee flexion during the swing phase, stride length, functional ambulation categories, plantar foot pressure; these are just a small selection of the more than 70 outcome measures used in

the seven publications on (non-)pharmacological interventions to ameliorate gait problems in people with HSP.⁴⁻¹⁰ This demonstrates the need for consensus on how to assess gait capacity in HSP, a need that has previously been recognized and extends beyond people with HSP.¹¹ However, reaching such a consensus is difficult, specifically for people with HSP, as no outcome measures have yet been validated. In this thesis, we have provided novel insights into outcome measures useful for assessing gait capacity in this population.

As in most other studies, we assessed gait capacity using overground lab-based assessments and clinical testing. We demonstrated that people with HSP scored poorer on the requirement *stepping* than healthy controls, which was in line with the literature.^{12,13} To this end, we recorded spatiotemporal gait parameters. Such spatiotemporal parameters can easily and quickly be obtained with the GAITRite® system (GAITRite Gold, CIR Systems, PA, USA). This pressure-sensitive, 3-meter walkway automatically calculates the spatiotemporal parameters after a person has walked across the mat. A more elaborate analysis is required to assess to which extent impairments in bodily functions impact stepping in HSP. Such an analysis often consists of a marker-based, 3D gait analysis and surface electromyography. Although this assessment is more time-consuming and costly, it provides an empirical basis for the underlying mechanisms causing stepping problems. For example, spasticity of the hamstring muscles may interfere with full knee extension at the end of the swing phase, hampering optimal step length.

We also demonstrated that people with HSP scored poorer on *dynamic balance* than healthy controls. We used the clinical Mini-BESTest and novel biomechanical measures of gait stability, such as Foot Placement Deviation (FPD) and Local Dynamic Exponents (LDEs). These biomechanical measures provide detailed information about dynamic balance control and potentially overcome some of the methodological limitations of clinical testing (e.g., the subjective interpretation by clinicians, floor and ceiling effects, or large minimal clinically detectable differences). However, from a practical viewpoint, assessing biomechanical gait stability measures requires sophisticated methods and expensive equipment. Biomechanical measures are still challenging to obtain and interpret and, thus, unfeasible for clinical practice. Furthermore, they do not seem to differentiate between fallers and non-fallers in people with HSP (chapter 6). To fully capture balance from a clinical and theoretical perspective, testing should incorporate items that assess: 1) steady-state balance (i.e., during unperturbed standing), 2) proactive balance (i.e., when anticipating a predictable perturbation), and 3) reactive balance (i.e., when responding to an unpredictable perturbation). To this end, the Mini-BESTest is a valuable tool for assessing balance in clinical practice and research: it incorporates steady-state, proactive, and reactive balance items, is quick to perform, requires few attributes, and has little ceiling effect. Unlike the biomechanical measures, the Mini-BESTest seems

to differentiate between fallers and non-fallers with HSP (chapter 6). Against this background, the added value of the proposed biomechanical measures to assess dynamic balance for clinical or research purposes in people with HSP has yet to be determined.

The assessment of *gait adaptability* requires context-specific tasks that reflect the expected and unexpected demands of everyday walking in the community. These tasks include crossing over unexpected physical objects, performing motor and cognitive dual tasks, participating in traffic, changing gait speed, et cetera. Including all these tasks in one clinical test is unfeasible, but some tests that assess at least various aspects of gait adaptability are available. The obstacle subtask of the Emory Functional Ambulation Profile has previously been used^{14,15} and includes the components of obstacle avoidance and temporal demands. We additionally used the newly developed ‘walking adaptability ladder test’ (WALT), which includes precision stepping and temporal demands. Furthermore, the subtest ‘dynamic gait’ of the Mini-BESTest incorporates cognitive dual-tasking, motor dual-tasking, obstacle avoidance, and temporal demands. All these clinical tests are standardized, quick, and require few or no attributes at all, which makes them feasible for clinical practice. Yet, a common limitation of these tests is that the testing environment is known to the participant, i.e., the tests do not include unpredictable perturbations. Such unpredictable perturbations, however, are common when walking in daily life, such as tripping over obstacles, slipping on a wet surface, or being bumped by someone in a crowd. Some tests have addressed these limitations and assessed ‘online’ gait adaptability requiring adaptation of ongoing pre-planned movements. Examples are the Interactive WalkWay (a walkway that uses augmented reality to project unexpected obstacles onto the floor^{16,17}) and instrumented obstacle avoidance (a task in which a physical obstacle is released from an electromagnet onto a treadmill at various moments of the gait cycle^{18,19}).

Including unexpected perturbations in clinical testing is valuable but challenging, as these tests require sophisticated equipment. ‘Online’ gait-adaptability testing in people with HSP is currently relatively unexplored.

Gait performance

To assess whether people actually do what they are able to do, it is important to evaluate daily life gait performance. Compared to the ‘snapshot’ evaluation of gait capacity, gait performance provides a more ecologically valid assessment associated with real life.^{2,20} Within this thesis, we included Activ8 monitors to provide insight into how much time participants were physically active during 24 hours.²¹ However, activity monitoring is still poorly validated in people with HSP. Furthermore, the Activ8 monitors are limited to identifying specific postures (standing, sitting, lying) and (the intensity of) specific activities (walking, running, cycling). This results in two

important limitations. Firstly, the Activ8 monitors are unable to provide information on the three gait requirements: stepping, dynamic balance, and gait adaptability. Secondly, some people with HSP perform regular physical activities but in an adapted form (e.g. lying when cycling on a recumbent bike or sitting when playing wheelchair basketball), which activities cannot be adequately measured with Activ8 monitors. Therefore, for future studies in HSP, it would be recommendable to use activity trackers that are validated for tracking physical activity in adapted sports. Furthermore, it would be recommendable to use wearables that can measure not only bouts (i.e., quantity) of walking, but also provide insight in how people walk (i.e., quality), with respect to all three requirements.

Lately, considerable progress has been made in the assessment of gait in people with HSP using digital technologies, which can be implemented in the future to assess gait performance^{12,22}. With one wearable sensor per foot, a validated method was developed to assess stride characteristics and changes in gait variability in a free-living environment. Remarkably, these measures correlated with fear of falling, quality of life, and progression of disease severity.¹² Similar results were found in detecting step characteristics with a single sensor on the lower back.²² Furthermore, the latter method demonstrated sufficient accuracy of step characteristics detection when walking both with and without various types of walking aid. This insight is essential to compare longitudinal data when an individual with HSP uses a walking aid due to disease progression.²² These studies provide novel opportunities to measure someone's gait in the home environment and, just as importantly, during community ambulation (e.g., in public areas, such as a park or a theatre, and in private locations, such as a family member's home). Of note, the outcome measures in both studies mainly reflect the gait requirement stepping. Therefore, the potential of wearables to assess dynamic balance and gait adaptability in people with HSP is still unknown and remains a future challenge. Future developments should provide insight into (possible discrepancies between) individual gait capacity vs. gait performance in people with HSP that could inform and potentially strengthen clinical practice and research. It should be possible to monitor which gait problems arise at home or in the community, when they occur, and whether they can be ameliorated through innovative interventions.

Gait perception

High-quality care requires that patients disclose the perceived effectiveness of a treatment, for example, by expressing their (dis-)satisfaction and providing feedback on the impact of the provided care. Recently, this viewpoint has been increasingly recognized in healthcare, which has led to the introduction of patient-reported outcomes (PROs).²³ PROs are also important for research, as the patient's viewpoint can help evaluate the efficacy and feasibility of interventions and provide information about the meaningfulness of outcome measures.

A PRO is “any report of the status of a patient’s health condition that comes directly from the patient without interpretation of the patient’s response by a clinician or anyone else”²⁴. Within this thesis, we have used the ABC-scale to reflect subjective balance confidence, a highly relevant assessment, as 73% of people with HSP experience fear of falling.²⁵ The ABC-scale demonstrated that also our participants with HSP experienced greater fear of falling than healthy controls. More importantly, it showed the potential to discriminate between fallers from non-fallers among our participants with HSP, highlighting the possible strength of a PRO. Possibly, a patient’s reflection on his/her balance problems may be a better indicator of fall risk than clinician-based or so-called ‘objective’ assessments. The assessment of gait perception may, however, be improved by adding how a person experiences his/her walking other than self-confidence, for instance, psychological satisfaction with gait, gait-related pain or fatigue, and emotional and social aspects related to gait. Several generic questionnaires assess emotional health, social participation, and quality of life (e.g., the 36-item Short Form Healthy Survey or the EuroQol 5D,²⁶ but it is probably more valid and sensitive to use goal-oriented assessments tailored to gait-related performance and social participation. For example, we could collect qualitative feedback from participants²⁷; use the Canadian Occupational Performance Measure (COPM), a self-assessment of performance and satisfaction with self-identified activities²⁸; or use a special scale to map the perceived impact of a specific problem, such as the impact of fatigue through the Fatigue Severity Scale.²⁹

Fall risk

Over 50% of people with HSP experience falls that lead to injuries, a problem that has been well-documented.²⁵ This thesis provides novel insight into the assessment of fall risk. We found that the ABC-scale, followed by the Mini-BESTest, has the potential to discriminate between fallers and non-fallers better than biomechanical measures of gait stability.

As a next step, we need to gain insight into measures that predict the ‘tipping point’ of increased fall risk in people with HSP. In other words, we should be able to individually predict when falls will likely occur more frequently than before, and when they will likely lead to injuries. Better insight into (the causes of) individually increased fall risk will allow for timely and targeted interventions, such as the prescription of ankle-foot orthoses, walking aids, or behavioral adjustments.

Identifying the individual tipping point can only be investigated in a large-scale, longitudinal cohort study including people with HSP that have fallen and those who have not yet fallen. In such a study, a fall should be defined as an unexpected event in which the participant comes to rest on a lower level. For an overall analysis, it would be good to include all falls, including those due to excessive force (e.g., while playing sports). This latter type of fall may provide insight into the level of

risk-taking by subgroups of people with HSP. The assessments should include measures of gait capacity, gait performance, and gait perception, next to the regular clinical examination of muscle tone, muscle strength, joint range of motion, and proprioception of the lower extremities. Following the baseline assessment, falls should be prospectively recorded at fixed time intervals across at least one year. A fall diary should include questions about the situation (activities) and environmental factors (indoor vs. outdoor, ambiance, footwear) surrounding the fall. This will provide insight into how and why falls occur; for instance, does a fall occur due to poor obstacle negotiation in the case of impaired proprioception or due to a sudden, spontaneous change in behavior in the case of urinary urgency. Preferably, such a study would be multicentered to enroll a sufficient number of participants and be able to obtain representative results.

Intervention

Multiple (combined) interventions can be administered to improve functional gait and mobility in people with HSP. As mentioned in the introduction, well-known interventions are pharmacological treatment (e.g., intramuscular botulinum toxin injections), orthotics, ankle-foot surgery (e.g., Achilles tendon lengthening), and training interventions. Within the context of this thesis, I will elaborate specifically on training interventions to improve gait adaptability and I will provide some considerations on the potential of (additional) lifestyle interventions.

Gait adaptability interventions

Chapter 4 reported that C-Mill training improved gait adaptability in people with HSP, but the observed improvements were similar to those found in a control group that received usual care. Several factors can be considered to advance future gait adaptability training in people with HSP. As a basis, our study showed that a treadmill-based intervention on the C-Mill (or likely similar devices such as the Gait Real-time Analysis Interactive Lab (GRAIL), Motek Medical BV, The Netherlands, or Computer Assisted Rehabilitation Environment (CAREN), Motek Medical BV, The Netherlands) could be a viable option to train gait adaptability in people with HSP. From a clinical perspective, however, our study did not show added value of the C-Mill over usual care in the entire group of participants with HSP. Given this unexpected neutral finding, the first factor to consider is a more targeted patient cohort. One example is gait adaptability training for people who experience debilitating fear of falling. To this end, specifically people with HSP in whom fear of falling is the main reason to avoid walking activities, despite their being physically capable of conducting such activities, should be targeted. This condition can be referred to as maladaptive fear of falling.³⁰

This maladaptive fear of falling hinders the efficacy of conventional gait training, but with e.g., C-Mill training people can practice their gait while a safe training

environment is ensured by a safety harness that prevents them from falling. To test the assumption that people with HSP and maladaptive fear of falling benefit more from C-Mill training than from conventional gait training, fear of falling could be used as a critical inclusion criterion. This can be done by using the newly developed Updated Perceived Control over Falling Scale, where a predetermined cut-off value of 13 points or lower is assumed to identify elderly persons in whom fear of falling can be considered maladaptive. Of note, this scale has not yet been validated for people with HSP.

An important limitation of treadmill-based training is that not all domains of gait adaptability can be included, such as terrain demands (e.g., walking over uneven surfaces), postural transitions (e.g., turning while walking), and interaction with physical obstacles. These limitations could be overcome by overground gait adaptability training. An example of such training is the Nijmegen Falls Prevention Program,³¹ a five-week exercise program that focuses on overground obstacle negotiation, walking exercises, in addition to training fall techniques. This program was proven beneficial compared to usual care in community-dwelling elderly.^{27,31} It is reasonable to assume that, as the basic principles of this training program are sound, people with HSP may also benefit from this type of overground training program. Moreover, overground-based programs are accessible for a broader population, such as people with HSP who have limited access to technically supported gait rehabilitation tools. Indeed, gait training devices are often only available at specialized hospitals or rehabilitation centers. For people with HSP living in rural areas or suffering from enhanced fatigability, the efforts to participate in technically supported gait training may be higher than the expected benefits, which limits adherence and feasibility. These considerations underline the relevance of also evaluating the efficacy, feasibility, and cost-effectiveness of overground gait adaptability training programs for people with HSP that can preferably be administered by community-based physiotherapists.

Recently, there has been an increasing interest in home-based serious gaming, i.e., performing games to promote physical activity and train specific motor skills. Several reviews on the feasibility and efficacy of serious gaming in neurodegenerative conditions have reported promising results.^{32,33} It was found that a home-based intervention using commercially available hardware (e.g., Nintendo Wii Fit Balance Board or Microsoft Kinect) was perceived as joyful, which resulted in a high adherence rate and improved balance capacity, gait capacity, and mobility. The home-based setting was generally reported as safe, but the studies used different approaches to ensure safety, for instance conducting a risk assessment at the participant's home, supervising the first session, or starting with an introduction at a specialized clinic. The recent introduction of balance and gait training through commercially available augmented reality goggles (HoloLens 2 and Magic Leap

2 by STROLL Limited) is of particular interest. Visual projections of objects (i.e., holograms) are projected into the real world such that the perception is comparable to real objects.

Different games have already been created, such as a boxing exercise where people have to walk around and punch holograms (e.g., a microwave, vase, or pillar).^{34,35} Whether such home-based interventions are feasible for people with HSP has yet to be evaluated. Furthermore, the need for supervision, the appropriate dose intensity, and the likelihood of retention of training effects should all be investigated, in addition to the continuous need to ensure safety as the disease progresses.

Any gait adaptability training can be complemented with exercises or other interventions that are aligned with specific gait problems that people with HSP may experience. For example, people with HSP often have a narrow-based gait due to spasticity of the hip adductor muscles. Such hip adductor spasticity may hinder gait adaptability and increase fall risk, as it limits the capacity to make lateral side steps upon expected or unexpected gait perturbations. People may even stumble over their own feet due to hooking of the feet. In these instances, it is important to include exercises that focus on maintaining or increasing the existing step width. For those people with severe hip adductor spasticity, this can be extremely difficult, which can be a reason to combine gait training with intramuscular botulinum toxin injections in the hip adductors. In this way, gait adaptability training is facilitated and the chance that the narrow-based gait becomes habitual is attenuated.

In addition to regular gait, several other tasks are essential for community ambulation. These include turning, initiating gait, or maintaining balance while having to stand still (e.g., waiting for a traffic light to turn green or standing in line at the supermarket). It is known that people with HSP experience great difficulties while standing still. A common method to train static balance control is to progress the execution of balance tasks from a solid surface with eyes opened to standing on a foam surface with eyes closed (i.e., creating situations of limited sensory input). For people with HSP, however, proprioception is often impaired due to degeneration of the dorsal columns, which is not amendable by training with limited sensory information. Hence, it is probably more beneficial to train static balance control with eyes opened while standing on a variety of firm (e.g., inclines) and uneven (e.g., cobblestones or sand) surfaces so that adequate and safe compensation strategies (e.g., taking a step or using the trunk) can be trained.

Irrespective of the training methods, it is important to set realistic goals.³⁶ To this end, it is essential to keep in mind that HSP is a progressive condition. As a result, people with HSP continuously need to adapt to a decline in physical functioning, activities, and participation, while the rate of progression and the endpoint are

unpredictable. Therefore, people with HSP generally focus on *maintaining* their current level of functioning rather than expecting improvements.³⁷ When setting goals for specific training interventions, it is important to define individual goals while taking into account personal factors. These include possible cognitive impairments that may limit realistic disease perception, particularly in people with complex forms of HSP, or false expectations due to mirroring their rate of disease progression to that of others (e.g., family members with HSP).

Lifestyle interventions

In addition to the three requirements for purposeful walking, a sufficient level of physical fitness is required to engage in daily life activities. Remarkably, a recent survey reported that only 25% of people with HSP reach recommended daily physical activity levels.^{38,39} In line with these results, we found that people with HSP were physically active (defined as walking or cycling) for only 9% of the day (24 hours). Furthermore, we showed an association between reduced physical activity levels and the perceived aggravation of several spasticity-related symptoms (Chapter 2). These results are in line with the study by Lallemand-Dudek and co-workers, in which people with HSP perceived a reduction in lower extremity spasticity with regular physical activity and physical therapy.³⁸ Independent of disease severity, most benefits were experienced with physical therapy three times a week.³⁸ Unfortunately, this study did not report on the content of the physical therapy provided. Moreover, it is possible that the supervision of a physical therapist who encouraged people with HSP to be physically active contributed to the perceived benefits.

Apart from physiotherapy-based physical activity and training, a general lifestyle intervention may encourage people with HSP to maintain a proper level of physical activity. There is ample evidence that a passive, sedentary lifestyle aggravates sensorimotor problems in various neurological conditions.⁴⁰⁻⁴⁵ There is also growing evidence for the fact that an active lifestyle and physical training slows down the natural progression in specific neurological diseases, such as Parkinson's disease⁴⁶ and dementia⁴⁷. Likewise, an active lifestyle may ameliorate gait and balance impairments in people with HSP, as well as spasticity-related symptoms such as pain, fatigue, and restless legs (Chapter 2). In practice, it is neither feasible nor desirable to propose that all people with HSP receive physical therapy three times a week. Therefore, evaluating alternatives to encourage people with HSP to stay physically active is key. Above, I already discussed the potential of home-based interventions for people with HSP. In people with Parkinson's disease, a home-based and remotely supervised intervention, consisting of aerobic exercises on a home trainer for 30-45 minutes three times a week, was found to be safe and increase physical activity.⁴⁶ The challenge for future studies in HSP will be to prove feasibility, efficacy and safety in this population as well, but – from a theoretical point of view – few arguments

can be given why results would turn out differently. More importantly, the challenge will be to investigate which (supervised) guidance and intervention protocol will be able to keep people with HSP physically active across their life span and, thus, have actual impact on their disease progression.

Chronic fatigue is often a barrier for many neurological patients to become or stay physically active. This is why a multidisciplinary intervention has been developed at Radboud University Medical Center for people with neurological conditions and chronic fatigue, called “Energetic”. This 16-week multidisciplinary day-care (1-2 times per week) group program comprises individually tailored gradually increasing physical exercises, education about exercise training, adopting energy conservation techniques, and creating real-life changes in (sports) activities to prevent relapse after cessation of the program. Energetic adopts various self-management principles and has proven its effectiveness on societal participation (assessed by individual goal setting with the Canadian Occupational Performance Measure) in people with various neuromuscular disorders. Energetic also proved to be cost-effective compared to usual care.⁴⁸ It is likely that people with HSP who are chronically fatigued respond equally well to a program like Energetic, but the specific frequency and content of this program would need to be adapted. This would be an interesting direction for future research.

Methodological considerations

In this thesis, we evaluated the efficacy of a novel gait adaptability training in people with HSP through an RCT. Some limitations related to the specific intervention and outcome measures have already been mentioned in Chapter 5, including the relatively short training period of five weeks, the absence of booster sessions, a potential ceiling effect on our primary walking adaptability outcome, and the lack of outcome measures that reflect gait performance and gait perception. Here, I consider some limitations from a broader perspective. In line with other studies, we used a five-week intervention period to evaluate the efficacy of a novel type of training. It is, however, questionable whether such a short, predetermined training period can make a difference in patient populations with progressive conditions who slowly build up their gait problems across many years. To be able to make a true impact, group differences in training activity should probably be maintained for many years as well, for instance as short physiotherapy-guided ‘booster sessions’ complemented with self-exercises at home in between. RCTs are generally accepted to generate data to acquire the highest level of scientific evidence for clinical interventions. They are conducted prospectively while their risk of bias is reduced by random group allocation.⁴⁹ On the downside, RCTs are often costly and time-consuming, and they require a sufficiently large sample size in a relatively short period of time to reach the necessary power for statistical analysis.

As a consequence, an RCT may not be the best design to evaluate the effectiveness of novel interventions over a prolonged period during the life span in people with HSP. Moreover, recent qualitative research from our group has shown that the long-term perspective for people with HSP is not so much to expect improvement, but rather to maintain a particular level of functioning as long as possible.³⁷ These considerations impact on the selection of the most appropriate study design, mode of intervention, and type of outcomes.

Single-case designs have recently been given increased attention in patient-centered healthcare research.⁵⁰ These so-called n-of-1 trials are prospective, crossover trials where each case is exposed to alternative interventions based on a predetermined order and time schedule.^{51,52} The major drawback of this crossover design, however, is the risk of transfer effects from one intervention period to the other, unless transfer effects are impossible or mitigated by sufficiently long 'wash-out periods'. This makes n-of-1 trials unfeasible for training interventions, where (retention of) learning effects is crucial.

In order to evaluate whether a novel type of intervention can impose an effect in the long term in people with a slowly progressive condition, large-scale longitudinal cohort studies are needed, preferably multi-centered. Although this study design does not randomly assign people to specific interventions and relies more on the natural variation of physical training and activity in the target population, its strength is the long follow-up and the representativeness of the results for the entire population. Longitudinal cohort studies are well suited to detect differences in study parameters across time between subgroups due to differences in training, physical activity or lifestyle. Moreover, the influence of various patient characteristics on the study outcomes can be investigated.

Future perspectives

In the previous paragraphs, I have already given several suggestions for future research focused on the mobility problems in people with HSP. In summary, I have discussed the following.

With regard to assessment, I have mentioned the relevance of research into 'online' gait adaptability testing to assess the *capacity* of patients to deal with unexpected disruptions of gait. The use of wearable sensors in the form of activity trackers would provide essential information about the real life *performance* of gait-related activities, while self-assessment of gait-related activities would add the important dimension of gait *perception* to the capacity and performance measures. Regarding people with HSP, research in all areas is still scarce, so there are many options to explore. Lastly, since falls are a major problem in this population, research into detecting the 'tipping point' where an individual shows increased *fall risk* would

potentially have great clinical benefit, because fall preventive measures could be taken well on time, which would reduce the risk of fall-related injuries and unnecessary fear of falling.

As for intervention, I have suggested to focus future HSP research on patients with maladaptive fear of falling, since this subgroup might benefit most from *instrumented* gait adaptability training on a treadmill, while safety is provided with a harness. On the other hand, the development of *overground* gait adaptability training programs for people with HSP as a whole would be essential, as all aspects of adaptability necessary for community ambulation can potentially be integrated, such as coping with terrain demands, postural transitions, quiet standing, and negotiating both expected and unexpected obstacles. In addition, the development of effective *home-based* intervention programs would allow people to train close to where they need their skills most. It would also create the possibility of 'life-long training', which is probably necessary to make a real difference with regard to attenuating the functional consequences of HSP in the long term. With an eye on the lifespan, *lifestyle* interventions that promote general physical activity and physical fitness might be equally important, given their proven effectiveness in many (other) conditions. As chronic fatigue is a problem in people with HSP, current *multidisciplinary* programs that have been proven effective to alleviate fatigue in other neurological conditions, should be tested in people with HSP as well.

To optimally tailor any type gait rehabilitation (aimed at stepping pattern, dynamic balance, and/or gait adaptability) to the individual with HSP, it is important to always consider the use of other interventions, such as orthotics, pharmacological and/or surgical treatment. In many instances, patients may profit from one or more of these *medical-technical interventions* that are meant to optimize the biomechanical prerequisites for effective gait training, such as plantigrade foot contact with the floor, sufficient foot elevation and knee flexion during swing, adequate ankle and knee stability during stance, and sufficient step width / length. Given the progressiveness of the disease, it is important to regularly evaluate whether the current clinical management plan aligns with the individually experienced problems and needs. Sometimes, it will be important to evaluate the gait problems from a broader perspective by taking a *multidisciplinary approach*, beyond the involvement of physicians and physical therapists. For example, an occupational therapist may be needed to provide advice on chronic fatigue, or a complicated work-life balance; or a psychologist to help to adopt an active coping style.⁵³

It should be acknowledged that the highest level of evidence for the effectiveness of specific intervention is hard to obtain for any rare disease, particularly if the disease of interest is characterized by a multitude of genetic causes and phenotypical expressions, such as in HSP. It will be even harder to obtain such evidence for the

interaction of two or more interventions. Hence, in the field of rare neurological conditions, there are still many areas of clinical practice where scientific evidence is lacking or contradicting; a situation that is not expected to change in the near future since rehabilitation research funds are notoriously hard to obtain for rare diseases. It is therefore essential to acknowledge that guidelines for clinical management in HSP cannot solely be based on scientific evidence, but should also rely on professional experience, patients' experiences and needs, and on mutual consensus. Consensus-based guidelines should be developed by a multidisciplinary, preferably international panel of experts and strive for recommendations agreed upon by the majority of experts. Unfortunately, until now, such guidelines do not yet exist for HSP. In order to fill this gap, I will be involved in developing consensus-based rehabilitation guidelines in collaboration with the European Reference Network of Rare Neurological Conditions (ERN-RND). The ERN-RND is pre-eminent in the development of such multidisciplinary guidelines, and arranges multiple educational activities to share and implement such guidelines. In order to develop the guideline for people with HSP, the ICF will be used to classify the consequences of HSP both in children and adults with HSP. Based on these findings, an ICF core set will be developed with a practical guideline on how signs and symptoms, activity limitations, and participation restrictions can best be identified. This guideline will be validated through a DELPHI procedure and be finalized with the development of consensus-based recommendations. These recommendations will support healthcare providers in the clinical management of people with HSP.

Reference list

1. World Health Organisation. How to use the ICF: A practical manual for using the International Classification of Functioning, Disability and Health (ICF). Geneva. October 2013.
2. Maetzler W, Rochester L, Bhidayasiri R, Espay AJ, Sánchez-Ferro A, van Uem JMT. Modernizing Daily Function Assessment in Parkinson's Disease Using Capacity, Perception, and Performance Measures. *Mov Disord*. 2021;36(1):76-82.
3. Balasubramanian CK, Clark DJ, Fox EJ. Walking adaptability after a stroke and its assessment in clinical settings. *Stroke Res Treat*. 2014;2014:591013.
4. Seo HG, Oh BM, Kim K. Robot-assisted gait training in a patient with hereditary spastic paraplegia. *Pm r*. 2015;7(2):210-213.
5. Bertolucci F, Di Martino S, Orsucci D, et al. Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. *NeuroRehabilitation*. 2015;36(1):93-99.
6. Sato M, Kannari K, Tomari M, Kawaguchi T. Physical therapy intervention with a low frequency of exercise for a patient with a complicated form of hereditary spastic paraplegia: a case report. *J Phys Ther Sci*. 2019;31(7):545-549.
7. Zhang Y, Roxburgh R, Huang L, Parsons J, Davies TC. The effect of hydrotherapy treatment on gait characteristics of hereditary spastic paraparesis patients. *Gait Posture*. 2014;39(4):1074-1079.
8. Rovito C, Paganoni S, Babu S, Tenforde AS. Improved Function in a Runner With Hereditary Spastic Paraparesis With Use of Extracorporeal Shockwave Therapy: Personal Clinical Experience. *Am J Phys Med Rehabil*. 2021;100(5):e66-e68.
9. Paparella G, Vavla M, Bernardi L, Girardi G, Stefan C, Martinuzzi A. Efficacy of a Combined Treatment of Botulinum Toxin and Intensive Physiotherapy in Hereditary Spastic Paraplegia. *Front Neurosci*. 2020;14:111.
10. van de Venis L, van de Warrenburg B, Weerdesteyn V, Geurts ACH, Nonnekes J. Gait-Adaptability Training in People With Hereditary Spastic Paraplegia: A Randomized Clinical Trial. *Neurorehabil Neural Repair*. 2023;37(1):27-36.
11. Kwakkel G, Lannin NA, Borschmann K, et al. Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *Int J Stroke*. 2017;12(5):451-461.
12. Regensburger M, Spatz IT, Ollenschläger M, et al. Inertial Gait Sensors to Measure Mobility and Functioning in Hereditary Spastic Paraplegia: A Cross-Sectional Multicenter Clinical Study. *Neurology*. 2022;99(10):e1079-1089.
13. Serrao M, Rinaldi M, Ranavolo A, et al. Gait Patterns in Patients with Hereditary Spastic Paraparesis. *PLoS One*. 2016;11(10):e0164623.
14. Fonteyn EM, Heeren A, Engels JJ, Boer JJ, van de Warrenburg BP, Weerdesteyn V. Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration. *Gait Posture*. 2014;40(1):247-251.
15. Heeren A, van Ooijen M, Geurts AC, et al. Step by step: a proof of concept study of C-Mill gait adaptability training in the chronic phase after stroke. *J Rehabil Med*. 2013;45(7):616-622.

16. Geerse DJ, Coolen BH, Roerdink M. Walking-adaptability assessments with the Interactive Walkway: Between-systems agreement and sensitivity to task and subject variations. *Gait Posture*. 2017;54:194-201.
17. Geerse DJ, Roerdink M, Marinus J, van Hilten JJ. Assessing Walking Adaptability in Parkinson's Disease: "The Interactive Walkway". *Front Neurol*. 2018;9:1096.
18. van Swigchem R, van Duijnhoven HJ, den Boer J, Geurts AC, Weerdesteyn V. Deficits in motor response to avoid sudden obstacles during gait in functional walkers poststroke. *Neurorehabil Neural Repair*. 2013;27(3):230-239.
19. van Ooijen MW, Heeren A, Smulders K, et al. Improved gait adjustments after gait adaptability training are associated with reduced attentional demands in persons with stroke. *Exp Brain Res*. 2015;233(3):1007-1018.
20. Hendriks MMS, Vos-van der Hulst M, Weijs RWJ, van Lotriningen JH, Geurts ACH, Keijsers NLW. Using Sensor Technology to Measure Gait Capacity and Gait Performance in Rehabilitation Inpatients with Neurological Disorders. *Sensors (Basel)*. 2022;22(21).
21. Horemans H, Kooijmans H, van den Berg-Emons R, Bussmann H. The Activ8 activity monitor: Validation of posture and movement classification. *J Rehabil Assist Technol Eng*. 2020;7:2055668319890535.
22. van Gelder LMA, Bonci T, Buckley EE, et al. A Single-Sensor Approach to Quantify Gait in Patients with Hereditary Spastic Paraplegia. *Sensors (Basel)*. 2023;23(14).
23. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Updated February Cochrane Handbook for Systematic Reviews of Interventions 2022; Version 6.3.
24. Administration FaD. Guidance for Industry: patient-reported outcome measures: use in medical product development to support labelling claims. 2009:6.
25. van Lith BJH, Kerstens H, van den Bemd LAC, et al. Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*. 2020;15(1):64.
26. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
27. Timmermans C, Roerdink M, Meskers CGM, Beek PJ, Janssen TWJ. Walking-adaptability therapy after stroke: results of a randomized controlled trial. *Trials*. 2021;22(1):923.
28. Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian occupational performance measure: an outcome measure for occupational therapy. *Can J Occup Ther*. 1990;57(2):82-87.
29. Johansson S, Kottorp A, Lee KA, Gay CL, Lerdal A. Can the Fatigue Severity Scale 7-item version be used across different patient populations as a generic fatigue measure--a comparative study using a Rasch model approach. *Health Qual Life Outcomes*. 2014;12:24.
30. Ellmers TJ, Wilson MR, Kal EC, Young WR. The perceived control model of falling: developing a unified framework to understand and assess maladaptive fear of falling. *Age Ageing*. 2023;52(7).
31. van Duijnhoven HJ, De Kam D, Hellebrand W, Smulders E, Geurts AC, Weerdesteyn V. Development and Process Evaluation of a 5-Week Exercise Program to Prevent Falls in People after Stroke: The FALLS Program. *Stroke Res Treat*. 2012;2012:407693.
32. Gallou-Guyot M, Nuic D, Mandigout S, et al. Effectiveness of home-based rehabilitation using active video games on quality of life, cognitive and motor functions in people with Parkinson's disease: a systematic review. *Disabil Rehabil*. 2022;44(26):8222-8233.

33. Dalmazane M, Gallou-Guyot M, Compagnat M, et al. Effects on gait and balance of home-based active video game interventions in persons with multiple sclerosis: A systematic review. *Mult Scler Relat Disord*. 2021;51:102928.
34. Geerse DJ, Coolen B, van Hilten JJ, Roerdink M. Holocue: A Wearable Holographic Cueing Application for Alleviating Freezing of Gait in Parkinson's Disease. *Front Neurol*. 2021;12:628388.
35. Geerse DJ. Cue X: a Gamified Gait-and-balance Exercise Program for Augmented-reality Glasses to Improve Parkinsonian Gait. In: <https://www.clinicaltrials.gov/>, ed. NCT05605249: Strolll, Ltd; 2022.
36. Tonnesen M, Nielsen CV. Navigating (un)certainty in 'downhill' trajectories: An ethnographic study about rehabilitees' and professionals' experiences of goal-setting in Parkinson's disease rehabilitation. *Clin Rehabil*. 2023;2692155231170690.
37. Kerstens H, Van Lith BJH, Nijkrake MJ, et al. Healthcare needs, expectations, utilization, and experienced treatment effects in patients with hereditary spastic paraplegia: a web-based survey in the Netherlands. *Orphanet J Rare Dis*. 2021;16(1):283.
38. Lallémand-Dudek PM, Parodi LP, Coarelli GM, et al. Individual perception of environmental factors that influence lower limbs spasticity in inherited spastic paraparesis. *Ann Phys Rehabil Med*. 2023;66(6):101732.
39. Sartori RDG, Marelli M, D'Angelo MG, Delle Fave A. Autonomy level and quality of everyday experience of people with Hereditary Spastic Paraplegia. *Health Soc Care Community*. 2019;27(5):e850-e860.
40. Cederberg KL, Motl RW, McAuley E. Physical Activity, Sedentary Behavior, and Physical Function in Older Adults With Multiple Sclerosis. *J Aging Phys Act*. 2018;26(2):177-182.
41. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(8):2532-2553.
42. Charron S, McKay KA, Tremlett H. Physical activity and disability outcomes in multiple sclerosis: A systematic review (2011-2016). *Mult Scler Relat Disord*. 2018;20:169-177.
43. Martín-Núñez J, Calvache-Mateo A, López-López L, et al. Effects of Exercise-Based Interventions on Physical Activity Levels in Persons With Parkinson's Disease: A Systematic Review With Meta-analysis. *J Geriatr Phys Ther*. 2023.
44. Selph SS, Skelly AC, Wasson N, et al. AHRQ Comparative Effectiveness Reviews. In: *Physical Activity and the Health of Wheelchair Users: A Systematic Review in Multiple Sclerosis, Cerebral Palsy, and Spinal Cord Injury*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021.
45. Abasıyanık Z, Kurt M, Kahraman T. COVID-19 and Physical Activity Behaviour in People with Neurological Diseases: A Systematic Review. *J Dev Phys Disabil*. 2022;34(6):987-1012.
46. van der Kolk NM, de Vries NM, Kessels RPC, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol*. 2019;18(11):998-1008.
47. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446.
48. Veenhuizen Y, Cup EHC, Jonker MA, et al. Self-management program improves participation in patients with neuromuscular disease: A randomized controlled trial. *Neurology*. 2019;93(18):e1720-e1731.

49. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *Bjog*. 2018;125(13):1716.
50. McDonald S, Nikles J. N-of-1 Trials in Healthcare. *Healthcare (Basel)*. 2021;9(3).
51. Janssen Daalen JM, Meinders MJ, Giardina F, et al. Multiple N-of-1 trials to investigate hypoxia therapy in Parkinson's disease: study rationale and protocol. *BMC Neurol*. 2022;22(1):262.
52. Mendonça M, Cotovio G, Barbosa R, Grunho M, Oliveira-Maia AJ. An Argument in Favor of Deep Brain Stimulation for Uncommon Movement Disorders: The Case for N-of-1 Trials in Holmes Tremor. *Front Hum Neurosci*. 2022;16:921523.
53. Shribman S, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *Lancet Neurol*. 2019;18(12):1136-1146.



Chapter 8

Samenvatting

Iedereen verstapt zich, struikelt, of valt wel eens. Maar wat als je merkt dat dit steeds vaker gebeurt? Als je je op het werk al verstapt als je een kop koffie gaat halen, of struikelt over de kleinste onregelmatigheid in de stoep? Je merkt dat je benen stijf voelen, en dit gevoel wordt steeds erger en vermoeiender. Ook al ben je graag onder de mensen, je kiest er soms voor om niet te gaan sporten, niet naar een verjaardag te gaan, maar binnen te blijven terwijl de boodschappen en pakketjes thuis worden bezorgd. Ondanks deze maatregelen neemt de stijfheid in je benen niet af. Collega's vragen zelfs of je een blessure hebt omdat je zo moeilijk loopt. Om aan hun uit te leggen wat je voelt, vertel je dat het lijkt alsof je met een zware zak aardappelen rondom je benen moet lopen: het is zwaar, het brengt je uit balans, en is hinderlijk bij elke stap die je zet. Verschillende familieleden hebben soortgelijke klachten, maar niemand heeft nog medische hulp gezocht. Bij de huisarts word je doorverwezen naar een neuroloog. Na verschillende onderzoeken blijkt dat de beenstijfheid die je ervaart 'spasticiteit' heet, en wordt veroorzaakt door een aandoening die 'hereditaire spastische paraplegie' heet. Je wordt vervolgens doorverwezen naar een revalidatiearts die je uitlegt dat door toenemende spierzwakte en verlies van gevoel in de benen je balans- en loopvaardigheid geleidelijk zal afnemen, maar dat het moeilijk is om het tempo hiervan te voorspellen.

Hereditaire Spastische Paraplegie (HSP) is een groep van zeldzame (erfelijke) neurologische aandoeningen. Er zijn twee vormen van HSP: mensen met een 'pure vorm' ervaren langzaam toenemende spasticiteit, spierzwakte, en verminderd gevoel in beide benen. Bij de 'complexe vorm' kunnen er ook problemen zijn met de coördinatie, het geheugen of epilepsie. Bij mensen met HSP werken sommige zenuwbanen niet goed. Dit zijn de zenuwbanen die vanuit de hersenen naar het ruggenmerg lopen om de beenspieren aan te sturen (bv. om te zorgen dat je je voet optilt om over een scheve stoeptegels te stappen), en de zenuwbanen die het bewegingsgevoel vanuit het ruggenmerg aan de hersenen doorgeven (bv. of je je voet hoog genoeg optilt om over de scheve stoeptegels te stappen). Balans en lopen is daarom een groot probleem voor mensen met HSP, en helaas vallen zij vaak.

In dit proefschrift heb ik onderzoek gedaan naar de balans- en loopproblemen van mensen met HSP. Specifiek heb ik onderzocht welke factoren de ernst van de spierstijfheid, balans- en loopproblemen kunnen beïnvloeden. Ook heb ik onderzocht welke testen gebruikt kunnen worden om te beoordelen of iemand met HSP een hoog valrisico heeft. Als laatste heb ik onderzocht of een specifieke looptraining het loopaanpassingsvermogen van mensen met een pure vorm van HSP kan verbeteren.

Hoofdstuk 1 geeft achtergrondinformatie over de aandoening HSP. Er wordt uitgelegd welke kenmerken en symptomen mensen met HSP hebben. Vervolgens wordt besproken hoe deze symptomen het moeilijk maken om balans te houden

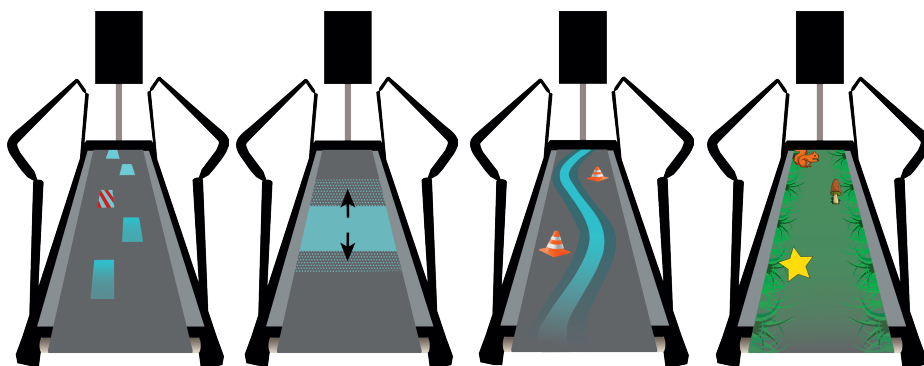
en te lopen, en hoe dit hinderlijk is in het dagelijkse leven van mensen met HSP. Als laatste wordt stil gestaan bij het feit dat er op dit moment nog geen genezing is voor HSP, maar dat er verschillende manieren zijn waarop de spasticiteit en de balans- en loopproblemen kunnen worden beïnvloed en behandeld.

Voor de behandeling van mensen met HSP is het belangrijk om te weten welke factoren de symptomen kunnen verminderen, of juist verergeren. Vanuit onze ervaring verwachtten wij dat voldoende dagelijkse beweging de ernst van de symptomen kan verminderen, terwijl stress de symptomen juist kan verergeren. In **Hoofdstuk 2** onderzocht ik of deze stelling klopt. Dit deed ik door de impact van de Covid-19 lockdown te onderzoeken op de ernst van de symptomen. Tijdens deze lockdown was het door de avondklok, het thuiswerken, en de sluiting van sportscholen en fysiotherapiepraktijken moeilijker om elke dag voldoende te bewegen. In totaal hebben 58 mensen met HSP een online vragenlijst ingevuld. Van deze groep was 74% minder in beweging tijdens de lockdown. Zij ervoeren daarbij een stijging van de spierstijfheid, pijn, lichamelijke vermoeidheid. Daarnaast hadden zij meer moeite met hun balans en het lopen. Bovendien gaf 43% van deze groep aan meer stress te ervaren tijdens de lockdown. Daarbij ervoeren zij een stijging van spierstijfheid, pijn, en vermoeidheid.

Mensen met HSP geven aan dat de balans- en loopproblemen tot hun meest hinderlijke symptomen horen. Meer inzicht in therapieën die deze balans- en loopproblemen kunnen behandelen is daarom van groot belang. Eerder onderzoek heeft aangetoond dat mensen baat hebben bij looptraining. Het is echter nog onduidelijk of door training de loopvaardigheid ook bij mensen met HSP kan verbeteren. In het bijzonder het loopaanpassingsvermogen: de vaardigheid om je aan te passen aan de eisen van de omgeving, zoals het vermijden van een stoeptegels die scheefliggen, het versnellen om een groen stoplicht te halen, of het lopen met een zware boodschappentas. Dit loopaanpassingsvermogen is erg belangrijk om veilig en zelfstandig te kunnen lopen. In **Hoofdstuk 3** wordt het onderzoeksprotocol uitgelegd waarmee ik heb onderzocht of 5 weken training het loopaanpassingsvermogen kan verbeteren.

Ik heb een trainingsgroep die deze training kreeg ter verbetering van het loopaanpassingsvermogen vergeleken met een controlegroep. De controlegroep begon met een 5-weekse wachtperiode. Tijdens deze wachtperiode gingen zij door met de zorg die zij normaal ontvingen (bv. fysiotherapie of fysiofitness). Op deze manier kon ik de nieuwe training vergelijken met de zorg die mensen met HSP doorgaans krijgen. Na de wachtperiode ontvingen deze deelnemers alsnog de loopvaardigheidstraining.

Het loopaanpassingsvermogen werd getraind op de 'C-Mill'. De C-Mill is een loopband waarbij er diverse projecties op de loopband kunnen worden afgebeeld (afbeelding 1). Zo kun je obstakels of een bospad nabootsen, en in een veilige omgeving trainen hoe je hiermee moet omgaan. De deelnemers trainden 5 weken, 2x per week, waarbij elke trainingssessie 60 minuten duurde. In totaal werd er 10 uur getraind op het loopaanpassingsvermogen. Iedere deelnemer volgde een persoonlijk trainingsschema onder begeleiding van een fysiotherapeut. De trainingsgroep en de controlegroep werden voor en na de vijf weken getest in het bewegingslaboratorium van het Radboudumc. Daarbij werden ze onderzocht op hun aanpassingsvaardigheid, balans- en loopcapaciteit, en vertrouwen in de eigen balans. Er werd ook gekeken naar het looppatroon: bijvoorbeeld hoe lang en hoe breed iemand een stap maakt. Daarnaast droegen de deelnemers een activiteitenmonitor die bijhield hoe vaak mensen lagen, zaten of stonden, en hoeveel zij wandelden, renden, of fietsten op één dag. Voor en na de training 15 weken lang een valdagboek bij, waarin ze aangaven of ze waren gevallen.



Figuur 1: De C-Mill loopband met verschillende oefeningen om de aanpassingsvaardigheid van het lopen te trainen.

In **Hoofdstuk 4** worden de resultaten van bovengenoemd onderzoek beschreven. Er deden 36 mensen met een pure vorm van HSP mee. Achttien deelnemers startten in de trainingsgroep, terwijl de andere 18 deelnemers een wachtperiode ingingen (controlegroep). Bij de start van het onderzoek waren deze twee groepen niet verschillend ten aanzien van leeftijd, geslacht of ziekteduur / ziekte-ernst. Alle deelnemers hebben het onderzoek volledig afgemaakt. Bovendien was de therapietrouw hoog; 99.7% van alle beoogde C-Mill trainingen werd gevolgd.

Het doel van dit onderzoek was om te evalueren of de C-Mill training helpt om de balans- en loopproblemen bij mensen met HSP te verminderen. Om deze vraag te beantwoorden heb ik eerst gekeken naar verschillen tussen de trainingsgroep en

de controlegroep. Hieruit bleek dat de loopvaardigheid van de trainingsgroep na vijf weken training niet beter was dan die van de controlegroep. Als tweede stap heb ik de twee groepen samengevoegd: zo kon ik van alle 36 mensen de testen voor en na de C-Mill training en de testen na de 15 weken van het valdagboek beoordelen. Hieruit bleek dat, gemiddeld genomen, de deelnemers na 5 weken C-Mill training verbeterden ten aanzien van balans- en loopvaardigheid. Ook maakten zij grotere stappen en liepen zij sneller. Hieruit werd geconcludeerd dat mensen met HSP na 5 weken C-Mill training wel verbeteren op hun balans- en loopvaardigheid, maar dat 5 weken C-Mill training niet beter is dan de normale zorg die zij ontvangen.

Mensen met HSP lopen vaak met toegenomen rompbeweging. Deze toename van rompbewegingen is vaak al zichtbaar in de vroege fase van de aandoening. Het blijft onduidelijk waarom mensen met HSP deze toegenomen rompbewegingen maken. Vaak wordt aangenomen dat zij deze als compensatie inzetten. Bijvoorbeeld, door de romp overdreven naar links en naar achteren te bewegen kan de rechtervoet makkelijker van de grond komen, en vervolgens los van de grond blijven om een stap te zetten. In **Hoofdstuk 5** onderzocht ik of deze extra rompbewegingen ook ingezet werden om beter in balans te blijven tijdens het lopen. Hiervoor heb ik video's van het looppatroon van 86 mensen met HSP bekeken en beoordeeld of hun rompbewegingen 'normaal', 'licht verhoogd' of 'sterk verhoogd' waren. Vervolgens heb ik onderzocht hoe deze categorisering samenhangt met scores op de balanstesten. Hierbij bleek dat mensen die liepen met toegenomen rompbewegingen lager scoorden op de balanstesten.

Het is bekend dat mensen drie basismechanismen hebben om hun balans te houden tijdens het lopen, waarbij ze een voorkeur hebben voor de voetplaatsingsstrategie. Hierbij wordt de voet van het zwaaibeen zorgvuldig geplaatst om onregelmatigheden op te vangen. Additioneel wordt de enkelstrategie ingezet om tijdens de stand fase van het lopen subtiele balanscorrecties te kunnen maken. Mensen met HSP kunnen beide strategieën niet optimaal benutten, aangezien spasticiteit, spierzwakte en gevoelsstoornissen in de benen zowel een accurate voetplaatsing als subtiele enkelbewegingen belemmeren. Ter compensatie is het daarom logisch dat mensen met HSP vaker heupstrategieën gebruiken, waarbij overmatige arm- en rompbewegingen worden ingezet om de balans te houden. De versterkte inzet van heupstrategieën kan daarom ook een reden zijn waarom mensen met HSP een toename van de rompbewegingen tijdens het lopen laten zien.

Valangst, vallen, en letsel na een val zijn bij mensen met HSP vaak het gevolg van balans- en loopproblemen. Om op de juiste manier valpreventie aan te bieden aan deze groep, is het belangrijk dat onderscheid kan worden gemaakt tussen mensen die een verhoogd risico hebben om te vallen, en mensen die dit niet hebben. In **Hoofdstuk 6** onderzocht ik welke testen en methoden het meest geschikt zijn

om dit te beoordelen. Hiervoor werden klinische testen gebruikt (testen die vaak gebruikt worden in de kliniek omdat ze snel zijn en weinig materiaal vereisen) en biomechanische testen (geïstrumenteerde testen die via wiskundige berekeningen gedetailleerd naar balansmechanismen kijken, die vooralsnog niet klinisch toepasbaar zijn). Ik heb eerst gekeken naar verschillen tussen mensen met HSP en gezonde controles. Hieruit bleek dat vertrouwen in de eigen balans, de klinisch gemeten balans- en loopcapaciteit, en diverse biomechanische maten lager waren bij mensen met HSP dan bij gezonde controles. Vervolgens heb ik gekeken naar twee groepen deelnemers met HSP: vellers (deelnemers die minstens 1x gevallen waren in de afgelopen 15 weken) en niet-vellers. Hierbij bleek dat vertrouwen in eigen balans en de klinische balans- en loopcapaciteit veelbelovende testen zijn om vellers van niet-vellers te onderscheiden, en dat deze testen dit beter deden dan de biomechanische testen.

Met deze thesis hoop ik een bijdrage te hebben geleverd aan het toekomstig onderzoek en de behandeling van balans- en loopproblemen bij mensen met HSP.



Appendices

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Cognitive Neuroscience

Dankwoord

Wat heb ik de afgelopen vier jaar een ontzettend leuke en fijne tijd gehad. Alle mensen die ik heb ontmoet, waarmee ik kon samenwerken, en waarbij ik de kunst af en toe mocht afkijken hebben mij geholpen. Ik wil graag iedereen bedanken die - op welke wijze dan ook - heeft bijgedragen aan deze leuke tijd. Een aantal mensen wil ik in het bijzonder noemen.

De deelnemers van Move-HSP: ontzettend bedankt voor jullie interesse, inzet en enthousiasme voor de onderzoeksprojecten! Jullie waren bereid om vanuit alle uithoeken naar Nijmegen te komen. We hebben flink wat tijd samen doorgebracht: de huisbezoeken, de metingen in het Bewegingslab van het Radboudumc, en bij een groot deel van jullie mocht ik daarbij ook de C-Mill loopvaardigheidstrainingen geven. Jullie persoonlijke verhalen, eerlijkheid en positiviteit zijn een bron van inspiratie.

Mijn promotieteam: Jorik, Sander, Bart en Vivian. Ik kan mijn sollicitatiegesprek nog goed herinneren. Zodra ik de deur van de vergaderruimte op de 4^e uitliep na het sollicitatiegesprek, wist ik dat ik deze baan ontzettend graag wilde. Jullie hadden mij al overtuigd van het fijne team en de mooie kansen die er binnen het onderzoek en de afdeling Revalidatie zouden liggen. Gelukkig kreeg ik al snel het telefoontje van Sander dat ik op het Move-HSP project aan de slag mocht. De tijd sindsdien is voorbij gevlogen.

Jorik, dat ik dit boekje nu in m'n handen heb, is voor een groot deel aan jou te danken. Je hebt me meegenomen in alle onderdelen van onderzoek, schrijven, en promoveren, waarbij ik mijn definitie van het woord 'pragmatisch' wat heb herzien in de afgelopen jaren. Met jouw expertise, efficiëntie, en creatieve ideeën is het super om samen te werken, en word ik steeds weer enthousiast en uitgedaagd in de onderzoeksprojecten. Ik weet dat ik altijd even kan binnenlopen als ik er niet helemaal uitkom. Hoe fijn is dan ook ons peer-support clubje over moeilijke namen, al zijn we het volgens mij nog niet helemaal eens over de reden waarvoor deze club is opgericht. Je denkt altijd mee en een stap vooruit; met jouw hulp zit ik nu helemaal op mijn plek zit als onderzoeker bij de bewegingsstoornissen, fysio Radboudumc en fysio LEC. Ik heb een fantastische tijd gehad in jouw onderzoeksgroep waarin ik de kunst van onderzoek doen met veel plezier van je heb afgekeken. Gelukkig kan ik dit de komende tijd nog even blijven doen!

Sander, vier jaar geleden begon het allemaal met het telefoontje waarin je vertelde dat ik was aangenomen op Move-HSP. Als eerste promotor ben je nauw betrokken geweest bij alle onderzoeken. Ondanks je drukke agenda heb ik altijd het gevoel gehad dat je tijd kon maken wanneer het nodig was. We hebben samen wel wat uurtjes op kantoor doorgebracht om te werken aan de laatste revisies. Ik heb veel

van je mogen leren, en gelukkig blijven we de komende tijd nog samenwerken op de poli! Ik hoop nog flink mee te liften en te leren van je expertise op wetenschappelijk gebied, revalidatie en de bewegingsstoornissen.

Bart, de afgelopen jaren heb je gelukkig veel van je kennis en adviezen met mij willen delen! Het was superfijn om af en toe samen een kopje koffie te drinken, en na te denken over keuzes waar ik voor stond. Je bent altijd betrokken en altijd geïnteresseerd. Jouw klinische blik en vertaling van onderzoek naar de klinische praktijk is inspirerend, en ik hoop op deze manier onderzoek te blijven doen. Fantastisch om de afgelopen jaren jouw carrière tot professor mee te hebben gemaakt!

Vivian, in het begin ben ik ontelbaar vaak jouw kantoor binnen gewandeld om je mening en expertise te vragen over van alles wat maar met balanscontrole en lopen te maken heeft, en eerlijk gezegd, doe ik dit nog steeds. Je parate kennis, inzicht en scherpheid in data en interpretaties zijn indrukwekkend. Naast Move-HSP mocht ik meewerken op het ROADS project, waar ik met veel plezier aan heb meegewerkt. Fantastisch om de afgelopen jaren ook jouw carrière tot professor mee te hebben gemaakt!

Prof. dr. D.H.J. Thijssen, Prof. dr. A. I. Buizer, en Prof. dr. C.J.C. Lamoth, bedankt dat jullie plaats wilden nemen in de manuscript commissie. **Prof. dr. J. Vermeulen, dr. M. Roerdink, dr. C.J.W. Kerstens**, bedankt dat jullie ook plaats willen nemen in de oppositie.

Lieve **Vera**, wij kennen elkaar al wat langer dan vandaag! In 2011 samen begonnen aan de opleiding Bewegingswetenschappen in Groningen. Ik verliet het hoge noorden na een kleine 2 jaar voor een andere opleiding in Antwerpen. Gelukkig bleven wij goede vriendinnen. Jij werkte al aan je promotieonderzoek bij revalidatie, en hebt mij op elk vlak geholpen tijdens mijn promotietraject. Ik ben ontzettend trots op hoe jij het de afgelopen jaren voor elkaar hebt gebokst, en daarnaast altijd tijd had om samen te sparren, te relativeren (al dan niet met een kantoorwijnkje), en onze mijlpalen te vieren! We hebben een boel lol gehad en hebben nog een boel lol te gaan. Ik ben blij dat jij mijn paranimf bent.

Lieve **Fleur**, ook wij kennen elkaar al vanaf de opleiding Bewegingswetenschappen in Groningen. Ondertussen zijn we heel wat mijlpalen, reizen, carpoolkaraoke en avonturen verder. Je onuitputbare positiviteit, no-nonsense en betrokkenheid werkt altijd motiverend. Het is fantastisch om te zien hoe jij je plek als docent hebt gevonden, en al je kansen creëert en aangrijpt. Ik kijk al uit naar alle volgende avonturen die we zullen beleven. Ik ben blij dat jij mijn paranimf bent.

Naast Vera en Fleur heb ik het geluk nog wat andere Smarties te kennen: lieve **Maud, Salina en Wendy**, ongelofelijk dat je van een introductieweekend Bewegingswetenschappen op een Waddeneiland zo'n 13 jaar geleden, zulke goede vrienden kan overhouden. Maud, van Airbnb hostess tijdens mijn stage in Beatrixoord tot mede-strijder op schrijfdagen, Salina, balkon mede-fluiter tot noem-een-willekeurige-plek mede-concert&musea-ganger, en Wendy, mede-peddelaar met de 100km MTB oefenritjes over de Veluwe. We hebben samen mooie reizen, momenten, en mijlpalen meegemaakt en gevierd, en kunnen ook altijd bij elkaar terecht als het verdrietig is. Bedankt voor alle interesse, gezelligheid en support! Lieve **Annemieke**, weet dat we met elk hert dat we zien, we altijd aan je denken.

Lieve **Anne**, wat hebben wij als huisgenoten in Antwerpen ontzettend veel lol gehad. We delen onze liefde voor kunst, eenpansgerechten, en spontane uitstapjes naar onverwachte plekken; zo sta je ineens in een spookhuis in Lichtaart, de IKEA, een survivalbaan in de Ardennen, in de zee, in de regen, of op het BK veldrijden. Ontzettend tof dat jouw creativiteit in dit boekje zit als de kunstenares van de prachtige ecoline prints van de cover en de tussenbladen. Ik ben benieuwd waar we nog meer zullen belanden.

De afgelopen jaren heb ik ook mogen samenwerken met een geweldige groep aan mede-promovendi, zoals de **Looptoppers! Anouk**, wat is het goed om te zien hoe jij je ambities waarmaakt. Als kantoorbuddies konden we altijd meedenken met elkaar, en vervulde jij glansrijk je rol als publicatietrofee-~~forceer~~beheerder. Ook buiten werk hebben we elkaar veel opgezocht met onze ThriftFlippers business als hoogtepunt! Ik beloof dat ik altijd terug zal zwaaien naar de medewerkersfietsenstalling. **Jamie**, al zijn we het niet vaak eens over de muzikzender of temperatuur op ons kantoor, ik kan altijd op je rekenen voor advies, matlab-oplossingen, en goede gesprekken. Ik kijk al uit naar de aankomende buddy wodjes! **Bente**, mijn trainingspartner en coach voor de 4daagse kilometers, heerlijk om tijdens onze wandelingen en borrels helemaal bij te kletsen over alles wat ons bezighoudt! **Ilse**, mede erfelijke bewegingsstoornissen onderzoeker, wij hebben wat trappen verslagen tussen de 1^e en 4^e voor onze koffiebreaKs! Dankjewel dat je altijd tijd maakt. **Joris, Cindel, Gijs, Ilse en Marleen**, ik kijk altijd uit naar de gezelligheid op kantoor, en samen met **Marijne, Jean en Joost** de looptopper borrels en fantastische stickeruitwisselingen. Ik kan me geen beter team aan collega's wensen.

Lieve **Sabine**, wij kwamen elkaar tegen bij de introductie toen we aan de start stonden van ons promotietraject binnen het expertisecentrum. Ondertussen zijn we heel wat etentjes, creatieve uitspattingen, sportuitjes, én klusmiddagen verder. Dankjewel dat ik altijd bij je mag binnenlopen om bij te kletsen, te brainstormen, en mee te liften op al je positiviteit en ideeën. Gelukkig zijn we ook nog eens buurvrouwen in Hatert geworden, en weten we elkaars achterdeur goed te vinden.

4e etage collega's, Wouter, 1 dag in de week mocht ik meedraaien op jouw ROADS project, een project waar ik met heel veel plezier aan heb meegewerkt! Fantastisch hoe jij je nooit echt druk lijkt te maken, misschien is de gouden tip hierin wel de urenlange bubbelbad sessies? **Mitchel**, idem de rust zelve. Je staat altijd klaar voor iedereen, met bouldertips, autobandwisselskills, maar vooral altijd met goed advies. **Lotte**, samen met **Irene** hebben wij heel wat uren, regenbuien, kilometers, en hoogtemeters getrotseerd met Duchenne Heroes. Dankjewel voor al je support rondom de gevreesde 80km klim! **Lucas, Sarah, Paul en Ilse**, dank voor alle discussies, technische support, tips and tricks, schrijfdagen en bubbelbad-sessies. Ik heb genoten van de samenwerking. **Mieke**, mede-strijder op woensdag-schrijfdag. We hebben heel wat kopjes koffie en thee gedronken terwijl we samen nadachten over onze stukken. Dankjewel voor alle support!

Een dankjewel aan de stagiaires **Lisanne, Aletta, Kim en Jenneke**. Jullie hebben mij tijdens de huisbezoeken, metingen, en de analyse van de data op de verschillende onderzoeken geholpen. Jullie inzet, enthousiasme en nieuwsgierigheid maakten het ontzettend fijn om met jullie samen te werken.

Maarten, Hanneke, Allan, Veerle, Jasper, Edith, Ingrid en Simone: het bewegingsstoornissen team. Sinds een paar maanden mag ik met jullie samenwerken op de poli, en wat ben ik hier warm ontvangen. Ik zit helemaal op m'n plek! Ik ben ongelooflijk blij met de kansen die gecreëerd zijn, en hoop dat we nog heel wat jaren met elkaar zullen samenwerken. **Collega's fysiotherapie Radboudumc**, wat is het indrukwekkend om te zien wat jullie allemaal opzetten, qua cursussen, onderwijs, en in de kliniek. Bedankt dat ik alles aan jullie kan vragen. Ik ben blij dat ik nu ook bij het team aan deze kant van de gang hoor!

Secretariaat patiëntenzorg en stafsecretariaat, wat was het soms een gepuzzel om alle trainingen organisatorisch rond te krijgen, en toch lukte het jullie altijd! Ik mocht (en gelukkig mag) altijd bij jullie binnenkomen als er iets geregeld moet worden.

LEC collega's, fantastisch om op vrijdag naar het LEC te komen en – onder het genot van een heerlijk kopje koffie – toch wel wat flauwe grapjes te maken. We hebben een fantastisch team, en wat doen we mooie dingen! **Lisa**, partner in crime op de maandag en vrijdag GBAs. **Lise**, partner in crime op de vrijdag GBA, en fotograaf van de prints in dit boekje! Toch wel de leaders of the group. Fantastisch om met jullie samen te werken en te sparren tijdens de gangbeelden. **Wieneke**, wat is het fijn dat je altijd mee wil denken over alle onderwerpen van werk, maar ook alle onderwerpen daarbuiten. **Jip, Fanny, Tim, Desiree, Willeke, Ileen, Thijs, Jacqueline, Annemieke, en Heleen**, heerlijk om in dit team te mogen werken. **Noël**, jouw kennis en kunde over alle aspecten van balans, lopen en matlab hebben mij

in de onderzoeksprojecten veel geholpen. Dankjewel dat je altijd de tijd nam voor uitleg over de balansmaten, scripts, maar ook om even te kletsen. Ik ben blij dat we tijdens mijn promotietraject konden samenwerken!

Lieve **Mendy**, wat kan ik veel doorzettingsvermogen van jou afkijken. Het is fantastisch om te zien hoe jij je weg baant en creëert, en je absoluut niet laat tegenhouden. Je staat altijd voor mij klaar, en jouw eerlijke adviezen en blik hebben mij meer dan eens geholpen.

Lieve **Deborah**, eigenlijk heb jij met ons profielwerkstuk het startsein gegeven voor onze onderzoek carrière! Wat hebben we vanaf de middelbare school veel beleefd en mijlpalen gevierd. Dankjewel dat je altijd luistert, meedenkt, en meehelpt.

Lieve **Inez en Kirsten**: wij waren direct een team toen we samen begonnen aan de opleiding Revalidatiewetenschappen aan de Universiteit Antwerpen. Ondanks dat we later andere windrichtingen op zijn gegaan, rijden we – bijna 10 jaar later - gelukkig vaak heen en weer tussen Nijmegen en Antwerpen. Bedankt voor al jullie support, fijne vriendschap, GINI, en alle mooie uitstapjes! Ik kijk al uit naar onze volgende avonturen.

Lieve **Charlotte**, mede-onderzoeker aan de Universiteit Antwerpen! We hebben veel gekletst, gestudeerd, en gereisd tijdens onze master Neurological Conditions. En gelukkig spreken we elkaar nog regelmatig. Het is superfijn om dan helemaal bij te kletsen en weer vol inspiratie naar huis te gaan!

Lieve **familie**, wat heb ik een geluk met zoveel support. Af en toe moet er zelfs even eentje komen opdraven als proefpersoon, zorgmedewerker, beeldhouwdocente, tuinman en verhuisteam, adviseur timmerman, danwel mede-muziek liefhebber en concertganger. Bedankt voor alle gezellige avonden, uitstapjes, maar bovenal alle interesse en support!

Anne, grote broer waar ik stiekem meer van heb afgekeken dan ik ooit zal toegeven: mijn liefde voor Britse Indie bands, actiefilms en tv-series, rondcrossen op een fiets door de bossen, naar welke middelbare school ik persé moest gaan. Je staat altijd klaar om me te helpen, waar ik als zusje natuurlijk graag misgebruik van maak als er een matlab-script, keuken of een vloertje geïnstalleerd moet worden. Lieve **Nathalie**, het is altijd fijn om met je te kletsen, en vaak ook nog onder het genot van een heerlijk zelfgebakken creatie. Jij weet altijd de goede vragen te stellen en mee te denken. Het is fantastisch om jullie met Melvin te zien. Ik had geen trotsere tante kunnen zijn.

Lieve pap, lieve mam. Ik heb het geluk dat ik écht de beste ouders in de wereld heb. Jullie hebben mij altijd aangemoedigd om mijn eigen weg te gaan, nieuwsgierig te zijn, en vooral te kiezen voor wat ik leuk en belangrijk vind. Tsja; dat betekende voor jullie dan wel een paar keer meehelpen met verhuizen - Groningen (2x), Antwerpen (6x) en Nijmegen (4x). We zijn er ondertussen best aardig in. Jullie hebben Anne en mij de mooiste plekken op de wereld laten zien en zijn onze grootste supporters - al wachtend op de tribunes bij een turnwedstrijd of saxofoon optreden, het halen van mijn VWO, master en dit promotietraject, tot het kopen én klussen in mijn huis en daarbuiten. Jullie zijn mijn belangrijkste sparringpartners, en bij jullie voel ik me altijd thuis.

Curriculum Vitae

Lotte van de Venis was born on May 11th, 1993 in Zwolle, the Netherlands. She graduated from secondary school in 2011 at Nuborgh College Lambert Franckens in Elburg. She obtained her bachelor degree in Rehabilitation Sciences and Physical Therapy from the University of Antwerp in 2017. During this time, she became interested in the field of neurological rehabilitation. In 2019, she obtained her master degree in Rehabilitation Sciences and Physical Therapy: Neurological Conditions. This specialized program was organized as a collaboration between the University of



Antwerp, Catholic University Leuven, University of Hasselt, and the Free University of Brussels. In 2019, she started as a PhD candidate on the Move-HSP project at the Radboud University Medical Centre in Nijmegen. The project was embedded in the Centre of Expertise for Rare and Genetic Movement Disorders. During this time, she continued working as a physical therapist on several research projects (e.g., 'ROADS to Recovery' under supervision of Prof. Dr. Weerdesteyn). In the final year of her PhD, Lotte was awarded the Young Scientist Award at the 4th Neurorehabilitation and Neural Repair conference in Maastricht. Currently, she combines clinical work with research by working as a physical therapist and research fellow in the hereditary movement disorders team at Radboud University Medical Centre in Nijmegen. In addition, she works as a physical therapist in the Gait Expertise Centre of the Sint Maartenskliniek in Nijmegen.

List of publications

This thesis

L. van de Venis, B.P.C. van de Warrenburg, V. Weerdesteyn, B.J.H. van Lith, A.C.H. Geurts, J. Nonnekes. Covid-19 reveals influence of physical activity on symptom severity in hereditary spastic paraplegia. *Journal of Neurology*. 2020 Dec;267(12):3462-3464.

L. van de Venis, B.P.C. van de Warrenburg, V. Weerdesteyn, B.J.H. van Lith, .C.H. Geurts, J. Nonnekes. Improving gait adaptability in patients with hereditary spastic paraplegia (Move-HSP): study protocol for a randomized clinical trial. *Trials*. 2021 Jan 7;22(1):32

L. van de Venis, B.P.C. van de Warrenburg, V. Weerdesteyn, A.C.H. Geurts, J. Nonnekes. Gait-adaptability training in Hereditary Spastic Paraplegia: a randomized clinical trial. *Neurorehabilitation and Neural Repair*, 2023;37(1): 27-36

L. van de Venis, V. Weerdesteyn, A. Konijnenburg, B.P.C. van de Warrenburg, A.C.H. Geurts, Jorik Nonnekes. Increased trunk movements in people with hereditary spastic paraplegia: do these involve balance correcting strategies? *Journal of Neurology*. 2022 Aug;269(8):4264-69

L van de Venis, J. Ormiston, S. M. Bruijn, A.C.H. Geurts, B.P.C. van de Warrenburg, V. Weerdesteyn, N. Keijsers, J. Nonnekes. Are clinical tests and biomechanical gait stability measures able to identify fallers in hereditary spastic paraplegia? *Submitted*

Additional publications

T. Buurke, **L. van de Venis**, N. Keijsers, J. Nonnekes. The effect of walking with reduced trunk motion on dynamic stability in healthy adults. *Gait & Posture* 103 (2023): 113–18.

T. Buurke, **L. van de Venis**, R. den Otter, J. Nonnekes, N. Keijsers. Comparison of ground reaction force and marker-based methods to estimate mediolateral center of mass displacement and margins of stability during walking. *Journal of Biomechanics* 146 (2023): 111415.

J. Nonnekes, M. Tibben, **L. van de Venis**, B.R. Bloem. Incongruent use of compensation strategies may help to diagnose functional freezing of gait. Accepted: *Practical Neurology*

Portfolio

Training activities	Organizers	YEAR	ECTS
Courses and workshops			
Statistics for PhD Candidates using SPSS	Radboud University	2019	2
Project management voor promovendi	Radboud University	2020	2
Introduction to programming using Matlab	Coursera	2020	1.33
Poster Pitching	Radboud University	2020	1
Radboud Talks Pitch	Radboud University	2020	0.33
Donders Graduate School Day	Donders Graduate School	2020 2021 2022 2023	1
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	Radboud University Medical Centre	2021	1.5
OGEN WIJD OPEN	Radboudumc Health Academy	2021	1.66
Scientific Integrity Course	Radboud University Medical Centre	2021	1
Basis Training Course on Gait Analysis and Research with the GRAIL – Operator Level 1	Motek	2021	1
Open Science	Radboud University	2021	1
Design and Illustration	Radboud University	2021	1
Writing Scientific Articles	Radboud University	2022	3.5
Spreken en Presenteren voor Promovendi	Spies&Spreken	2023	0.33
Spring School – Toward @home Motor Rehabilitation after Stroke	CareTech	2023	1.25

Seminars and Lectures		YEAR	ECTS
(Inter) national Symposia and Congresses			
Loop Expertise Centrum Symposium	Nijmegen	2019, 2022	0.25
Poster Sessions Donders	Nijmegen	2020, 2022	0.25
Verder in Beweging Congres	Nijmegen	2021, 2022	0.25
ICMS Event	Nijmegen	2021, 2022	0.25
Movement Disorders Theme Meeting	Nijmegen	2022	0.25
International Society of Posture and Gait (ISPGR)	Montreal	2022	1.5
world congress	Virtual	2023	
Spierziektecongres Spierziekte Nederland	Virtual,	2020	0.25
	Veldhoven	2022	
Society for Movement Analysis Laboratories in the Low Lands (SMALLL) congress	Hasselt	2022	1
Neurorehabilitation and Neural Repair (NNR) congress	Maastricht	2023	1
RehabWeek	Singapore	2023	1.5
Organizing Member			
Society for Movement Analysis Laboratories in the Low Lands (SMALLL) congress	Nijmegen	2023	2
Virtual Webinars			
European Reference Network – Rare Neurological Diseases		2019, 2020, 2021, 2022	0.25
International Society of Posture and Gait (ISPGR)		2020, 2022	0.25
Mobilise-D Consortium		2021, 2022	0.25
European Joint Program – Rare Diseases		2023	
Other			
Labmeeting Radboudumc		2019 - 2023	4
Movement Disorders Meeting Radboudumc		2019 - 2023	2
Meeting Centre of Expertise		2019 - 2023	0.5

Teaching activities		YEAR	ECTS
Supervision of internships			
Supervision of Bachelor student Biomedical Sciences (RU)		2021	1
Supervision of Master student Medicine (RU)		2020, 2021	2
Supervision of Master student Geriatric Physiotherapy (HU)		2021	1
Supervision of student groups			
Minor Moving Questions (RU)		2020	1
Supervision Honors-track Movement Disorders (RU)		2021	1
Minor Movement Science in Rehabilitation (RU)		2022	1
Minor Meet the PhD (RU)		2021, 2022	2

Presentations at (inter)national conferences and seminars

Conferences

July 2022	International Society of Posture and Gait (ISPGR) world congress Title: "Augmented reality gait training does not improve gait adaptability in people with hereditary spastic paraplegia: results of a randomized controlled trial"	Oral
May 2022	Neurorehabilitation and Neural Repair congress Title: "Gait-adaptability training in people with hereditary spastic paraplegia"	Oral + Poster
Oct 2022	HSP Congres – Spierziekte Nederland Loopvaardigheidstraining in HSP: Het move-HSP onderzoek	Oral
July 2023	International Society of Posture and Gait (ISPGR) world congress Title: "How to identify fallers and non-fallers in hereditary spastic paraplegia – an exploratory cohort study"	Poster
Sep 2023	RehabWeek Title: The functional evaluation of a gyroscopic actuated backpack	Poster

Seminars

Mar 2020	Refereer Fysiotherapie Radboudumc Move-HSP: loopvaardigheidstraining bij mensen met HSP	Presentation
May 2021	C-Mill User Group Move-HSP: loopvaardigheidstraining bij mensen met HSP	Presentation
Sep 2022	Loop Expertise Centrum Behandeling van loopproblemen bij mensen met Parkinson en Bewegingsstoornissen	Workshop

Research data management

General information about the data collection

This research followed the applicable laws and ethical guidelines. Research data management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethics and privacy

The chapters within this thesis are based on the results of human studies that were conducted in accordance with the principles of the declaration of Helsinki. All studies met the requirements of the medical ethical committee review – Regio Oost-Nederland, Nijmegen, The Netherlands and were approved by the Board of Directors of the Radboud University Medical Centre. The principles of Good Clinical Practice were followed. All participants provided written informed consent prior to any study procedure. The protocol of the studies described in chapters 3 and 4 was registered at ClinicalTrials.gov [NTC04180098]. The privacy of the participants was warranted through the use of encrypted individual participant codes. The encrypted codes were stored separately from the research data and only accessible to members of the project based on their role. The chapters 2,3,4 and 5 were funded by the Jacques and Gloria Gossweiler Foundation, and chapters 3 and 4 were additionally funded by a grant from Ipsen Pharmaceuticals. The funders had no role in the development or executing of the study protocol, nor in the interpretation or reporting of study outcomes.

FAIR-principles

Findable: Data were stored on the server of the Rehabilitation department at the Radboud University Medical Centre (Q:\Research\102 MOVE-HSP). The paper versions of the case report forms were stored at the Rehabilitation Department (Room M352.04.141) and transferred to the Rehabilitation department archive after publication of the study (Room M653.-1.337).

Accessible: All data is available upon reasonable request by contacting the staff secretary of the Rehabilitation department of rehabilitation at the Radboud University Medical Centre, Nijmegen (NL): (secretariaatstaf.reval@radboudumc.nl).

Interoperable: Documentation with reference to locations and descriptions was added to the data sets to make the data interpretable. Data were stored using the following formats: XLSX (Microsoft Office Excel), .SAV and .SPS (SPSS) and .MAT (Matlab Mathworks, USA). No existing data standards were used such as vocabularies, ontologies or thesauri.

Reusable: Data will be stored for at least fifteen years after finalizing the study. The use of these data in future research is possible after renewed permission by the participants as recorded in their informed consents.

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 recognised 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: <http://www.ru.nl/donders/graduate-school/phd/>

