Improving
walking capacity
after spinal cord
injury

Eline Zwijgers

Improving
walking capacity
after spinal cord
injury

Eline Zwijgers

© E. Zwijgers, 2025

Improving walking capacity
af er spinal cord injury

Proefschrif

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 17 januari 2025
om 12:30 uur precies

door

Eline Zwijgers
geboren op 24 september 1995
te Utrecht

Promotoren
Prof. dr. A.C.H. Geurts
Prof. dr. N.L.W. Keijsers

Copromotor
Dr. I.J.W. van Nes (Sint Maartenskliniek)

Manuscriptcommissie
Prof. dr. M. de Kleuver (voorzitter)
Prof. dr. ing. H. Vallery (RWTH Aachen University, Duitsland)
Prof. dr. J.H. van Dieën (Vrije Universiteit Amsterdam)

Table of contents

Chapter 1

General introduction
and outline of the thesis

1

General introduction

1

Walking is one of the fundamental activities of daily living and allows us to move around and connect with our environment. Beyond mere transportation from point A to B, it plays an important role in numerous everyday tasks, including household, social, and leisure activities. Consequently, walking plays a pivotal role in ensuring independence,[1-3] promoting social interaction,[4,5] and enhancing overall quality of life.[4-6] Moreover, it serves as a cornerstone in sustaining physical activity, thereby maintaining general health.[7,8]

Walking capacity

Successful walking in everyday life requires an optimal level of walking capacity. Walking capacity refers to a person's ability to walk and comprises, according to the tripartite model of Balasubramanian, three fundamental elements: stepping, dynamic stability, and walking adaptability (see Figure 1).[9]
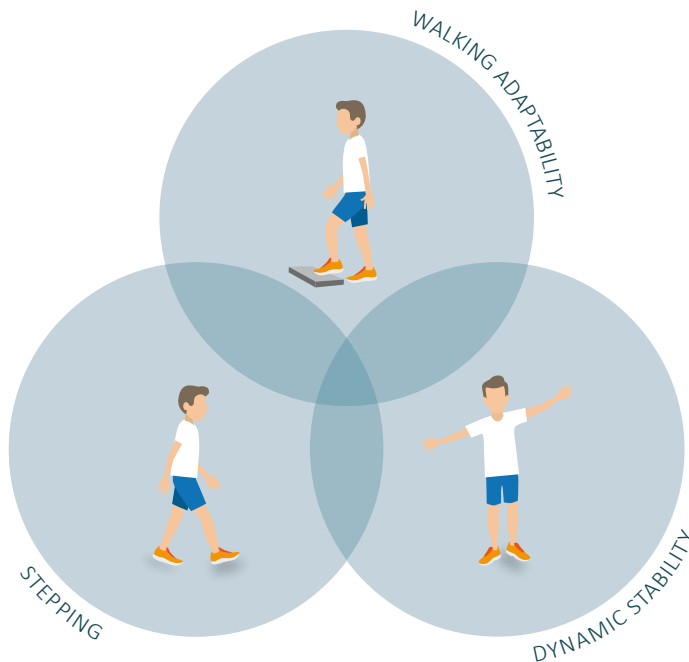

Figure 1 Theoretical framework illustrating the three fundamental elements essential for achieving an optimal level of walking capacity.[9]

1

Stepping

Stepping refers to the ability to use two legs, alternately, to progress forward. It requires sufficient leg motor control, which involves interactions between the central nervous system and the skeletal muscles through the peripheral nervous system. Signals from the brain are transmitted through motor pathways to initiate and regulate leg movements. Various muscles in the legs are activated in a coordinated manner to execute a step. Sensory feedback from muscle proprioceptors provides information about the position, movement, and soft-tissue tension of the legs, playing a crucial role in real-time adjustments to the leg movements.[10]

Dynamic stability

Dynamic stability refers to the ability of the body to maintain balance and equilibrium during walking. It requires adequate balance control, which involves coordination of the center of mass (COM) relative to the changing base of support (BOS). The brain estimates the COM and BOS by integrating sensory information from three main modalities: the proprioceptive, visual, and vestibular systems.[11] The relation between the COM and BOS is typically modulated by three main strategies: the hip, ankle, and foot placement strategy.[12,13] The ankle strategy involves modulation of the ankle moment to displace the center of pressure in order to control the COM within a given BOS.[13] The hip strategy involves rotations of body segments with regard to one another to either counteract or assist gravity in angular accelerations of the body segments in order to control the COM in relation to the BOS.[14,15] The foot placement strategy involves adjustments to the BOS by controlling the location and timing of foot placement.[12,13]

Walking adaptability

Walking adaptability refers to the ability of an individual to modify his/her walking pattern in response to environmental challenges. It involves the ability to adjust various aspects of walking, such as step length, step width, walking speed, and foot placement, to accommodate different terrains, obstacles, or unexpected disruptions of the gait pattern or the dynamic stability.[16] For example, when walking on an uneven surface, the body needs to make rapid adjustments to maintain balance and prevent stumbling. Similarly, when navigating through crowded areas, quick changes in direction and pace may be necessary. Additionally, unexpected disturbances such as a sudden push or slip necessitate immediate adaptive responses to regain stability and prevent a fall. Walking adaptability requires a complex interplay between leg motor control and balance control to make real-time adjustments while walking.[17]

Spinal cord injury

While most individuals have an optimal level of walking capacity, this capacity can be affected by many pathologies. An example of a condition affecting walking capacity is spinal cord injury (SCI).

SCI is characterized by damage to the spinal cord, leading to impairments of motor, sensory, and/or autonomic functions. The global incidence of SCI is estimated to range between 250,000 and 500,000 cases annually.[18] In the Netherlands, the estimated total number of

persons living with SCI falls between 10,000 and 15,000.[19] Predominantly affecting males, the SCI population maintains a global male-to-female ratio of 3:1.[20,21] Trauma to the spinal cord accounts for approximately 35-60% of the injuries,[22-24] stemming from various sources such as motor vehicle accidents, falls, acts of violence, and sports-related incidents.[25] On the other hand, non-traumatic injuries arise from (gradual) internal damage to the spinal cord, for instance due to spinal column degeneration, infections, and tumors.[26] SCI can result in various levels and severities of impairment, depending on the location and extent of the damage to the spinal cord.

Level and severity of injury

Injury to the spinal cord may occur at various locations. Generally, higher lesion levels lead to more severe motor and sensory impairments.[27] For example, injury to the lumbar spine affects predominantly leg and autonomic functions of bladder and bowel, resulting in paraplegia and decreased control of bladder, bowel, and sexual functions. Conversely, injury to the cervical spine also affects arm and chest muscles, leading to concomitant tetraplegia and respiratory problems.

The degree to which muscles below the injury are affected depends on the extent of spinal cord damage. Partial damage results in incomplete loss of sensory, motor and/or autonomic functions, defined as an incomplete lesion.[28] Individuals with incomplete SCI commonly experience muscle weakness, impaired muscle coordination, altered muscle tone, and loss of sensation below the injury level.[29] A complete interruption of the spinal cord leads to the total loss of both sensation and control over movement, defined as a complete lesion.[28] Individuals with complete SCI experience paralysis in the affected muscles and complete loss of sensation below the injury site.[28]

Classification of spinal cord injury

The classification of SCI follows the International Standards for Neurological Classification of SCI (ISNCSCI) established by the American Spinal Injury Association (ASIA).[30] This classification relies on the ASIA Impairment Scale (AIS) score and the neurological level of the injury (see Figure 2). The AIS distinguishes between several types, ranging from AIS A to AIS E. AIS A indicates a complete loss of both motor and sensory functions in the sacral segments S4-5. AIS B signifies complete motor loss, but incomplete sensory loss below the lesion level, including the sacral segments S4-5. AIS C and D indicate incomplete motor and sensory losses, with the AIS score depending on the degree of preserved motor function below the lesion level. AIS E signifies normal motor and sensory function after recovery from prior deficits. Determining the neurological level of injury involves identifying the most caudal segment of the spinal cord with intact sensation and antigravity muscle strength, provided normal sensory and motor function above that level.[30]

1

ASIA Impairment Scale

A
Motor complete
Sensory complete

B
Motor complete
Sensory incomplete

C
D
Motor incomplete
Sensory incomplete

E
Normal motor and
sensory function

Neurological level

High
Cervical spine
C1-C8

Mid
Thoracic spine
T1-T12

Low
Lumbar spine
L1-L5
Sacrum
S1-S5
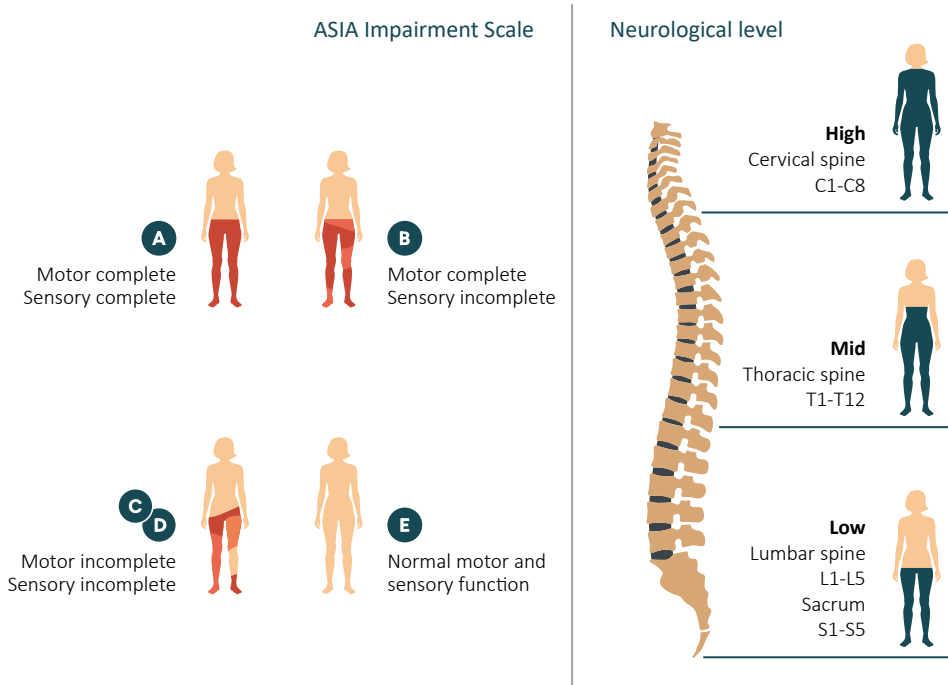
Figure 2 Schematic representation of the classification of spinal cord injury (SCI) following the International Standards for Neurological Classification of SCI (ISNCSCI) established by the American Spinal Injury Association (ASIA). This classification relies on the ASIA Impairment Scale (AIS) score and the neurological level of the injury.

Rehabilitation after spinal cord injury

Rehabilitation plays a crucial role following SCI, aiming to improve functional recovery, prevent secondary complications, and improve quality of life. Rehabilitation can be divided into three phases: acute, subacute, and chronic. While the exact timing of these phases lacks consensus, during the acute and subacute phases spontaneous neurological recovery is still possible, whereas during the chronic phase this neurological recovery has plateaued.[31]

The acute phase focuses on stabilizing the patient's neurological state, preventing complications, and initiating early mobilization.[27] The subacute phase involves intensive interdisciplinary interventions to optimize functional recovery, aiming to promote independence and prepare for discharge.[27] Functional recovery may be the result of either 'restitution' or 'substitution' of function. Restitution of function involves the recovery of sensorimotor functions

comparable to preinjury movement patterns, whereas substitution of function involves the use of compensatory movement patterns, behaviors, and/or use of assistive devices to regain functioning.[32] During the acute and subacute phases, individuals with SCI show functional improvements due to both mechanisms.[33]

The chronic phase addresses the long-term needs and challenges of living with SCI. The most important rehabilitation goal during this phase is enhancing and maintaining independent mobility.[27] As the neurological recovery has plateaued in the chronic phase,[34] rehabilitation interventions mainly depend on substitution of function, including the learning of adaptive balance and walking strategies and the use of assistive devices. Furthermore, it is important to note that the suitable rehabilitation approach to enhance mobility varies between motor *incomplete* and motor *complete* SCI, given the disparity in preserved functions between these groups.

Motor *incomplete* spinal cord injury

While many individuals with motor incomplete SCI retain the ability to walk, their walking capacity is often compromised.[29] Rehabilitation interventions aimed at enhancing walking capacity in this group concentrate on either stepping, dynamic stability, walking adaptability, or a combination of these elements. Currently, in clinical practice, most rehabilitation interventions for people with motor incomplete SCI primarily focus on stepping to improve walking capacity. These interventions, categorized as locomotor interventions, involve repetitive steady-state walking. Examples of these interventions include overground or treadmill-based gait training either with or without body-weight-support.[35,36] Additional examples include technological interventions such as robot-assisted gait training.[37] This form of training assists stepping cycles by providing body weight support and facilitating leg movements. Moreover, overground, treadmill-based or robot-assisted gait training can be supplemented with functional electrical stimulation to induce muscle contractions.[38] While these interventions exhibit potential for enhancing walking capacity, no single intervention has demonstrated superiority over the others.[35,36]

In the past decade, there has been a notable shift of rehabilitation interventions towards emphasizing walking adaptability.[39-45] This shift is due to an increased emphasis on tailoring training to real-life walking scenarios. Walking adaptability training aims to enhance an individual's ability to adjust his/her walking pattern to various environmental circumstances. This training can be conducted overground by manually placing targets and obstacles.[41] However, advancements in technology have enabled the implementation of walking adaptability training on treadmills within virtual reality environments.[42,43,45] These innovative treadmills enable users to interact with and respond to a simulated virtual environment that replicates real-life walking scenarios, providing a safe learning environment. Although walking adaptability training has shown promising results in people with motor incomplete SCI,[45] it remains uncertain whether this type of training is more effective than conventional locomotor interventions.

1

Addressing dynamic stability in individuals with motor incomplete SCI is also crucial. However, interventions specifically targeting dynamic stability are lacking.[46] The challenge lies in separating training for dynamic stability from walking adaptability, given their interconnected reliance on balance control. Perturbation-based balance training is one example that targets dynamic stability while also addressing walking adaptability.[47] Furthermore, research investigating balance control during walking within this population is limited,[48-53] resulting in limited knowledge about dynamic stability in motor incomplete SCI.

Motor *complete* spinal cord injury

Individuals with motor complete SCI have no preserved motor function below the injury level, leading to a permanent loss of walking capacity and reliance on wheelchairs for mobility. Over the past decade, wearable exoskeletons have emerged as potential assistive mobility devices for this population.[54] These motorized orthoses offer the ability for individuals with motor complete SCI to maintain a standing position and facilitate stepping, both within the clinical setting and beyond.

Although exoskeletons enable individuals with motor complete SCI to regain stepping capacity, most exoskeletons do not contribute to dynamic stability, placing this responsibility on users.[54] However, people with motor complete SCI lack some or all proprioceptive information below the injury level to estimate the COM and BOS. Furthermore, they are limited or unable to use the hip, ankle, and/or foot placement strategy. Consequently, to maintain dynamic stability while using an exoskeleton, individuals with motor complete SCI often rely on e.g. crutches or a walker to control their COM-to-BOS relationship. Moreover, they may employ sensory reweighting, relying more on alternative sensory modalities instead of proprioceptive information to estimate their COM and BOS.[55-57] One potential solution to help individuals with motor complete SCI to enhance dynamic stability involves compensating for the loss of proprioceptive information through sensory substitution. This principle, extensively investigated among various patient groups who lack essential sensory input,[58-61] has remained unexplored in individuals with motor complete SCI controlling an exoskeleton.

In addition to dynamic stability challenges, current exoskeletons lack walking adaptability, as they operate based on predetermined trajectories initiated by users.[54] Consequently, these devices do not adapt to environmental changes in daily-life scenarios, limiting their functional use for people with motor complete SCI.[62]

1

Outline of the thesis

The aim of this thesis is to explore possibilities for improving walking capacity in individuals with SCI. The thesis is divided into two parts. Part I focuses on individuals with motor *incomplete* SCI, while part II centers on those with motor *complete* SCI.

Part I comprises three comprehensive chapters. **Chapter 2** addresses a randomized controlled trial to assess the efficacy of walking adaptability training compared to a similarly dosed conventional locomotor and strength training for improving walking capacity in people with motor incomplete SCI. **Chapter 3** builds upon the insights gained from this trial, presenting the follow-up findings of the randomized controlled trial, as it was a priori designed as a two-armed cross-over study, allowing to examine the effect of two consecutive intervention periods and possible sequence effects. **Chapter 4** delves into balance control during walking in people with motor incomplete SCI. More specifically, this chapter investigates if the foot placement strategy is impaired in people with motor incomplete SCI.

Part II consists of two chapters, shifting the focus to individuals with motor complete SCI. **Chapter 5** addresses the effect of limited visual and/or auditory information on exoskeleton control in people with motor complete SCI, while **chapter 6** investigates the effect of sensory feedback on exoskeleton control in individuals with motor complete SCI.

Finally, **chapter 7** summarizes and discusses the findings and implications showed throughout this thesis, while **chapter 8** provides a summary in Dutch.

1

References

1.   Shinkai S, Watanabe S, Kumagai S, et al. Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing. 2000;29:441–446.

2.   Shimada H, Suzuki T, Suzukawa M, et al. Performance-based assessments and demand for personal care in older Japanese people: A cross-sectional study. BMJ Open. 2013;3:1–7.

3.   Verghese J, Wang C, Holtzer R. Relationship of clinic based gait speed measurement to limitations in community based activities in older adults. Arch Phys Med Rehabil. 2011;92:1-844–846.

4.   Ekström H, Dahlin-Ivanoff S, Elmståhl S. Effects of walking speed and results of timed get-up-and-go tests on quality of life and social participation in elderly individuals with a history of osteoporosis-related fractures. J Aging Health. 2011;23:1379–1399.

5.   Ada L, Dean CM, Lindley R, Lloyd G. Improving community ambulation after stroke: The AMBULATE trial. BMC Neurol. 2009;9:1–6.

6.   Schmid A, Duncan PW, Studenski S, et al. Improvements in speed-based gait classifications are meaningful. Stroke. 2007;38:2096–2100.

7.   Cesari M, Kritchevsky SB, Penninx BWHJ, et al. Prognostic value of usual gait speed in well-functioning older people- Results from the health, aging and body composition study. J Am Geriatr Soc. 2005;53:1675–1680.

8.   Studenski S, Perera S, Patel K, et al. Gait Speed and Dismobility in Older Adults. Arch Phys Med Rehabil. 2015;96:1641–1645.

9.   Balasubramanian CK, Clark DJ, Fox EJ. Walking Adaptability after a Stroke and Its Assessment in Clinical Settings. Stroke Res Treat. 2014;2014:591013.

10. McMahon TA. Muscles, Reflexes, and Locomotion. Princeton University Press; 1984.

11. Bruijn SM, Van Dieën JH. Control of human gait stability through foot placement. J R Soc Interface. 2018;15:1–11.

12. Reimann H, Fettrow TD, Thompson ED, Agada P, McFadyen BJ, Jeka JJ. Complementary mechanisms for upright balance during walking. PLoS One. 2017;12:1–16.

13. Reimann H, Fettrow T, Jeka JJ. Strategies for the control of balance during locomotion. Kinesiology Review. 2018;7:18–25.

14. Vlutters M, van Asseldonk EHF, van der Kooij H. Reduced center of pressure modulation elicits foot placement adjustments, but no additional trunk motion during anteroposterior-perturbed walking. J Biomech. 2018;68:93–98.

15. Curtze C, Hof AL, Postema K, Otten B. The relative contributions of the prosthetic and sound limb to balance control in unilateral transtibial amputees. Gait Posture. 2012;36:276–281.

16. Weerdesteyn V, Hollands KL, Hollands MA. Gait adaptability. 1st ed. Elsevier B.V.; 2018.

17. van Duijnhoven H. The challenges of dynamic balance & gait for people after stroke (dissertation). Nijmegen (NL): Donders Institute for Brain, Cognition and Behaviour, Radboud Univerisity Medical Center; 2019.

18. World Health Organization. Spinal cord injury. 2013.

19. Nijendijk JHB, Post MWM, Van Asbeck FWA. Epidemiology of traumatic spinal cord injuries in the Netherlands in 2010. Spinal Cord. 2014;52:258–263.

20. Bourguignon L, Tong B, Geisler F, et al. International surveillance study in acute spinal cord injury confirms viability of multinational clinical trials. BMC Med. 2022;20:1–18.

21.   National Spinal Cord Injury Statistical Center. Facts and Figures at a Glance. 2020;30:304–305.

22.   Ge L, Arul K, Ikpeze T, Baldwin A, Nickels JL, Mesfin A. Traumatic and Nontraumatic Spinal Cord Injuries. World Neurosurg. 2018;111:e142–e148.

23.   Dwarslaesie Organisatie Nederland. Dwarlaesie in cijfers. Dwarslaesie magazine. 2018:7.

24.   Gedde MH, Lilleberg HS, Aßmus J, Gilhus NE, Rekand T. Traumatic vs non-traumatic spinal cord injury: A comparison of primary rehabilitation outcomes and complications during hospitalization. Journal of Spinal Cord Medicine. 2019;42:695–701.

25.   Chen Y, Tang Y, Vogel LC, Devivo MJ. Causes of spinal cord injury. Med Today. 2002;3:7.

26.   Müller-Jensen L, Ploner CJ, Kroneberg D, Schmidt WU. Clinical Presentation and Causes of Non-traumatic Spinal Cord Injury: An Observational Study in Emergency Patients. Front Neurol. 2021;12:1–12.

27.   Nas K, Yazmalar L, Şah V, Aydin A, Öneş K. Rehabilitation of spinal cord injuries. World J Orthop. 2015;6:8–16.

28.   van Asbeck FWA. Handboek dwarslaesierevalidatie. Bohn Stafleu van Loghum; 2006.

29.   Barbeau H, Nadeau S, Garneau C. Physical Determinants, Emerging Concepts, and Training Approaches in Gait of Individuals with Spinal Cord Injury. J Neurotrauma. 2006;23:571–585.

30.   Kirshblum SC, Waring W, Biering-Sorensen F, et al. Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. Journal of Spinal Cord Medicine. 2011;34:547–554.

31.   Burns AS, Marino RJ, Flanders AE, Flett H. Clinical diagnosis and prognosis following spinal cord injury. In: Handbook of Clinical Neurology.Vol 109. 1st ed. Elsevier B.V.; 2012:47–62.

32.   Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensationg" mean in patients following stroke? Neurorehabil Neural Repair. 2009;23:313–319.

33.   Curt A, Van Hedel HJA, Klaus D, Dietz V. Recovery from a spinal cord injury: Significance of compensation, neural plasticity, and repair. J Neurotrauma. 2008;25:677–685.

34.   Burns GT, Deneweth Zendler J, Zernicke RF. Validation of a wireless shoe insole for ground reaction force measurement. J Sports Sci. 2019;37:1129–1138.

35.   Morawietz C, Moffat F. Effects of locomotor training after incomplete spinal cord injury: A systematic review. Arch Phys Med Rehabil. 2013;94:2297–2308.

36.   Mehrholz J, Harvey LA, Thomas S, Elsner B. Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. Spinal Cord. 2017;55:722–729.

37.   Nam KY, Kim HJ, Kwon BS, Park JW, Lee HJ, Yoo A. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. J Neuroeng Rehabil. 2017;14:1–13.

38.   Karamian BA, Siegel N, Nourie B, et al. The role of electrical stimulation for rehabilitation and regeneration after spinal cord injury. Journal of Orthopaedics and Traumatology. 2022;23.

39.   Houdijk H, van Ooijen MW, Kraal JJ, et al. Assessing gait adaptability in people with unilateral amputation on an instrumented treadmill with a projected visual context. Phys Ther. 2012;92:1452–1460.

40.   Heeren A, van Ooijen MW, Geurts ACH, 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;45:616–622.

41.   Yang JF, Musselman KE, Livingstone D, et al. Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial. Neurorehabil Neural Repair. 2014;28:314–324.

1

42. Timmermans C, Roerdink M, Meskers CGM, Beek PJ, Janssen TWJ. Walking-adaptability therapy after stroke: results of a randomized controlled trial. Trials. 2021;22:923.

43. de Rooij IJM, van de Port IGL, Punt M, et al. Effect of Virtual Reality Gait Training on Participation in Survivors of Subacute Stroke: A Randomized Controlled Trial. Phys Ther. 2021;101.

44. Venis L Van De, Warrenburg B Van De, Weerdesteyn V, Geurts ACH, Nonnekes J. Gait-Adaptability Training in People With Hereditary Spastic Paraplegia : A Randomized Clinical Trial. Neurorehabil Neural Repair. 2023;37:27–36.

45. van Dijsseldonk RB, de Jong LAF, Groen BE, Vos-van der Hulst M, Geurts ACH, Keijsers NLW. Gait stability training in a virtual environment improves gait and dynamic balance capacity in incomplete spinal cord injury patients. Front Neurol. 2018;9:963.

46. Yang JF, Musselman KE. Training to achieve over ground walking after spinal cord injury: A review of who, what, when, and how. Journal of Spinal Cord Medicine. 2012;35:293–304.

47. Unger J, Chan K, Lee JW, et al. The Effect of Perturbation-Based Balance Training and Conventional Intensive Balance Training on Reactive Stepping Ability in Individuals With Incomplete Spinal Cord Injury or Disease: A Randomized Clinical Trial. Front Neurol. 2021;12:1–13.

48. Day K V., Kautz SA, Wu SS, Suter SP, Behrman AL. Foot placement variability as a walking balance mechanism post-spinal cord injury. Clinical Biomechanics. 2012;23:1–7.

49. Lemay JF, Duclos C, Nadeau S, Gagnon D, Desrosiers É. Postural and dynamic balance while walking in adults with incomplete spinal cord injury. Journal of Electromyography and Kinesiology. 2014;24:739–746.

50. Cornwell T, Woodward J, Ochs W, Gordon KE. Stabilization Strategies for Fast Walking in Challenging Environments With Incomplete Spinal Cord Injury. Frontiers in Rehabilitation Sciences. 2021;2:1–14.

51. Arora T, Musselman KE, Lanovaz JL, et al. Reactive balance responses to an unexpected slip perturbation in individuals with incomplete spinal cord injury. Clinical Biomechanics. 2020;78:105099.

52. Ochs WL, Woodward J, Cornwell T, Gordon KE. Meaningful measurements of maneuvers: People with incomplete spinal cord injury 'step up' to the challenges of altered stability requirements. J Neuroeng Rehabil. 2021;18:1–13.

53. Matsubara JH, Wu M, Gordon KE. Metabolic cost of lateral stabilization during walking in people with incomplete spinal cord injury. Gait Posture. 2015;41:646–651.

54. Lee H, Ferguson PW, Rosen J. Lower limb exoskeleton systems-overview. In: Wearable Robotics: Systems and Applications. INC; 2020:207–229.

55. Ionta S, Villiger M, Jutzeler CR, Freund P, Curt A, Gassert R. Spinal cord injury affects the interplay between visual and sensorimotor representations of the body. Sci Rep. 2016;6.

56. Lee GE, Bae H, Yoon TS, Kim JS, Yi TI, Park JS. Factors that influence quiet standing balance of patients with incomplete cervical spinal cord injuries. Ann Rehabil Med. 2012;36:530–537.

57. Lemay JF, Gagnon D, Duclos C, Grangeon M, Gauthier C, Nadeau S. Influence of visual inputs on quasi-static standing postural steadiness in individuals with spinal cord injury. Gait Posture. 2013;38:357–360.

58. Crea S, Cipriani C, Donati M, Carrozza MC, Vitiello N. Providing Time-Discrete Gait Information by Wearable Feedback Apparatus for Lower-Limb Amputees: Usability and Functional Validation. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2015;23:250–257.

59. Crea S, Edin BB, Knaepen K, Meeusen R, Vitiello N. Time-Discrete Vibrotactile Feedback Contributes to Improved Gait Symmetry in Patients With Lower Limb Amputations: Case Series. Phys Ther. 2017;97:198–207.

1

60. Vimal AK, Godiyal AK, Singh U, Bhasin S, Joshi D. Transfemoral amputee's limit of stability and sway analysis during weight shifting exercise with a vibrotactile feedback system. Somatosens Mot Res. 2019;36:31–41.

61. Raveh E, Friedman J, Portnoy S. Evaluation of the effects of adding vibrotactile feedback to myoelectric prosthesis users on performance and visual attention in a dual-task paradigm. Clin Rehabil. 2018;32:1308–1316.

62. van Dijsseldonk RB, van Nes IJW, Geurts ACH, Keijsers NLW. Exoskeleton home and community use in people with complete spinal cord injury. Sci Rep. 2020;10:1–8.

Part I

Rehabilitation approaches to
improve walking capacity after motor
incomplete spinal cord injury

Chapter 2

Efficacy of walking adaptability training on walking capacity in ambulatory people with motor incomplete spinal cord injury:
A multicenter pragmatic randomized controlled trial

Eline Zwijgers
Rosanne B. van Dijsseldonk
Marije Vos-van der Hulst
Juha M. Hijmans
Alexander C.H. Geurts
Noël L.W. Keijsers

2

Abstract

Background

Balance and walking capacity are often impaired in people with motor incomplete spinal cord injury (iSCI), frequently resulting in reduced functional ambulation and participation. This study aimed to assess the efficacy of walking adaptability training compared to similarly dosed conventional locomotor and strength training for improving walking capacity, functional ambulation, balance confidence, and participation in ambulatory people with iSCI.

Methods

We conducted a two-center, parallel-group, pragmatic randomized controlled trial. Forty-one people with iSCI were randomized to six weeks of (i) walking adaptability training (11 hours of GRAIL training - a treadmill in a virtual reality environment) or (ii) conventional locomotor and strength training (11 hours of treadmill training and lower-body strength exercises). The primary measure of walking capacity was maximal walking speed, measured with an overground 2-minute walk test. Secondary outcome measures included the Spinal Cord Injury-Functional Ambulation Profile (SCI-FAP), the Activities-specific Balance Confidence (ABC) scale, and the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P).

Results

No significant difference in maximal walking speed between the walking adaptability (n = 17) and conventional locomotor and strength (n = 18) training groups was found six weeks after training at follow-up (-0.05 m/s; 95% CI = -0.12 − 0.03). In addition, no significant group differences in secondary outcomes were found. However, independent of intervention, significant improvements over time were found for maximal walking speed, SCI-FAP, ABC, and USER-P restrictions scores.

Conclusion

Our findings suggest that walking adaptability training may not be superior to conventional locomotor and strength training for improving walking capacity, functional ambulation, balance confidence, or participation in ambulatory people with iSCI.

2

Background

Although most people with motor incomplete spinal cord injury (iSCI) can walk after inpatient rehabilitation,[1] the quality and efficiency of ambulation are affected.[2] People with iSCI generally walk at a lower preferred speed[3] and have an increased risk of falling.[4-6] Furthermore, impaired walking capacity often restricts people with iSCI in the performance of mobility-related daily life activities (i.e., functional ambulation)[7] and their participation in the community (e.g., work, household, and social activities).[8] Hence, an important rehabilitation goal of people with iSCI is to improve their walking capacity to successfully ambulate in their home and community settings.[9]

Successful ambulation in daily life requires stepping, dynamic stability, and walking adaptability.[10] Stepping is necessary to progress forward, while dynamic stability ensures an upright body position in space through control of the center of mass with respect to the changing base of support. Walking adaptability is the ability to modify the gait pattern when environmental circumstances change, encompassing both proactive and reactive gait adaptations.[11] Proactive adaptations, triggered by visual stimuli, entail activities such as walking on irregular terrain or navigating through crowded areas, while reactive adaptations involve responses to mechanical perturbations, such as stumbling over a doorstep or withstand a strong crosswind. Currently, iSCI outpatient rehabilitation interventions mainly focus on the aspect of stepping to improve walking capacity.[12,13] Examples of such locomotor interventions are overground or treadmill-based gait training with or without body-weight-support, as well as robotic-assisted gait training; either with or without manual assistance and/or functional electrical stimulation.[12,13] In clinical practice, these interventions are usually combined with lower-body strength exercises to enhance muscle strength and the overall effectiveness of the gait training. All these types of interventions show some potential for improving walking speed but without established supremacy over another.[12,13]

In recent years, walking adaptability training has emerged as a potential rehabilitation intervention for people with iSCI, as it is expected to enhance walking capacity beyond the benefits of conventional interventions.[14,15] Walking adaptability training targets the improvement of walking capacity by provoking gait adaptations through precision stepping, obstacle avoidance, and/or reacting to perturbations.[15-18] In the work of van Dijsseldonk and colleagues,[15] ambulatory people with iSCI improved walking speed, dynamic stability, and balance confidence after six weeks of walking adaptability training in a virtual environment. This training increased walking speed by a similar amount as reported in the literature for conventional interventions.[19,20] However, the number of training sessions for these conventional interventions was more than three times higher compared to the walking adaptability training. In a randomized controlled trial conducted by Yang and colleagues,[14] walking adaptability training (consisting of overground walking over obstacles and targets) was compared with treadmill-based gait training. This study reported significantly more improvement in endurance after treadmill-based gait training, along with similar improvements in walking

2

speed, functional ambulation, and balance confidence for both interventions. However, it should be noted that the interventions were not directly comparable in terms of the number of steps per session, favoring treadmill-based gait training.[14] Previous research has indicated that a higher dosage (i.e., the number of training sessions as well as the number of steps per session) can positively influence the training effect.[21] Hence, a study is needed to determine the efficacy of walking adaptability training versus conventional training for improving walking capacity, ensuring comparability in dosage between the interventions.

The primary objective of this pragmatic randomized controlled trial was to assess the efficacy of walking adaptability training compared to similarly dosed conventional locomotor and strength training for improving walking capacity in ambulatory people with iSCI. Walking capacity was operationalized as walking speed due to its established correlation with various functional ambulation skills, such as walking around curves, avoiding obstacles, and performing dual tasks.[22] We hypothesized that walking adaptability training would improve walking speed more than conventional locomotor and strength training.[14,15,19,20] In addition, we measured the effects of both interventions on secondary outcome measures, including functional ambulation, balance confidence, and participation in the community.

Methods

Study design

A two-center, parallel-group, pragmatic randomized controlled trial was conducted at the Sint Maartenskliniek (SMK) and the University Medical Center Groningen (UMCG) in the Netherlands (trial register identifier: Dutch Trial Register; Effect of GRAIL training in incomplete spinal cord injury). To ensure that both groups could benefit from the alternative training approach as well, the initial group comparison (including a follow-up period without intervention) was extended with a crossover design. The current article specifically focuses on the initial randomized controlled trial of the overall study design. The study was approved by the regional medical ethics committee Oost-Nederland (NL69379.091.19) and by the internal review board of the Sint Maartenskliniek. All research activities were carried out in accordance with the guidelines and regulations of the Medical Research involving Human Subjects Act (WMO) and the Netherlands Code of Conduct for Research Integrity. Furthermore, the study was reported according to the consolidated standards of reporting trials.

Participants

People with iSCI were recruited by their rehabilitation physician during visits to the outpatient clinic, including check-up appointments or self-initiated appointments to discuss complaints regarding their walking capacity. The following inclusion criteria were used: 1) being diagnosed with motor incomplete spinal cord injury from a traumatic or non-traumatic origin (American spinal injury association Impairment Scale (AIS) C or D), 2) minimally six months post-injury, 3) ability to walk at least ten meters with or without a walking aid, but without physical

2

assistance, 4) ability to walk at a comfortable speed between 0.3 and 1.0 m/s, 5) having a rehabilitation goal to improve walking capacity, 6) willingness and ability to cancel other interventions (e.g., physiotherapy, botulinum toxin injections in the leg muscles) aimed at improving walking capacity during the study period, and 7) age ≥ 18 years. Exclusion criteria were: 1) other impairments of the nervous system or lower limbs that might affect walking or balance, 2) expected interference with one's activity level by planned events such as an operation or moving, 4) walking adaptability training within the previous six months, and 5) insufficient understanding or mastery of the Dutch language. Participant characteristics (demographic, injury-related, and mobility-related) were registered at baseline. Demographic characteristics included age, weight, height, and sex. Injury-related characteristics included AIS, level of injury, time post injury, and cause. Furthermore, mobility-related characteristics included the Functional Ambulation Categories and the use of walking aids outdoors and/or ankle foot orthoses.

Procedures

Participants were randomly assigned to receive either walking adaptability or conventional locomotor and strength training in a 1:1 allocation ratio. The randomization process was performed using a computer-generated randomization schedule deployed in Matlab (R2019b, MathWorks). To ensure balanced group assignments, the schedule employed permuted blocks of varying sizes (4 and 6). Group allocation was revealed by the Matlab program only after participant enrollment. The investigators enrolled and assigned participants to their respective interventions. Participants, physiotherapists, and investigators were not blinded to group allocation due to the nature of the intervention. In addition, assessors were not blinded due to practical and organizational constraints. The assessment of the primary outcome measure occurred at three time points: baseline, immediately post-intervention, and at follow-up. The follow-up assessment took place at six weeks post-intervention and served as our primary endpoint. The assessment of secondary outcome measures was conducted at baseline and during the follow-up assessment.

Interventions

Both interventions consisted of 11 training sessions of 60 minutes over a period of six weeks (on average two training sessions per week). The training interventions were designed to contain approximately 20 minutes of active walking to ensure a similar number of steps per session for both interventions. We chose a duration of 20 minutes based on clinical experience, as 20 minutes of walking is physically demanding for most iSCI individuals with limited walking capacity. The number of steps taken during a session was monitored with a pedometer (Polar A360; Polar Electro (SMK) and Fitbit Zip; Fitbit, Inc. (UMCG)). The level of physical tiredness before and after each training session was assessed using a 15-point scale ranging from 6 to 20 (similar to the Borg Rating of Perceived Exertion scale), where 6 represented 'not tired at all' and 20 indicated 'fully tired'. The perceived intensity of each training session was quantified as the difference between the physical tiredness ratings recorded at the end and

2

the beginning of the session. Adherence was determined by counting the number of sessions completed by each individual. Participants were allowed to make up for missed sessions with a maximum of two sessions, which occasionally extended the training period to 7 weeks. Participants' experience was assessed with a visual analogue scale measuring the subjective satisfaction of the received intervention on a range from 0 to 10, with higher scores indicating more satisfaction. Participants completed the visual analogue scale directly after finishing the intervention.

Walking adaptability training

The walking adaptability training was conducted using the Gait Real-time Analysis Interactive Lab (GRAIL; Motek Medical B.V.). The GRAIL incorporates an instrumented split-belt treadmill with adjustable pitch and sway, a ten-camera motion capture system (Vicon Motion Systems), and a 180° semi-cylindrical screen for the projection of synchronized virtual reality environments. The walking adaptability training was conducted by a physiotherapist certified to work with the GRAIL. For safety reasons, participants wore a safety harness attached to a rail on the ceiling without body weight support. During a training session, multiple walking adaptability tasks were performed, including precision stepping, obstacle avoidance, and/or reacting to perturbations. Precision stepping involved precise and accurate foot placement. Obstacle avoidance required participants to effectively maneuver around or step over virtually projected obstacles. Reacting to perturbations involved exposing participants to unexpected disturbances, such as sudden surface pitch or sway. The physiotherapist selected the tasks based on the participant's goals and gradually increased the training complexity according to the participant's abilities. Based on a prior study[15] and clinical experience, we learned that participants typically are able to engage in about 20 minutes of walking adaptability tasks during a 60-minute session. Therefore, the physiotherapists were instructed to provide approximately 20 minutes of walking adaptability tasks. In the remaining time available during the session, physiotherapists could incorporate standing balance tasks, including weight shifting and/or performing foot clearance exercises during standing. The duration of active time performing standing balance tasks typically ranged from 0 to 10 minutes.

Conventional locomotor and strength training

The conventional locomotor and strength training consisted of treadmill training and lower-body strength exercises and was conducted by a physiotherapist. The therapists were instructed to provide approximately 20 minutes of treadmill training. The physiotherapist adjusted the treadmill settings and walking speed to each participant's individual physical and walking capacity and the progress the participant made during the intervention. In the remaining time available during the session, lower-body strength exercises were performed including leg press, seated leg curl, hip abduction, and/or adduction. The physiotherapist selected the strength exercises based on the participant's abilities, and resistance of the strength exercises was gradually increased according to the number of correctly executed repetitions based on van de Goolberg's strength-training rehabilitation system (KRS—Kracht Revalidatie Systeem).[23] The duration of active time performing strength exercises typically ranged from 10 to 20 minutes.

2

Primary outcome measure

The primary outcome measure was maximal walking speed as measured with an overground 2-minute Walk Test (2mWT), which is a valid and reliable test to assess walking capacity in people with iSCI.[24] Participants were instructed to walk as far as possible, but safely, over an 18 meter course. An examiner accompanied each participant for safety reasons, walking behind the participant to allow her/him to set the pace. Walking aids were allowed and kept constant between all 2mWT assessments. Also short rest breaks were allowed, but without stopping the time.

Secondary outcome measures

The Spinal Cord Injury Functional Ambulation Profile (SCI-FAP) was used as secondary outcome measure to evaluate functional ambulation.[25] The SCI-FAP includes seven functional walking tasks, such as overcoming obstacles, doors, and stairs. The score is based on the time and assistance needed to complete the tasks at a comfortable pace. Higher scores indicate lower functioning (more time or assistance needed to complete tasks) with a maximum score of 2100. The assistance needed by a participant to complete a specific task was kept constant between all SCI-FAP assessments. This approach was chosen based on previous research demonstrating a correlation between SCI-FAP time and overall score changes.[26] Moreover, this approach was adopted to prevent participants from modifying their required assistance at follow-up assessment, as they were aware of being scored on the assistance needed.

Balance confidence was measured with the Activities-specific Balance Confidence (ABC) scale.[27] This scale comprises 16 items regarding different daily life activities. The total score ranges from 0 to 100, with higher scores indicating more balance confidence.

Participation was measured with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P).[28] This scale comprises 31 items and covers three aspects of participation with three separate scales: frequency, restrictions, and satisfaction. Each subscale ranges from 0 to 100, with higher scores indicating higher levels of participation (higher frequency, less restrictions, higher satisfaction).

Sample size

The required sample size was calculated for an analysis of covariance (ANCOVA).[29] This approach takes into account the correlation (r) between baseline and follow-up scores at the end of the treatment period, and it has been established that ANCOVA with $n \cdot (1-r^2)$ subjects in each group provides the same statistical power as a t-test with n subjects in each group based on a conventional power calculation. To estimate the expected effect of the walking adaptability training, we refer to the study by van Dijsseldonk and colleagues.[15] Within their dataset, we selected participants who met our current inclusion criteria (n = 9) and observed an increase in walking speed of 0.23 m/s. For the expected effect of the conventional locomotor and strength training, we examined two similar interventions among individuals with iSCI: treadmill-based gait training[14] and resistance training combined with aerobic training.[19] These interventions

led to improvements in walking speed of 0.07 m/s and 0.13 m/s, respectively, with a mean improvement of 0.10 m/s. Consequently, we expected a mean difference of 0.13 m/s (0.23 m/s minus 0.10 m/s) between walking adaptability training and conventional locomotor and strength training. To estimate the expected standard deviation (SD) in walking speed and the correlation between baseline and follow-up scores at the end of the treatment period, we refer to the study by van Dijsseldonk and colleagues.[15] Considering a statistical power of 80%, a 2-sided significance level of 5%, a correlation of 0.94, and a dropout rate of 10%, we determined that our study would require an inclusion of 40 participants with iSCI (20 in each group) to detect a mean group difference of 0.13 m/s (SD = 0.4 m/s) in walking speed.

Statistical analysis

All outcome measures at follow-up were compared between the group that received walking adaptability training and the group that received conventional locomotor and strength training using ANCOVA. The performance at baseline was included as a covariate. When the assumption of normality was violated, data transformations were performed. No intention-to-treat approach was followed, as we were primarily interested in the functional effects that could truly be attributed to the interventions.

The effect of time on maximal walking speed was analyzed using repeated-measures ANOVA (baseline, post-intervention, and follow-up) supplemented with post-hoc t-tests using Bonferroni correction. The effect of time on secondary outcome measures was analyzed using dependent t-tests. Data of both interventions were pooled if no significant group difference at follow-up was found.

The mean number of steps taken during a session, the perceived intensity, and participants' experience were compared between groups using independent t-tests, or with Mann-Whitney U tests if the assumption of normality was violated.

All analyses were performed in SPSS version 25 (IBM Corp). The level of significance (α) was set at 0.05.

Results

Participant enrollment commenced August 2019, and the last participant completed follow-up in August 2022. In total, 41 participants were included (31 in the SMK and 10 in the UMCG), of whom 21 were allocated to the walking adaptability training group and 20 to the conventional locomotor and strength training group (see Figure 1). Thirty-five participants completed post-intervention and follow-up assessments and were included in the analysis. Participant characteristics at baseline are shown in Table 1.

2
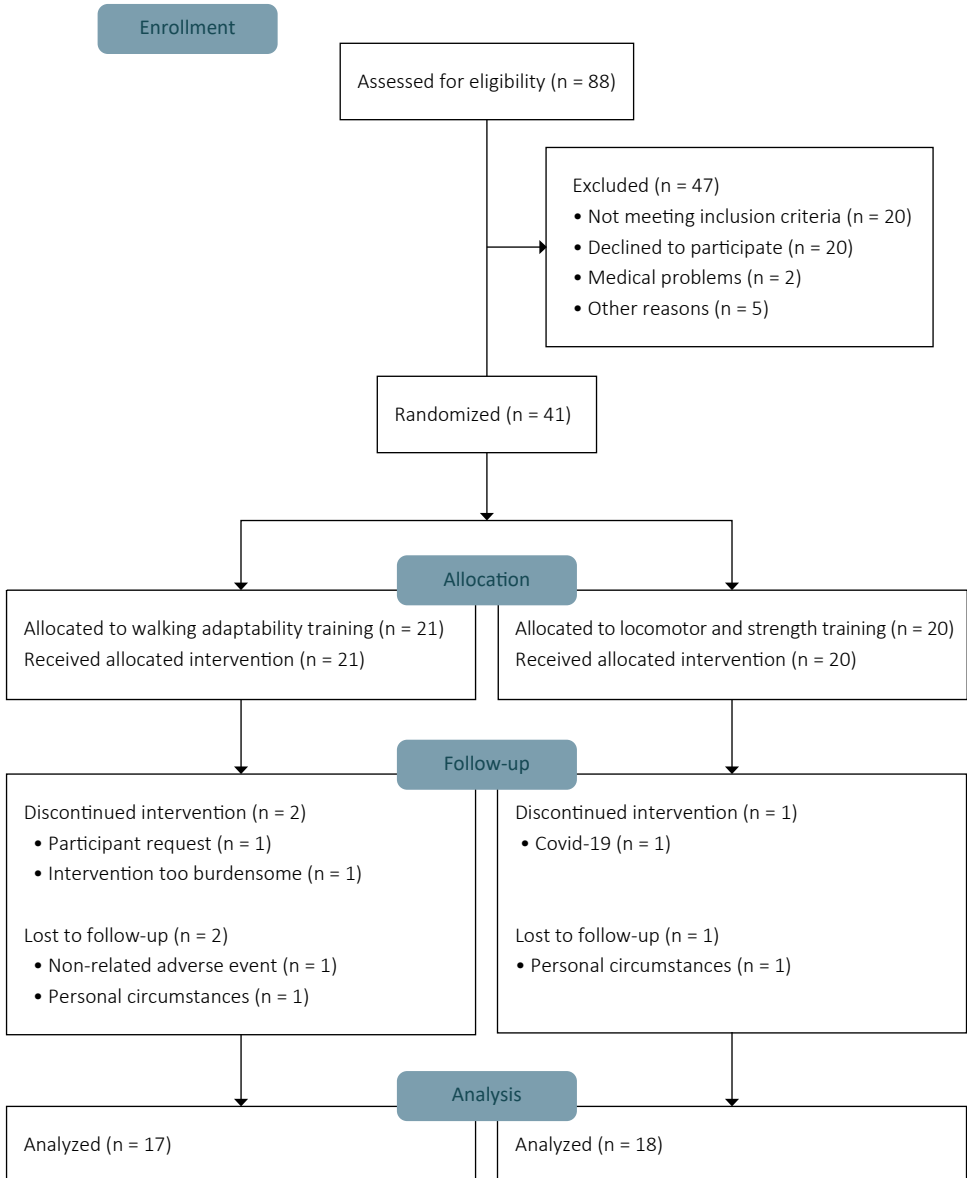
Figure 1 Flow diagram of participants.

Table 1 Participant characteristics at baseline [a]

	Walking adaptability training group	Conventional locomotor and strength training group
N	17	18
Demographic		
Age (yr) [b]	62 (56-71)	67 (60-72)
Weight (kg) [c]	84 ± 16	79 ± 13
Height (cm) [c]	176 ± 11	173 ± 11
Sex		
Men	10	9
Women	7	9
Injury-related		
AIS		
Grade C	2	1
Grade D	15	17
Level of injury		
Cervical	8	10
Thoracic	3	5
Lumbar	6	3
Time post injury (mth) [b]	47 (20-120)	66 (20-135)
Cause		
Traumatic	6	9
Non-traumatic	11	9
Mobility-related		
Functional Ambulation Categories		
Cat 4	4	4
Cat 5	13	14
Use of walking aids outdoors	12	13
Single-point cane or crutch	5	5
Two crutches	1	3
Walker	6	5
Use of ankle-foot orthoses	2	5

[a] Values are reported as number of participants unless stated otherwise. [b] Reported as median (interquartile range). [c] Reported as mean ± standard deviation. AIS = American spinal injury association Impairment Scale.

2

Participants' adherence and experience

All participants attended nine or more training sessions of 60 minutes each, with the same median of 11 (range 9-11) sessions for both the walking adaptability and the conventional locomotor and strength training group. The number of steps per training session was somewhat higher for the walking adaptability training group (median (interquartile range (IQR)) = 2670 (2261-3352)) compared to the conventional locomotor and strength training group (median (IQR) = 2400 (1490-2555)) ($z = -2.18$, $p = 0.03$). The walking adaptability training group reported an average physical tiredness level of 9.0 (SD = 1.6) before the training session, which increased to 14.3 (SD = 1.6) after the session. The conventional locomotor and strength training group reported an average of 8.5 (SD = 2.2) before and 12.3 (SD = 2.0) after the training session. Thus, the perceived intensity, defined as the difference between the ratings of physical tiredness before and after, was higher for the walking adaptability training group (mean ± SD = 5.3 ± 1.9) compared to the conventional locomotor and strength training group (mean ± SD = 3.8 ± 2.0) ($t(33) = 2.36$, $p = 0.03$). One adverse event (foot pain) during the walking adaptability training was reported, but did not lead to discontinuation of the intervention. Participant experience was not different between both groups with a median of 8.5 (range 7-10) for the walking adaptability training group and 9 (range 6-10) for the conventional locomotor and strength training group ($z = -0.45$, $p = 0.67$).

Walking capacity

Maximal walking speed data at baseline, post-intervention, and follow-up are shown in Table 2 and Figure 2. ANCOVA showed no significant group difference in maximal walking speed at follow-up ($F(1, 32) = 1.48$, $p = 0.23$). The mean group difference in maximal walking speed at follow-up adjusted for group differences at baseline (adaptability- locomotor and strength training group) was -0.05 m/s (95% CI = -0.12 – 0.03).

Repeated-measures ANOVA showed an effect of time ($F(1.66, 56.36) = 16.87$, $p < 0.01$). Post-hoc analysis showed significant improvement in maximal walking speed between baseline and post-intervention ($p < 0.01$) and between baseline and follow-up ($p < 0.01$). Independent of intervention, maximal walking speed increased by 0.07 m/s (95% CI = 0.03 – 0.11) at post-intervention and by 0.10 m/s (95% CI = 0.06 – 0.14) at follow-up relative to baseline.

Functional ambulation, balance confidence, and participation

ANCOVA showed no significant group differences in any secondary outcome measures at follow-up (Table 3; Figure 3). Independent of intervention, dependent t-tests revealed significant improvements across time between baseline and follow-up for the SCI-FAP score (median difference = -3.3 points, IQR = -6.0 – -0.3, $p < 0.01$), ABC score (mean difference = 4.9 points, 95% CI = 0.6 – 9.2, $p = 0.03$), and USER-P restrictions score (mean difference = 6.2 points, 95% CI = 1.8 – 10.6, $p < 0.01$).

2

Table 2 Walking capacity at baseline, post-intervention, and follow-up assessment [a]

	Walking adaptability training group (n = 17)			Conventional locomotor and strength training group (n = 18)			ANCOVA (mean group difference) [b]	ANCOVA (stats)
	Baseline	Post-intervention	Follow-up	Baseline	Post-intervention	Follow-up	Follow-up	Follow-up
Maximal walking speed (m/s)	0.81 ± 0.30	0.88 ± 0.31	0.89 ± 0.33	0.84 ± 0.28	0.91 ± 0.35	0.97 ± 0.33	-0.05 (-0.12 − 0.03)	$F_{(1, 32)} = 1.48$, p = 0.23

[a] Values are reported as mean ± standard deviation unless stated otherwise. [b] Reported as mean (95% confidence interval); mean group difference in walking adaptability training - conventional locomotor and strength training, adjusted for group differences at baseline. ANCOVA = analysis of covariance.
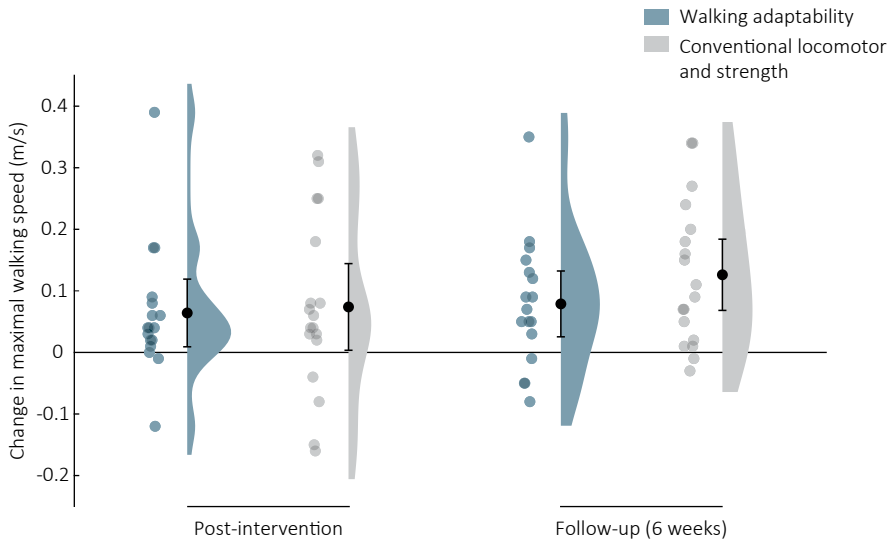
Figure 2 Raincloud plot of the changes in maximal walking speed with respect to baseline. Dots represent the individual data points and bars the means with 95% confidence intervals.

Discussion

Contrary to our hypothesis, we did not observe a superior effect of walking adaptability training over conventional locomotor and strength training for improving walking capacity – operationalized as maximal walking speed during a 2mWT – in individuals with iSCI. When comparing two gait training interventions, it is essential to ensure that they involve a similar dose, as a higher dosage (i.e., number of training sessions and number of steps per session) can positively influence the training effect.[21] Therefore, both training interventions in our study were designed to ensure the same number of sessions and a similar number of steps per session. The number of sessions was the same for both interventions; however, we observed that the mean number of steps taken during the walking adaptability training was about 10% higher compared to the conventional locomotor and strength training. It is interesting to note that the randomized controlled trial conducted by Yang and colleagues[14] reported a much greater group difference in the number of steps taken. Specifically, the number of steps taken during walking adaptability training was three times lower than during the treadmill-based gait training (400 vs. 1200 steps). Yet, despite this large difference, the treadmill-based gait training only showed a significantly superior effect on one out of six walking capacity measures. Therefore, it seems unlikely that the relatively small difference in the number of steps in the current study has influenced our results.

2

Table 3 Functional ambulation, balance confidence and participation at baseline and follow-up [a]

	Walking adaptability training group (n = 17)		Conventional locomotor and strength training group (n = 18)		ANCOVA (mean group difference) [b]	ANCOVA (stats)
	Baseline	Follow-up	Baseline	Follow-up	Follow-up	Follow-up
SCI-FAP score [c]	25 (15-49)	24 (10-49)	21 (13-38)	19 (11-34)	- [d]	$F_{(1, 32)} = 0.08$, $p = 0.79$
ABC score	55 ± 18	59 ± 18	57 ± 19	64 ± 16	-3.7 (-11.5 – 4.1)	$F_{(1, 32)} = 0.94$, $p = 0.34$
USER-P score						
Frequency	30 ± 8	29 ± 8	33 ± 8	32 ± 8	-1.7 (-6.7 – 3.3)	$F_{(1, 32)} = 0.48$, $p = 0.49$
Restrictions	73 ± 17	76 ± 13	70 ± 17	79 ± 11	-5.0 (-11.1 – 1.2)	$F_{(1, 32)} = 2.71$, $p = 0.11$
Satisfaction	64 ± 13	66 ± 7	67 ± 16	66 ± 17	2.3 (-5.1 – 9.7)	$F_{(1, 32)} = 0.41$, $p = 0.53$

[a] Values are reported as mean ± standard deviation unless stated otherwise. [b] Reported as mean (95% confidence interval); mean group difference in walking adaptability training – conventional locomotor and strength training, adjusted for group differences at baseline. [c] Reported as median (interquartile range). [d] Data are LOG-transformed, therefore no mean difference is reported. SCI-FAP = Spinal Cord Injury Functional Ambulation Profile (range 0-2100, lower scores indicate higher functioning); ABC = Activities-specific Balance (range 0-100); USER-P = Utrecht Scale for Evaluation of Rehabilitation-Participation (range 0-100); ANCOVA = analysis of covariance.
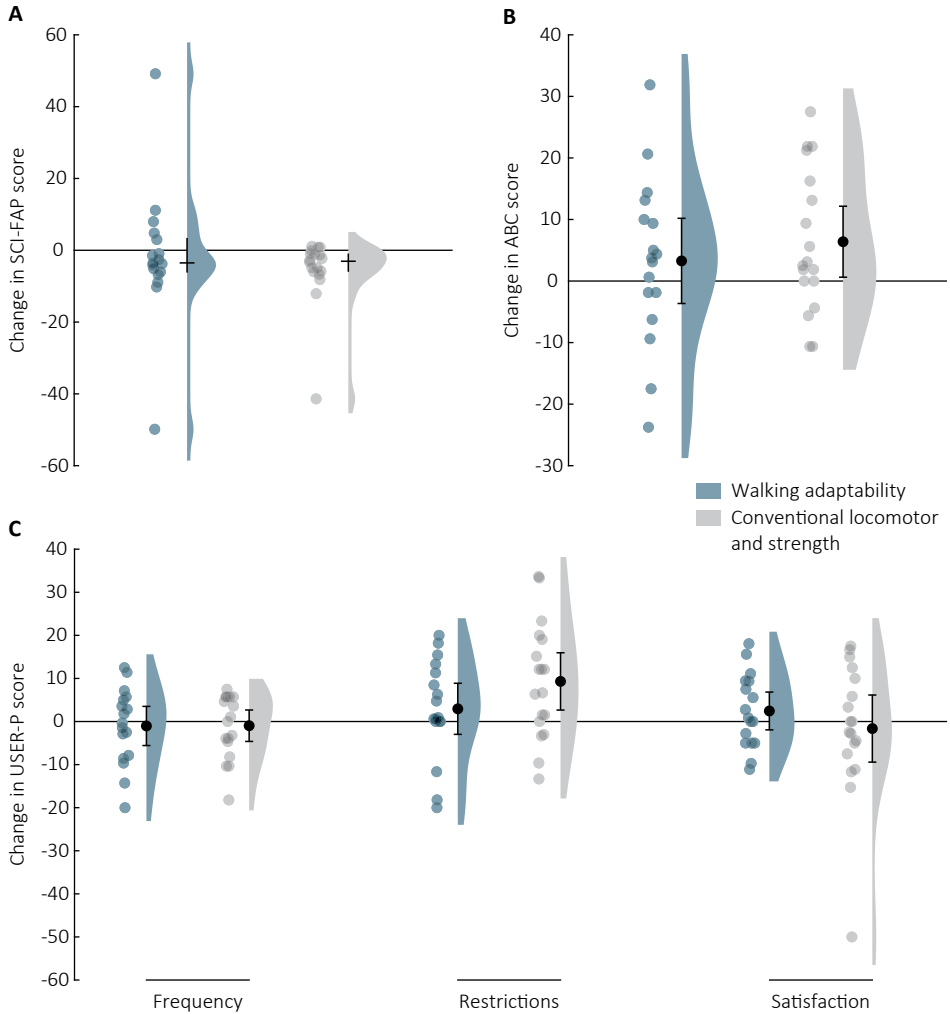
Figure 3 Raincloud plots of the changes in Spinal Cord Injury Functional Ambulation Profile (SCI-FAP) scores (A), the changes in Activities-specific Balance Confidence (ABC) scores (B), and the changes in Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) scores (C) between baseline and follow-up. Dots represent the individual data points and bars the medians with interquartile ranges (A) or means with 95% confidence intervals (B, C).

In addition to the dosage, the intensity of an intervention is an important determinant of effectiveness.[21,30] Although the average active time for the walking adaptability training was lower compared to the conventional locomotor and strength training, we found that the difference in perceived intensity was higher for the walking adaptability training than for the conventional locomotor and strength training. Given the higher perceived intensity for the walking adaptability training, a larger effect on maximal walking speed compared to the conventional locomotor and strength training would have been logical but, instead, no significant group difference was found. Thus, our findings suggest that we can reject our hypothesis that walking adaptability training as provided in the current study is superior to conventional locomotor and strength training for improving maximal walking speed in ambulatory people with iSCI. This conclusion aligns with recently published research comparing walking adaptability training to conventional training in other neurological populations.[31,32]

Compared to conventional locomotor and strength training, walking adaptability training yielded similar effects on functional ambulation, balance confidence, and participation. This pattern of results is understandable given the non-differential effects of the interventions on maximal walking speed. Moreover, in people with other chronic neurological conditions, similar (non-differential) effects have been reported, such as after stroke.[32]

The lack of observed differences between the two interventions in our study may be attributed to the incorporation of lower-body strength exercises within the conventional training. This decision was guided by the common clinical practice of combining locomotor interventions with lower-body strength exercises, aiming to improve muscle strength and overall effectiveness of the gait training. However, it is worth noting that despite including both treadmill training and lower-body strength exercises in the conventional training, the observed improvements in walking speed after the intervention fell within the range of previously reported changes following just treadmill training.[14,33] Furthermore, a recent review by Hornby and colleagues has highlighted inconsistent evidence regarding the potential benefits of lower-body strength training on walking speed.[34] This suggests that the addition of lower-body strength exercises may not have yielded benefits beyond what is typically achieved with treadmill training alone. An alternative cause of the non-differential results observed in this study may be attributed to variations in participant motivation. Previous research has highlighted differences in the improvement of physical function during rehabilitation between highly motivated and less motivated stroke survivors.[35] However, it is noteworthy that participant experiences were similar for both interventions, suggesting that motivation levels did not significantly influence the study outcomes.

It is important to recognize that, independent of intervention, maximal walking speed increased by 0.07 m/s after six weeks of training, which result was retained or even reinforced at six-week follow-up with a 0.10 m/s improvement relative to baseline. The amount of improvement at follow-up is clinically relevant, as it aligns with the reported minimal clinically important difference (MCID) of 0.10 m/s for walking speed.[36] Previous research on

gait training in individuals with iSCI has revealed variable results concerning improvements in walking speed, ranging from minimal changes (around 0.00 m/s) to significant increases (up to 0.16 m/s).[14,19,20,33,37,38] Our study's findings on improvement in walking speed lie around the midpoint of this range, suggesting a noteworthy effect on participants' walking speed compared to previous studies. Concurrently with the observed improvement in maximal walking speed in our study, both functional ambulation and balance confidence increased at follow-up compared to baseline, regardless of the intervention. Participants also reported less participation restrictions in daily life activities, such as work, household chores, and social activities. At an individual level, 15 out of 35 participants (43%) showed improvements in maximal walking speed that exceeded the MCID of 0.10 m/s at follow-up.[36] No MCID values for the secondary outcome measures in the iSCI population have been reported in the existing literature. Therefore, we employed a distribution-based approach to determine the MCID for the SCI-FAP, ABC, and USER-P restrictions scores, which was 0.5 SD of their baseline values, according to a systematic review conducted by Norman and colleagues.[39] Similar to the observed improvement in maximal walking speed, 37% (13/35) of the participants exceeded the MCID on the ABC scale (9.1 points) and 43% (15/35) exceeded the MCID on the USER-P restrictions scale (8.5 points), indicating a clinically meaningful change. For the SCI-FAP score, only 6% (2/35) of the participants exceeded the MCID (21.9 points).

Since we found no evidence that walking adaptability training is superior to conventional locomotor and strength training, a rehabilitation professional may indicate both interventions for an individual with iSCI to enhance walking capacity and functional ambulation in the home and community setting. Based on participant experience, there does not seem to be an overall preference either. The conventional locomotor and strength training in our study implicated a treadmill and lower body exercise machines, which combination can be more easily integrated into the community care system compared to walking adaptability training using the GRAIL system. Therefore, we believe that conventional (locomotor and strength) training as provided in our study holds the greatest potential for widespread use.

Our study had some limitations that should be considered when interpreting the results. First, the sample size was calculated based on improvements in walking speed observed in previous studies that were not directly comparable to our specific study design in terms of the number of training sessions or timing and type of assessment. This may have introduced a source of error in our sample size calculation. Therefore, we cannot rule out the possibility that a significant group difference would have been observed with a larger sample size. Second, the study was partly conducted during the Covid-19 pandemic, which may have influenced the results of the USER-P frequency subscale, as participants were restricted in their ability to engage in leisure and social activities. Third, both the SCI-FAP and USER-P restrictions subscales have a ceiling effect,[25,28] which may have reduced their responsiveness given the relatively high baseline performance of our participants. Fourth, it is important to note that the assessors were not blinded, which may have introduced bias into the assessment process. Fifth, a limitation of this study is the notion that the dosing of the interventions may have been suboptimal for

2

certain participants. To ensure consistency, we selected a duration of 20 minutes of active walking based on clinical experience, aiming to achieve a comparable number of steps per session for both interventions. However, it is possible that some participants may have been capable of performing more than 20 minutes of active walking. Sixth, we did not evaluate the effectiveness and quality of the participants' gait performance during the walking adaptability training. This limitation arises from the complexity inherent in assessing certain performance outcomes on the GRAIL system. While some outcomes can be quantified by a single parameter, such as completion time or the number of successful maneuvers, others involve multiple measures or less objective assessments, such as reactions to perturbations or an application combining precision stepping, obstacle avoidance and perturbations. Therefore, reporting an outcome to indicate the effectiveness and quality of the participants' gait performance across all applications turned out to be unfeasible. Nevertheless, it is important to note that the physiotherapists have extensive experience in tailoring interventions to the capacities of individuals with iSCI, with the objective to adjust training sessions to the quality of participants' gait performance. Finally, while the primary outcome walking speed has shown correlations with various functional ambulation skills,[22] it may overlook or fail to fully capture the concept of walking adaptability. Unfortunately, at the start of our study, alternative outcome measures more closely related to walking adaptability were either unavailable or too much reliant on a certain level of walking proficiency.[26] To address this limitation and better capture the concept of walking adaptability in future studies, it is crucial to develop and incorporate outcome measures more closely related to walking adaptability. One promising measure that could be considered is the Walk Ladder Test, recently developed by Kuijpers and colleagues,[40,41] as it specifically assesses walking adaptability. Implementing such measures in future studies would provide a more targeted evaluation of the efficacy and impact of walking adaptability interventions in people with iSCI.

Conclusion

Our findings suggest that walking adaptability training may not be superior to conventional locomotor and strength training for improving walking capacity, functional ambulation, balance confidence, or participation in ambulatory people with iSCI. Yet, both interventions showed improvements on all outcome measures at six weeks after the intervention. These findings suggest that both walking adaptability training and conventional locomotor and strength training can be considered viable options for enhancing walking capacity and functional ambulation in the home and community setting in individuals with iSCI.

2

References

1. Waters RL, Adkins RH, Yakura JS, Sie I. Motor and Sensory Recovery Following Incomplete Paraplegia. Arch Phys Med Rehabil. 1994;75:67–72.

2. Barbeau H, Nadeau S, Garneau C. Physical Determinants, Emerging Concepts, and Training Approaches in Gait of Individuals with Spinal Cord Injury. J Neurotrauma. 2006;23:571–585.

3. Lapointe R, Lajoie Y, Serresse O, Barbeau H. Functional community ambulation requirements in incomplete spinal cord injured subjects. Spinal Cord. 2001;39:327–335.

4. Brotherton SS, Krause JS, Nietert PJ. Falls in individuals with incomplete spinal cord injury. Spinal Cord. 2007;45:37–40.

5. Phonthee S, Saengsuwan J, Siritaratiwat W, Amatachaya S. Incidence and factors associated with falls in independent ambulatory individuals with spinal cord injury: A 6-month prospective study. Phys Ther. 2013;93:1061–1072.

6. Khan A, Pujol C, Laylor M, et al. Falls after spinal cord injury: a systematic review and meta-analysis of incidence proportion and contributing factors. Spinal Cord. 2019;57:526–539.

7. van Hedel HJA. Gait speed in relation to categories of functional ambulation after spinal cord injury. Neurorehabil Neural Repair. 2009;23:343–350.

8. Lund ML, Nordlund A, Nygård L, Lexell J, Bernspång B. Perceptions of participation and predictors of perceived problems with participation in persons with spinal cord injury. J Rehabil Med. 2005;37:3–8.

9. Nas K, Yazmalar L, Şah V, Aydin A, Öneş K. Rehabilitation of spinal cord injuries. World J Orthop. 2015;6:8–16.

10. Balasubramanian CK, Clark DJ, Fox EJ. Walking Adaptability after a Stroke and Its Assessment in Clinical Settings. Stroke Res Treat. 2014;2014:591013.

11. Weerdesteyn V, Hollands KL, Hollands MA. Gait adaptability. 1st ed. Elsevier B.V.; 2018.

12. Mehrholz J, Harvey LA, Thomas S, Elsner B. Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. Spinal Cord. 2017;55:722–729.

13. Morawietz C, Moffat F. Effects of locomotor training after incomplete spinal cord injury: A systematic review. Arch Phys Med Rehabil. 2013;94:2297–2308.

14. Yang JF, Musselman KE, Livingstone D, et al. Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial. Neurorehabil Neural Repair. 2014;28:314–324.

15. van Dijsseldonk RB, de Jong LAF, Groen BE, Vos-van der Hulst M, Geurts ACH, Keijsers NLW. Gait stability training in a virtual environment improves gait and dynamic balance capacity in incomplete spinal cord injury patients. Front Neurol. 2018;9:963.

16. Heeren A, van Ooijen MW, Geurts ACH, 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;45:616–622.

17. Houdijk H, van Ooijen MW, Kraal JJ, et al. Assessing gait adaptability in people with unilateral amputation on an instrumented treadmill with a projected visual context. Phys Ther. 2012;92:1452–1460.

18. Timmermans C, Roerdink M, Meskers CGM, Beek PJ, Janssen TWJ. Walking-adaptability therapy after stroke: results of a randomized controlled trial. Trials. 2021;22:923.

2

19. Kapadia N, Masani K, Craven CB, et al. A randomized trial of functional electrical stimulation for walking in incomplete spinal cord injury: Effects on walking competency. Journal of Spinal Cord Medicine. 2014;37:511–524.

20. Alexeeva N, Sames C, Jacobs PL, et al. Comparison of training methods to improve walking in persons with chronic spinal cord injury: a randomized clinical trial. Journal of Spinal Cord Medicine. 2011;34:362–379.

21. Hornby T, Straube D, Kinnaird C, et al. Importance of specificity, amount, and intensity of locomotor training to improve ambulatory function in patients poststroke. Top Stroke Rehabil. 2011;18:293–307.

22. Labruyère R, Van Hedel HJ. Curve walking is not better than straight walking in estimating ambulation-related domains after incomplete spinal cord injury. Arch Phys Med Rehabil. 2012;93:796–801.

23. van de Goolberg T, van de Goolberg A. Het KrachtRevalidatieSysteem. Physios. 2014;6:46–52.

24. Willi R, Widmer M, Merz N, Bastiaenen CHG, Zörner B, Bolliger M. Validity and reliability of the 2-minute walk test in individuals with spinal cord injury. Spinal Cord. 2022;61:15–21.

25. Musselman K, Brunton K, Lam T, Yang J. Spinal Cord Injury Functional Ambulation Profile: A New Measure of Walking Ability. Neurorehabil Neural Repair. 2011;25:285–293.

26. Musselman KE, Yang JF. Spinal Cord Injury Functional Ambulation Profile: A Preliminary Look at Responsiveness. Phys Ther. 2014;94:240–250.

27. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. J Gerontol A Biol Sci Med Sci. 1995;50A:M28–M34.

28. Post MWM, van Der Zee CH, Hennink J, Schafrat CG, Visser-Meily JMA, van Berlekom SB. Validity of the Utrecht Scale for Evaluation of Rehabilitation- Participation. Disabil Rehabil. 2012;34:478–485.

29. Borm GF, Fransen J, Lemmens WAJG. A simple sample size formula for analysis of covariance in randomized clinical trials. J Clin Epidemiol. 2007;60:1234–1238.

30. Brazg G, Fahey M, Holleran CL, et al. Effects of training intensity on locomotor performance in individuals with chronic spinal cord injury: a randomized crossover study. Neurorehabil Neural Repair. 2017;31:944–954.

31. Clark DJ, Rose DK, Butera KA, et al. Rehabilitation with accurate adaptability walking tasks or steady state walking: A randomized clinical trial in adults post-stroke. Clin Rehabil. 2021;35:1196–1206.

32. de Rooij IJM, van de Port IGL, Punt M, et al. Effect of Virtual Reality Gait Training on Participation in Survivors of Subacute Stroke: A Randomized Controlled Trial. Phys Ther. 2021;101.

33. Field-Fote EC, Roach KE. Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: A randomized clinical trial. Phys Ther. 2011;91:48–60.

34. Hornby TG, Reisman DS, Ward IG, et al. Clinical Practice Guideline to Improve Locomotor Function Following Chronic Stroke, Incomplete Spinal Cord Injury, and Brain Injury. Journal of Neurologic Physical Therapy. 2020;44:49–100.

35. Wang YH, Yang YR, Pan PJ, Wang RY. Modeling factors predictive of functional improvement following acute stroke. Journal of the Chinese Medical Association. 2014;77:469–476.

36. Forrest GF, Hutchinson K, Lorenz DJ, et al. Are the 10 meter and 6 minute walk tests redundant in patients with spinal cord injury? PLoS One. 2014;9:e94108.

37. Field-Fote EC, Lindley SD, Sherman AL. Locomotor training approaches for individuals with spinal cord injury: A preliminary report of walking-related outcomes. Journal of Neurologic Physical Therapy. 2005;29:127–137.

38. Wirz M, Zemon DH, Rupp R, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: A multicenter trial. Arch Phys Med Rehabil. 2005;86:672–680.

39. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003;41:582–592.

40. Kuijpers R, Smulders E, Groen BE, Smits-Engelsman BCM, Nijhuis-van der Sanden MWG, Weerdesteyn V. Walking adaptability improves after treadmill training in children with Developmental Coordination Disorder: A proof-of-concept study. Gait Posture. 2022;92:258–263.

41. Kuijpers R, Smulders E, Groen BE, Smits-Engelsman BCM, Nijhuis-van der Sanden MWG, Weerdesteyn V. 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;44:1489–1497.

2

Chapter 3

Conventional locomotor and strength training and walking adaptability training for ambulatory people with motor incomplete spinal cord injury: Does intervention sequence matter?

Eline Zwijgers
Marije Vos-van der Hulst
Rosanne B. van Dijsseldonk
Taha Y. Temlali
Juha M. Hijmans
Ilse J.W. van Nes
Alexander C.H. Geurts
Noël L.W. Keijsers

Abstract

Background

Walking capacity is often impaired in individuals with motor incomplete spinal cord injury, leading to limitations in performing mobility-related daily life activities (i.e., functional ambulation) and participating in the community. To address these challenges, various rehabilitation interventions have been developed with the aim to improve walking capacity. This study aimed to assess the efficacy of two intervention sequences – including conventional locomotor and strength training (CLS) and walking adaptability training (WA) – for improving walking capacity, functional ambulation, balance confidence, and participation in ambulatory people with motor incomplete spinal cord injury (iSCI).

Methods

We conducted a two-center randomized cross-over trial. Forty-one participants with iSCI (≥ six months post injury) were randomized to the CLS-WA or WA-CLS sequence. CLS consisted of treadmill training and lower-body strength exercises and WA consisted of treadmill training in a virtual reality environment. Both interventions lasted six weeks with a six-week interval in between. The primary outcome was maximal walking speed, assessed with an overground 2-minute walk test. Secondary outcomes included the Spinal Cord Injury-Functional Ambulation Profile (SCI-FAP), the Activities-specific Balance Confidence (ABC) scale, and the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P).

Results

No significant difference in maximal walking speed or SCI-FAP score between the CLS-WA (n=14) and WA-CLS (n=14) groups was found at six weeks after completion of the second intervention. However, the CLS-WA group exhibited greater improvements in the ABC and USER-P restriction scores compared to the WA-CLS group.

Conclusion

Administering CLS before WA led to similar improvements in walking capacity and functional ambulation in individuals with iSCI compared to the reversed intervention sequence. However, the CLS-WA sequence resulted in a superior effect in terms of improving balance confidence and reducing participation restrictions compared to the WA-CLS sequence.

3

Background

Individuals with motor incomplete spinal cord injury (iSCI) experience muscle weakness, impaired muscle coordination, altered muscle tone, and loss of sensation below the injury level. Consequently, their walking capacity is often impaired,[1,2] leading to limitations in performing mobility-related daily life activities (i.e., functional ambulation)[3] and participating in the community.[4] To address these challenges, various rehabilitation interventions have been developed with the aim to improve walking capacity in individuals with iSCI.[5,6]

In clinical practice, most outpatient rehabilitation interventions for individuals with iSCI involve repetitive practice of steady-state walking. We defined these interventions as conventional locomotor interventions, including overground, treadmill-based, or robot-assisted gait training,[6,7] often complemented by lower-body strength exercises. However, in the last decade, there has been a shift toward rehabilitation interventions that specifically target walking adaptability.[8-14] This shift is driven by the integration of new technological innovations and a stronger emphasis on tailoring training to real-life walking scenarios. Walking adaptability training aims to enhance an individual's ability to adapt his/her walking pattern to various environmental circumstances, including walking on different surfaces, precision stepping, overcoming obstacles, and effectively responding to perturbations.

A previous study has shown promising results of walking adaptability training in people with iSCI.[14] Building upon this evidence, we conducted a randomized controlled trial (RCT) to evaluate the effectiveness of walking adaptability training compared to similarly dosed conventional locomotor and strength training in individuals with iSCI.[15] Our findings demonstrated that both training approaches yielded similar improvements in walking capacity, functional ambulation, balance confidence, and participation. In this chapter, we present the follow-up findings of this RCT, as it was a priori designed as a two-armed cross-over study, allowing to examine the effect of two consecutive intervention periods and possible sequence effects.

Given that conventional locomotor and strength training and walking adaptability training primarily target different aspects of walking capacity,[15] the sequence in which these interventions is administered might be important. The requirements for optimal walking capacity encompass stepping, dynamic stability, and walking adaptability.[16] Stepping, which is crucial to progress forward, primarily relies on sufficient leg motor control, while dynamic stability relies on adequate balance control.[17] As walking adaptability refers to the ability to adjust one's walking pattern to environmental challenges, this requirement depends on a complex interplay between leg motor control and balance control.[17] Conventional locomotor and strength training predominantly targets stepping and dynamic stability under predictable and fixed circumstances, whereas walking adaptability training targets both aspects under unpredictable and changing circumstances. From this perspective, it might be beneficial to train basic leg motor control (including muscle strength) and balance control before starting with walking adaptability training instead of training in the reversed order. Indeed, previous

research has suggested that good leg muscle strength is associated with successful walking adaptability,[18,19] indicating that basic leg motor control and lower-body strength exercises might have a potential conditioning effect for training walking adaptability.

The objective of this study was to investigate the effectiveness of two different intervention sequences for improving walking capacity in ambulatory people with iSCI. The interventions were conventional locomotor and strength training and walking adaptability training. We hypothesized that administering conventional locomotor and strength training before initiating walking adaptability training would be more effective to improve walking capacity in people with iSCI than administering the interventions in the reverse sequence. Furthermore, we evaluated the effects of intervention sequence on secondary outcomes, such as functional ambulation, balance confidence, and participation.

Methods

Study design

The study was conducted at two medical institutions in the Netherlands: the Sint Maartenskliniek (SMK) and the University Medical Center Groningen (UMCG). The study was a two-armed, randomized cross-over trial and was registered in the Dutch Trial Register under the title 'Effect of GRAIL training in incomplete spinal cord injury'. Ethical approval for the study was obtained from the regional medical ethics committee Oost-Nederland (NL69379.091.19) and the internal review board of the Sint Maartenskliniek. The entire research process strictly adhered to the guidelines and regulations outlined in the Medical Research involving Human Subjects Act (WMO) and the Netherlands Code of Conduct for Research Integrity. Participants provided written informed consent under the Declaration of Helsinki.

Participants

Participants with iSCI were enrolled in the study during their outpatient clinic visits, which included check-ups or appointments initiated by the participants themselves to address concerns related to their walking ability. The inclusion criteria were: 1) diagnosed with motor incomplete spinal cord injury, classified as American spinal injury association Impairment Scale (AIS) C or D, caused by either traumatic or non-traumatic origin, 2) at least six months post injury, 3) ability to walk a minimum distance of ten meters without physical assistance, 4) preferred comfortable walking speed ranging from 0.3 to 1.0 m/s, 5) expressing a personal aim to enhance walking capacity, 6) willingness and ability to refrain from other physical interventions (e.g., physiotherapy, botulinum toxin injections) targeted at improving walking capacity during the study period, and 7) age 18 years or older. Exclusion criteria were: 1) other impairments of the nervous system or lower limbs that might affect walking or balance, 2) anticipated disruption of individual activity level due to scheduled events, such as surgery or relocation of home situation, 3) having participated in walking adaptability training within the past six months, and 4) inadequate understanding of the Dutch language.

Participant characteristics, including demographic details (age, weight, height, and sex), injury-related factors (AIS, level of injury, and time post injury), and mobility-related aspects (Functional Ambulation Categories and usage of ankle foot orthoses and/or outdoor walking aids) were recorded at baseline.

Procedures

The participants were randomly assigned following group allocation in a 1:1 ratio. One group started with walking adaptability training (WA) and crossed over to conventional locomotor and strength training (CLS) (WA-CLS group), whereas the other group started with conventional locomotor and strength training and crossed over to walking adaptability training (CLS-WA group). The second training intervention started six weeks after the completion of the initial intervention. Outcome measures were evaluated at three time points: at baseline, six weeks after the completion of the first intervention (at the beginning of the second intervention) (T1), and six weeks after the completion of the second intervention (T2). See Figure 1 for a schematic overview of the study design. Blinding of participants, physiotherapists, or investigators to group allocation was not feasible given the nature of the interventions. In addition, assessors were not blinded due to practical and organizational constraints.
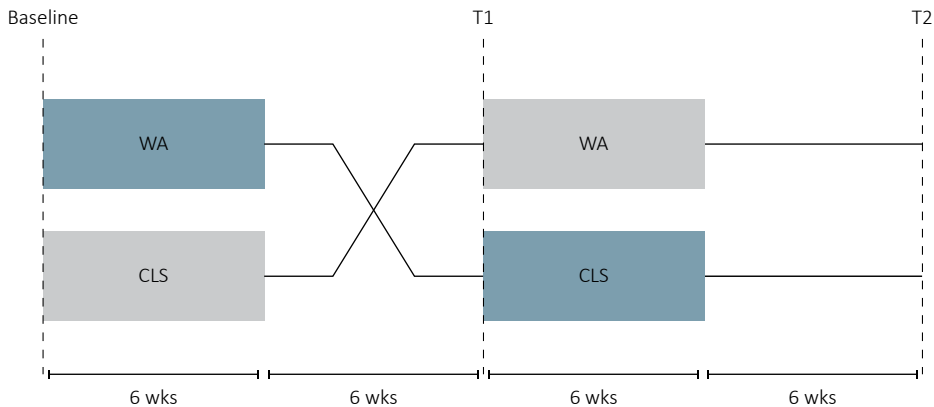
Figure 1 Schematic overview of the study design. Assessments were performed at baseline, T1, and T2. WA = Walking Adaptability training; CLS = Conventional Locomotor and Strength training.

Interventions

Both interventions comprised 11 training sessions, each lasting 60 minutes, conducted over a six-week period (on average two sessions per week). Adherence to the training was assessed by tracking the number of completed sessions for each participant. Individuals were permitted to make up for missed sessions, with a maximum of two sessions, occasionally extending the training period to seven weeks.

3

Walking adaptability training

The walking adaptability training was conducted using the Gait Real-time Analysis Interactive Lab (GRAIL; Motek Medical B.V.). The GRAIL incorporates an instrumented split-belt treadmill with adjustable pitch and sway, a ten-camera motion capture system (Vicon Motion Systems), and a 180° semi-cylindrical screen for synchronized virtual reality environments. Participants were equipped with a safety harness attached to the ceiling for added safety during the training sessions. A certified physiotherapist conducted the training, including multiple walking adaptability tasks, such as precision stepping, obstacle avoidance, and reacting to perturbations. Precision stepping involved precise foot placement on virtually projected targets. Obstacle avoidance required maneuvering around or stepping over virtually projected obstacles. Reacting to perturbations involved responding to unexpected disturbances such as a sudden acceleration of one of the treadmill belts or mediolateral platform translations. Training tasks were selected based on the participant's goals and training complexity was gradually increased according to individual ability. Typically, about 20 minutes of walking adaptability training was provided during a 60-minute session. In the remaining time, standing balance tasks, including weight shifting and foot clearance exercises, were trained. Due to breaks, task explanation, and task setup, the total active training time typically varied between 20 and 30 minutes.

Conventional locomotor and strength training

The conventional locomotor and strength training included treadmill training on a regular treadmill and lower-body strength exercises, supervised by a physiotherapist. The training session comprised approximately 20 minutes of treadmill training during each 60-minute session, in which the treadmill settings and walking speed was gradually increased over sessions according to the participant's ability. In the remaining time, lower-body strength exercises, such as leg press, seated leg curl, hip abduction, and/or adduction exercises, were performed. The selection of strength exercises was based on each individual's abilities and resistance was gradually increased based on the number of correctly executed repetitions, following van de Goolberg's strength-training rehabilitation system (KRS—Kracht Revalidatie Systeem).[20] Due to breaks, task explanations, and task setup, the total active training time typically varied between 30 and 40 minutes.

Primary outcome

The primary outcome was maximal walking speed, assessed with an overground 2-minute Walk Test (2mWT), which is commonly considered to be a valid and reliable measure of walking capacity in individuals with iSCI.[21] Participants were instructed to walk as far as possible within the given time across an 18-meter course. To maintain safety, an examiner accompanied each participant, walking behind the person to allow him/her to set one's own pace. During all 2mWT assessments, participants were permitted to use walking aids, and the type of aids remained consistent across all 2mWT assessments. In addition, short rest breaks were allowed without stopping the timing. Maximal walking speed assessed at T2 served as the primary endpoint.

3

Secondary outcomes

Functional ambulation was assessed with the Spinal Cord Injury Functional Ambulation Profile (SCI-FAP).[22] This assessment includes seven functional walking tasks, such as walking on different surfaces, overcoming obstacles, negotiating doors, and taking stairs. Participants were scored based on the time and assistance required to complete these tasks at a comfortable pace, with higher scores indicating lower functioning (i.e., more time or assistance needed to complete the tasks) (maximum score 2100). To ensure consistency, the assistance needed to complete a specific task was kept constant throughout all SCI-FAP assessments. This approach was adopted to prevent any potential subjective influence from participants who might otherwise modify their required assistance during the assessments, as they were aware of being scored based on the assistance needed. In addition, previous research demonstrated a correlation between the SCI-FAP time and overall score changes.[23]

Balance confidence was assessed with the Activities-specific Balance Confidence (ABC) scale.[24] This questionnaire consists of 16 items related to various daily life activities. The total score ranges from 0 to 100, with higher scores indicating higher levels of balance confidence.

Participation was assessed with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P).[25] This questionnaire comprises 31 items and encompasses three aspects of participation, each represented by a separate scale: frequency, restrictions, and satisfaction. Each subscale ranges from 0 to 100, with higher scores indicating higher levels of participation (i.e., higher frequency, fewer restrictions, and greater satisfaction).

Statistical analysis

To compare outcomes at T2 between the WA-CLS and CLS-WA groups, we performed an analysis of covariance (ANCOVA) with baseline scores included as covariates. If the assumption of normality was violated, data transformation was applied. If ANCOVA revealed a significant group difference at T2, we conducted an additional ANCOVA to check for group differences at T1, again with baseline scores included as covariates for each outcome. In the absence of group differences, we evaluated the effect of time on each outcome for both groups together, using a repeated-measures ANOVA, considering three time points: baseline, T1, and T2. Post-hoc t-tests with Bonferroni correction were performed in case of a significant effect of time. We did not adopt an intention-to-treat approach because our primary focus was on examining the functional effects that could genuinely be attributed to the followed intervention sequence. All statistical analyses were carried out using SPSS version 25 (IBM Corp), with a predetermined significance level (α) set at 0.05.

Results

Participant enrollment started in August 2019, and the last participant finished in November 2022. A total of 41 participants were included (31 from SMK and 10 from UMCG). Among them, 21 were allocated to the WA-CLS group, while the remaining 20 were assigned to the

3

CLS-WA group. Six participants dropped out during the first intervention period, leaving 35 participants to proceed with the second intervention period (Figure 2). In the second period of the CLS-WA group, two intervention-related adverse events occurred: shoulder pain and a trip incident leading to an ankle injury. These events led to discontinuation of the intervention. Additionally, five other participants dropped out during the second intervention period (Figure 2). Eventually, a total of 28 participants, evenly distributed between both groups completed both T1 and T2 assessments and were included in the analysis. Of these, one participant from the CLS-WA group did not complete the USER-P and ABC questionnaires due to non-response. The baseline characteristics of the participants are presented in Table 1. Participants attended a minimum of nine training sessions for each intervention, with a median of 11 sessions (range 9-11) for both interventions.

Walking capacity

Maximal walking speed data at baseline, T1, and T2 are presented in Table 2 and Figure 3. ANCOVA showed no significant group difference in maximal walking speed at T2 ($F_{(1, 25)}$ = 1.05, p = 0.32) with a mean group difference of 0.07 m/s (95% CI = -0.07 – 0.22; adjusted for baseline values; CLS-WA minus WA-CLS). Irrespective of intervention order, repeated-measures ANOVA indicated a significant effect of time ($F_{(1.26, 33.88)}$ = 19.31, p < 0.01). Post-hoc analysis revealed significant improvements in maximal walking speed between baseline and T1 (p < 0.01) and between baseline and T2 (p < 0.01). No significant difference was found between T1 and T2 (p = 0.17). Irrespective of intervention order, maximal walking speed increased by 0.12 m/s (95% CI = 0.06 – 0.17) at T1 and by 0.15 m/s (95% CI = 0.06 – 0.23) at T2 relative to baseline.

Functional ambulation

ANCOVA showed no significant group difference in the SCI-FAP score at T2 ($F_{(1,25)}$ = 0.31, p = 0.58) (Table 2). Irrespective of intervention order, repeated-measures ANOVA indicated a significant effect of time ($F_{(1.57, 42.48)}$ = 6.66, p < 0.01). Post-hoc analysis revealed significant improvements in the SCI-FAP score between baseline and T1 (median difference = -1.6 points, interquartile range (IQR) = -4.9 – -0.8, p = 0.02) and between baseline and T2 (median difference = -1.9 points, IQR = -6.7 – -0.4, p = 0.03). No significant difference was found between T1 and T2 (p = 1.00)

Balance confidence

ANCOVA showed a significant group difference in the ABC score at T2 ($F_{(1, 24)}$ = 8.45, p < 0.01). The CLS-WA group exhibited 13 points (95% CI = 3.8 – 22.3; adjusted for baseline values) more improvement in terms of the ABC score in comparison to the WA-CLS group (Table 2; Figure 4). No significant group difference for the ABC score was found at T1.
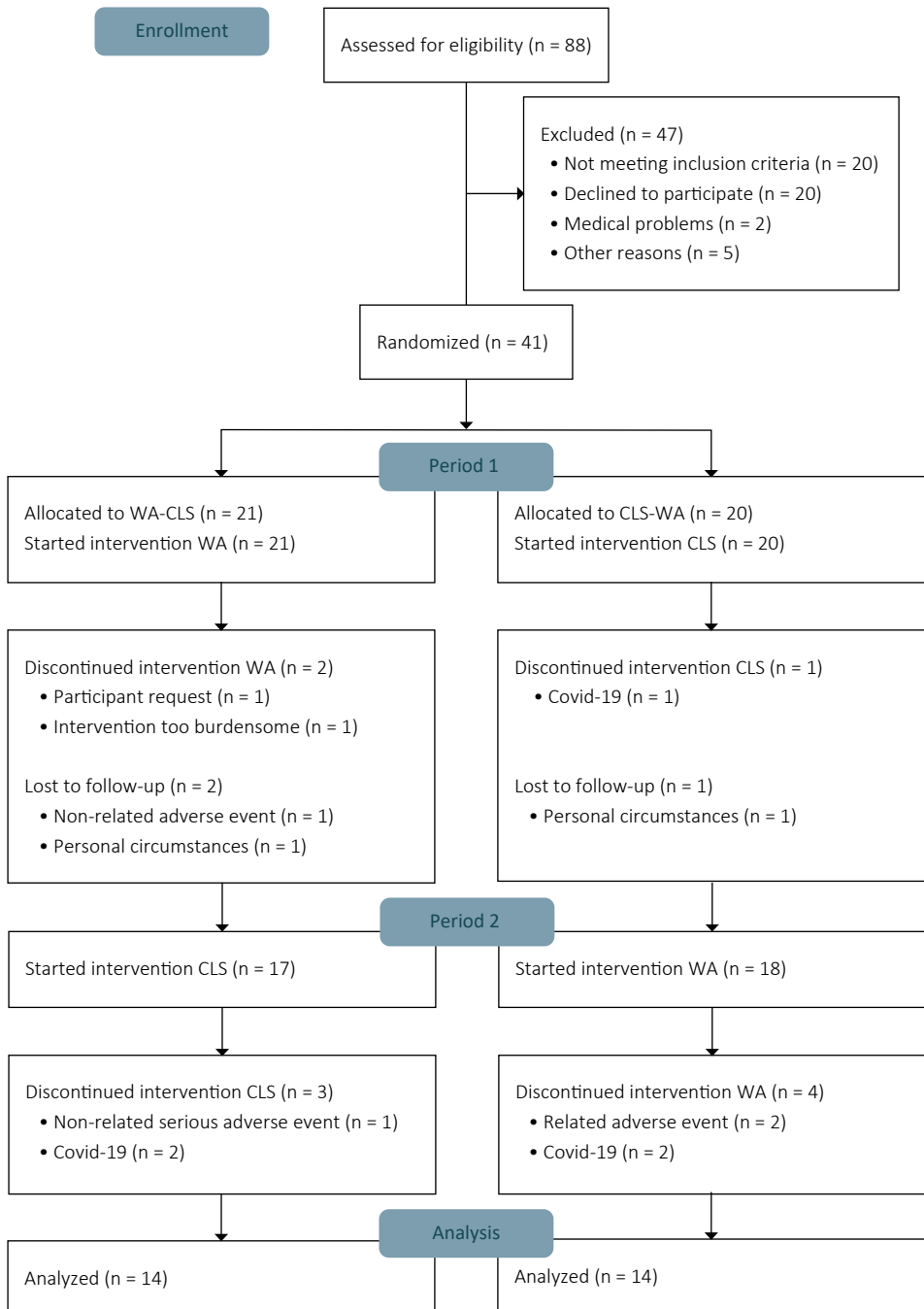
Figure 2 Flow diagram of participants. WA = Walking Adaptability training; CLS = Conventional Locomotor and Strength training.

3

Table 1 Participant characteristics at baseline [a]

	Included		Analyzed	
	WA-CLS group	**CLS-WA group**	**WA-CLS group**	**CLS-WA group**
N	21	20	14	14
Demographic				
Age (year) [b]	60 (53-67)	66 (62-72)	61 (53-71)	66 (50-73)
Weight (kg) [c]	84 ± 14	79 ± 13	82 ± 14	80 ± 14
Height (cm) [c]	177 ± 10	173 ± 11	176 ± 10	174 ± 12
Sex				
Men	14	10	8	7
Women	7	10	6	7
Injury-related				
AIS				
Grade C	2	2	2	1
Grade D	19	18	12	13
Level of injury				
Cervical	11	10	7	7
Thoracic	4	6	2	4
Lumbar	6	4	5	3
Time post injury (month) [b]	50 (21-120)	66 (20-135)	31 (18-120)	62 (20-102)
Cause				
Traumatic	6	7	6	4
Non-traumatic	15	13	8	10
Mobility-related				
Functional Ambulation Categories				
Cat 4	6	6	4	3
Cat 5	15	14	10	11
Use of outdoor walking aids	14	15	10	9
Single-point cane or crutch	5	5	4	4
Two crutches	2	4	1	2
Walker	7	6	5	3
Use of ankle-foot orthoses	3	6	1	4

[a] Values are reported as number of participants unless stated otherwise. [b] Reported as median (interquartile range). [c] Reported as mean ± standard deviation. WA = Walking Adaptability training; CLS = Conventional Locomotor and Strength training; AIS = American spinal injury association Impairment Scale.

3

Table 2 Walking capacity, functional ambulation, balance confidence and participation at baseline, T1, and T2 [a]

	WA-CLS group (n = 14)			CLS-WA group (n = 14)			ANCOVA (mean group difference) [b]	ANCOVA (stats)
	Baseline	T1	T2	Baseline	T1	T2	T2	T2
Maximal walking speed (m/s)	0.76 ± 0.26	0.85 ± 0.32	0.87 ± 0.31	0.93 ± 0.24	1.07 ± 0.30	1.12 ± 0.30	0.07 (-0.07 – 0.22)	$F_{(1, 25)} = 1.05$, $p = 0.32$
SCI-FAP score [c]	26 (17-70)	26 (12-63)	24 (13- 62)	15 (11-28)	11 (10-26)	12 (9-25)	- [d]	$F_{(1, 25)} = 0.31$, $p = 0.58$
ABC score	55 ± 19	57 ± 19	54 ± 19	58 ± 17	65 ± 11	71 ± 18 [e]	13.0 (3.8 – 22.3)	$F_{(1,24)} = 8.45$, $p < 0.01$
USER-P score								
Frequency	29 ± 8	28 ± 8	28 ± 7	34 ± 8	33 ± 9	34 ± 8 [e]	3.7 (-1.3 – 8.7)	$F_{(1,24)} = 2.37$, $p = 0.14$
Restrictions	71 ± 17	76 ± 13	77 ± 13	70 ± 19	79 ± 10	84 ± 12 [e]	8.2 (0.5 – 16.0)	$F_{(1,24)} = 4.80$, $p = 0.04$
Satisfaction	63 ± 13	66 ± 8	62 ± 9	66 ± 17	64 ± 16	68 ± 19 [e]	4.1 (-2.3 – 10.5)	$F_{(1,24)} = 1.74$, $p = 0.20$

[a] Values are reported as mean ± standard deviation unless stated otherwise. [b] Reported as mean (95% confidence interval); CLS-WA group minus WA-CLS group, adjusted for group differences at baseline. [c] Reported as median (interquartile range). [d] Data are LOG-transformed, therefore no mean difference is reported. [e] n = 13. WA = Walking Adaptability training; CLS = Conventional Locomotor and Strength training; SCI-FAP = Spinal Cord Injury Functional Ambulation Profile (range of 0 to 2100, lower scores indicate higher functioning); ABC = Activities-specific Balance (range of 0 to 100); USER-P = Utrecht Scale for Evaluation of Rehabilitation-Participation (range of 0 to 100); ANOCVA = analysis of covariance.
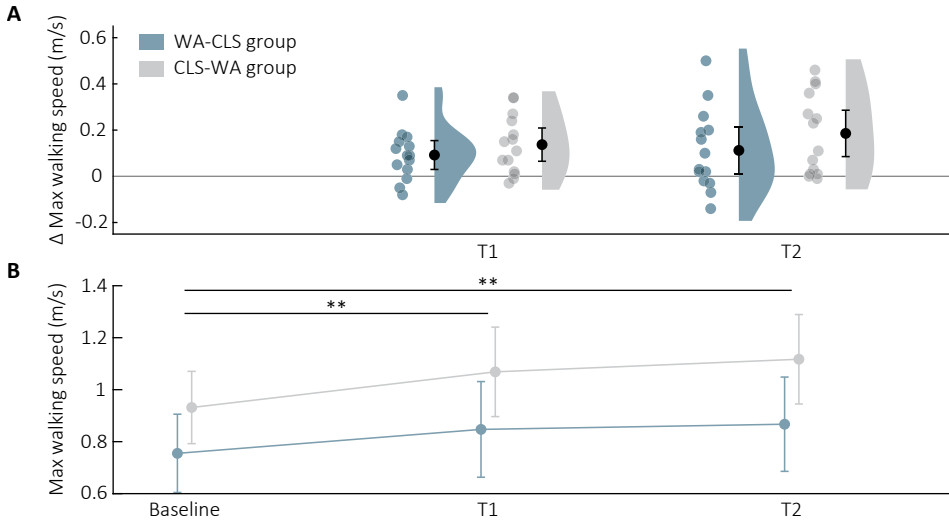
3

Figure 3 Changes in maximal walking speed over time with respect to baseline (A) and absolute maximal walking speed over time (B). Dots represent the individual data points and bars the means with 95% confidence intervals. WA = Walking Adaptability training; CLS = Conventional Locomotor and Strength training. ** represents a significant time effect when data of both groups are pooled.

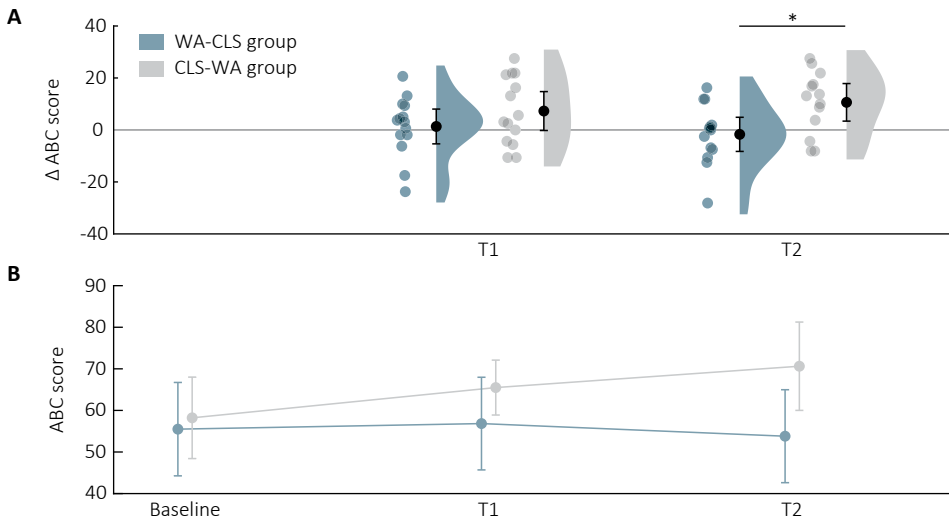**Figure 4** Changes in Activities-specific Balance Confidence (ABC) scores over time with respect to baseline (A) and absolute ABC scores over time (B). Dots represent the individual data points and bars the means with 95% confidence intervals. WA = Walking Adaptability training; CLS = Conventional Locomotor and Strength training. * represents a significant group difference as measured with analysis of covariance.

Participation

ANCOVA showed a significant group difference in the USER-P restrictions score at T2 ($F_{(1, 24)}$ = 4.80, p = 0.04). The CLS-WA group exhibited 8 points (95% CI = 0.5 – 16.0; adjusted for baseline values) more improvement in terms of the USER-P restrictions score in comparison to the WA-CLS group (Table 2; Figure 5). No significant group difference for the USER-P restrictions score was found at T1. Furthermore, no significant group differences or time effects were found for the USER-P frequency or satisfaction scores (Table 2).
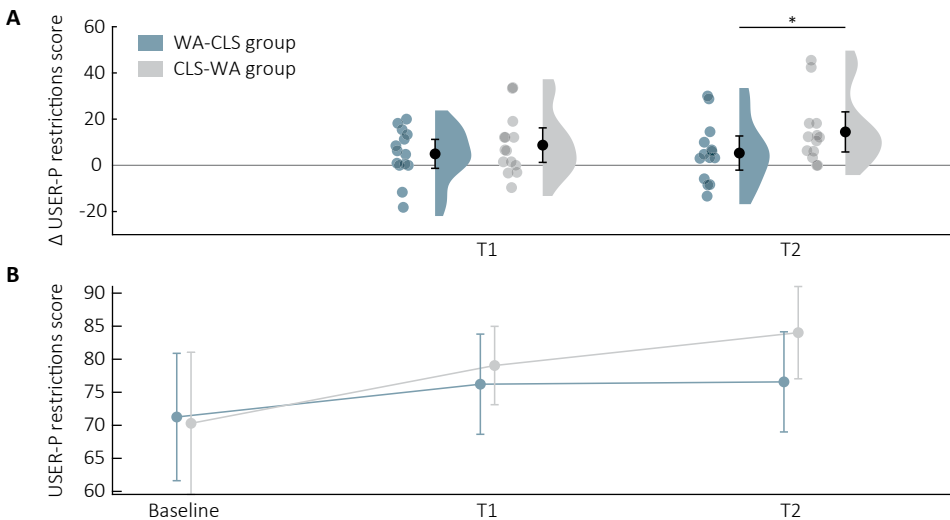

Figure 5 Changes in Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) restrictions scores over time with respect to baseline (A) and absolute USER-P restrictions scores over time (B). Dots represent the individual data points and bars the means with 95% confidence intervals. WA = Walking Adaptability training; CLS = Conventional Locomotor and Strength training. * represents a significant group difference as measured with analysis of covariance.

Discussion

Contrary to our hypothesis, conventional locomotor and strength training followed by walking adaptability training did not yield superior improvement in walking capacity among individuals with iSCI when compared to training in the reversed order. This unexpected result might be attributed to the choice of our primary outcome measure of walking capacity, which was operationalized as maximal walking speed during a 2mWT. While walking speed is a widely accepted measure of walking capacity with established correlations to various

functional ambulation skills,[26-28] it may fail to fully capture all aspects of walking adaptability. However, alternative outcome measures capable of measuring walking adaptability more comprehensively were unavailable at the onset of our study. In an effort to evaluate walking adaptability more comprehensively, we included the SCI-FAP as a secondary outcome of functional ambulation. The SCI-FAP is a measure of functional walking skills including tasks that require participants to overcome obstacles and adjust steps. Yet, similar to the 2mWT, the SCI-FAP failed to reveal a significant difference between the two intervention sequences. Consequently, our findings do not underscore a superior effect of the CLS-WA sequence on walking capacity or functional ambulation in individuals with iSCI compared to the WA-CLS sequence.

In addition to evaluating walking capacity and functional ambulation, we also assessed the influence of the intervention sequence on balance confidence and participation. The CLS-WA sequence resulted in a superior effect on balance confidence compared to the WA-CLS sequence, perhaps due to a difference in mental focus of the interventions. While CLS primarily promotes balance under predictable and fixed circumstances, WA is likely to boost balance confidence under unpredictable and changing circumstances. If CLS is administered prior to WA, individuals are exposed to an increasing level of task difficulty, which may help them to progressively build up their confidence. In case of the reversed administration sequence, some of the built-up confidence may be lost during the second intervention period and follow-up.

Similar to balance confidence, the CLS-WA sequence resulted in a superior effect on reducing participation restrictions compared to the WA-CLS sequence. Previous studies have shown that lower balance confidence and fear of falling are associated with reduced participation among older persons,[29] individuals with SCI,[30] and unilateral lower-limb amputation.[31] Therefore, the finding of reduced participation restrictions is congruent with the larger improvement in balance confidence in the CLS-WA group. Previous studies have also linked low balance confidence and fear of falling to reduced physical activity in people with iSCI[32] and other neurological impairments,[32,33] potentially leading to a lower quality of life.[34,35] Given these associations, it would be interesting to investigate whether the greater improvement in balance confidence after CLS-WA administration would translate into a larger increase in daily life physical activity and better quality of life among people with iSCI compared to WA-CLS administration.

Irrespective of the type of intervention, we observed increased maximal walking speed and improved functional ambulation after the first intervention period. These improvements were retained after the second intervention period, with merely a small (non-significant) further enhancement of maximal walking speed or functional ambulation. Consequently, our findings suggest that a second intervention period does not provide additional benefits in terms of maximal walking speed or functional ambulation. The absence of further improvement during the second intervention period is surprising, particularly in light of previous research highlighting a positive relation between a higher number of training sessions and training effect.[36] This

result might be attributable to participants who had already attained their maximal functional capacity during the initial six-week intervention. Reaching a plateau in functional capacity at T1 may also have contributed to the absence of significant group differences between both intervention sequences at T2.

Our study had several limitations that should be acknowledged. Firstly, it is important to note that this study was explorative in nature, aiming to gain a preliminary understanding of the effect of intervention sequence. Secondly, the study took place during the Covid-19 pandemic, which might have impacted the outcomes of the USER-P frequency subscale due to limited engagement in leisure and social activities. Thirdly, the Covid-19 pandemic resulted in a higher drop-out rate than initially anticipated, which reduced the statistical power of our study. Moreover, the SCI-FAP has a known ceiling effect,[22] which may have reduced its responsiveness given the relatively high baseline performance of our participants. Indeed, at T2, 21% of the participants achieved a SCI-FAP score lower than 9.6, which is the maximum score observed in able-bodied individuals.[22] Similarly, the USER-P restrictions subscale has an established ceiling effect[25] and at T2, 26% of the participants had a USER-P restrictions score of 90 or higher. Hence, although we observed a significant difference between intervention sequence on this subscale, it is possible that the observed effect size is an underestimation. Finally, the lack of blinding in the assessments may have introduced bias in the evaluation of study outcomes.

Conclusion

Administering conventional locomotor and strength training prior to walking adaptability training did not lead to a superior improvement in walking capacity or functional ambulation among ambulatory individuals with iSCI, compared to the reversed order of training. However, the sequence of conventional locomotor and strength training preceding walking adaptability training resulted in a superior effect on balance confidence and participation restrictions.

3

References

1. Barbeau H, Nadeau S, Garneau C. Physical Determinants, Emerging Concepts, and Training Approaches in Gait of Individuals with Spinal Cord Injury. J Neurotrauma. 2006;23:571–585.

2. van der Salm A, Nene A V., Maxwell DJ, Veltink PH, Hermens HJ, Ijzerman MJ. Gait impairments in a group of patients with incomplete spinal cord injury and their relevance regarding therapeutic approaches using functional electrical stimulation. Artif Organs. 2005;29:8–14.

3. van Hedel HJA. Gait speed in relation to categories of functional ambulation after spinal cord injury. Neurorehabil Neural Repair. 2009;23:343–350.

4. Lund ML, Nordlund A, Nygård L, Lexell J, Bernspång B. Perceptions of participation and predictors of perceived problems with participation in persons with spinal cord injury. J Rehabil Med. 2005;37:3–8.

5. Yang JF, Musselman KE. Training to achieve over ground walking after spinal cord injury: A review of who, what, when, and how. Journal of Spinal Cord Medicine. 2012;35:293–304.

6. Morawietz C, Moffat F. Effects of locomotor training after incomplete spinal cord injury: A systematic review. Arch Phys Med Rehabil. 2013;94:2297–2308.

7. Mehrholz J, Harvey LA, Thomas S, Elsner B. Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. Spinal Cord. 2017;55:722–729.

8. Houdijk H, van Ooijen MW, Kraal JJ, et al. Assessing gait adaptability in people with unilateral amputation on an instrumented treadmill with a projected visual context. Phys Ther. 2012;92:1452–1460.

9. Heeren A, van Ooijen MW, Geurts ACH, 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;45:616–622.

10. Yang JF, Musselman KE, Livingstone D, et al. Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial. Neurorehabil Neural Repair. 2014;28:314–324.

11. Timmermans C, Roerdink M, Meskers CGM, Beek PJ, Janssen TWJ. Walking-adaptability therapy after stroke: results of a randomized controlled trial. Trials. 2021;22:923.

12. de Rooij IJM, van de Port IGL, Punt M, et al. Effect of Virtual Reality Gait Training on Participation in Survivors of Subacute Stroke: A Randomized Controlled Trial. Phys Ther. 2021;101.

13. Venis L Van De, Warrenburg B Van De, Weerdesteyn V, Geurts ACH, Nonnekes J. Gait-Adaptability Training in People With Hereditary Spastic Paraplegia : A Randomized Clinical Trial. Neurorehabil Neural Repair. 2023;37:27–36.

14. van Dijsseldonk RB, de Jong LAF, Groen BE, Vos-van der Hulst M, Geurts ACH, Keijsers NLW. Gait stability training in a virtual environment improves gait and dynamic balance capacity in incomplete spinal cord injury patients. Front Neurol. 2018;9:963.

15. Zwijgers E, van Dijsseldonk RB, Vos- van der Hulst M, Hijmans JM, Geurts ACH, Keijsers NLW. Efficacy of walking adaptability training on walking capacity in ambulatory people with motor incomplete spinal cord injury: a multicenter pragmatic randomized controlled trial. Neurorehabil Neural Repair. 2024;38(6):413-424.

16. Balasubramanian CK, Clark DJ, Fox EJ. Walking Adaptability after a Stroke and Its Assessment in Clinical Settings. Stroke Res Treat. 2014;2014:591013.

3

17.   Duijnhoven H van. The challenges of dynamic balance & gait for people after stroke (dissertation). Nijmegen (NL): Donders Institute for Brain, Cognition and Behaviour, Radboud Univerisity Medical Center; 2019.

18.   Tuijtelaars J, Jeukens-Visser M, Nollet F, Brehm MA. Factors Associated With Walking Adaptability and Its Relationship With Falling in Polio Survivors. Arch Phys Med Rehabil. 2022;103:1983–1991.

19.   Pijnappels M, van der Burg JCE, Reeves ND, van Dieën JH. Identification of elderly fallers by muscle strength measures. Eur J Appl Physiol. 2008;102:585–592.

20.   van de Goolberg T, van de Goolberg A. Het KrachtRevalidatieSysteem. Physios. 2014;6:46–52.

21.   Willi R, Widmer M, Merz N, Bastiaenen CHG, Zörner B, Bolliger M. Validity and reliability of the 2-minute walk test in individuals with spinal cord injury. Spinal Cord. 2022;61:15–21.

22.   Musselman K, Brunton K, Lam T, Yang J. Spinal Cord Injury Functional Ambulation Profile: A New Measure of Walking Ability. Neurorehabil Neural Repair. 2011;25:285–293.

23.   Musselman KE, Yang JF. Spinal Cord Injury Functional Ambulation Profile: A Preliminary Look at Responsiveness. Phys Ther. 2014;94:240–250.

24.   Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. J Gerontol A Biol Sci Med Sci. 1995;50A:M28–M34.

25.   Post MWM, van Der Zee CH, Hennink J, Schafrat CG, Visser-Meily JMA, van Berlekom SB. Validity of the Utrecht Scale for Evaluation of Rehabilitation- Participation. Disabil Rehabil. 2012;34:478–485.

26.   Labruyère R, Van Hedel HJ. Curve walking is not better than straight walking in estimating ambulation-related domains after incomplete spinal cord injury. Arch Phys Med Rehabil. 2012;93:796–801.

27.   Verghese J, Wang C, Holtzer R. Relationship of clinic based gait speed measurement to limitations in community based activities in older adults. Arch Phys Med Rehabil. 2011;92:1-844–846.

28.   Fritz S, Lusardi M. White Paper: "Walking Speed: the Sixth Vital Sign." Journal of Geriatric Physical Therapy. 2009;32:2–5.

29.   Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE. Fear of falling: Measurement strategy, prevalence, risk factors and consequences among older persons. Age Ageing. 2008;37:19–24.

30.   Chan K, Habib Perez O, Singh H, Marinho-Buzelli AR, Hitzig SL, Musselman KE. Impact of Falls and Fear of Falling on Participation, Autonomy and Life Satisfaction in the First Year After Spinal Cord Injury. Frontiers in Rehabilitation Sciences. 2022;3:1–8.

31.   Sions JM, Manal TJ, Horne JR, Sarlo FB, Pohlig RT. Balance-Confidence is Associated with Community Participation, Perceived Physical Mobility, and Performance- Based Function among Individuals with a Unilateral Amputation. 2020;36:1–8.

32.   Matsuda PN, Eagen T, Hreha KP, Finlayson ML, Molton IR. Relationship Between Fear of Falling and Physical Activity in People Aging With a Disability. PM and R. 2020;12:454–461.

33.   Bryant MS, Rintala DH, Hou JG, Protas EJ. Relationship of falls and fear of falling to activity limitations and physical inactivity in parkinson's disease. J Aging Phys Act. 2015;23:187–193.

34.   Soriano JE, Squair JW, Cragg JJ, et al. A national survey of physical activity after spinal cord injury. Sci Rep. 2022;12:1–10.

35.   Stevens SL, Caputo JL, Fuller DK, Morgan DW. Physical activity and quality of life in adults with spinal cord injury. Journal of Spinal Cord Medicine. 2008;31:373–378.

36.   Hornby T, Straube D, Kinnaird C, et al. Importance of specificity, amount, and intensity of locomotor training to improve ambulatory function in patients poststroke. Top Stroke Rehabil. 2011;18:293–307.

Chapter 4

Impaired foot placement strategy during walking in people with incomplete spinal cord injury

Eline Zwijgers
Edwin H.F. van Asseldonk
Marije Vos-van der Hulst
Alexander C.H. Geurts
Noël L.W. Keijsers

4

Abstract

Background

Impaired balance during walking is a common problem in people with incomplete spinal cord injury (iSCI). To improve walking capacity, it is crucial to characterize balance control and how it is affected in this population. The foot placement strategy, a dominant mechanism to maintain balance in the mediolateral (ML) direction during walking, can be affected in people with iSCI due to impaired sensorimotor control. This study aimed to determine if the ML foot placement strategy is impaired in people with iSCI compared to healthy controls.

Methods

People with iSCI (n = 28) and healthy controls (n = 19) performed a 2-minute walk test at a self-paced walking speed on an instrumented treadmill. Healthy controls performed one extra test at a fixed speed set at 50% of their preferred speed. To study the foot placement strategy of a participant, linear regression was used to predict the ML foot placement based on the ML center of mass position and velocity. The accuracy of the foot placement strategy was evaluated by the root mean square error between the predicted and actual foot placements and referred to as foot placement deviation. Independent t-tests were performed to compare foot placement deviation of people with iSCI versus healthy controls walking at two different walking speeds.

Results

Foot placement deviation was significantly higher in people with iSCI compared to healthy controls independent of walking speed. Participants with iSCI walking in the self-paced condition exhibited 0.40 cm (51%) and 0.33 cm (38%) higher foot placement deviation compared to healthy controls walking in the self-paced and the fixed-speed 50% condition, respectively.

Conclusion

Higher foot placement deviation in people with iSCI indicates an impaired ML foot placement strategy in individuals with iSCI compared to healthy controls.

Background

Impaired balance during walking is a common problem in people with incomplete spinal cord injury (iSCI).[1] Indeed, individuals with iSCI experience reduced functional ambulation[2] and increased fall risk.[3] Hence, improving dynamic balance is essential to them. Characterizing balance control during walking and how dynamic balance is affected in people with iSCI is crucial for designing and improving effective intervention strategies. However, only few studies have investigated balance control during walking in people with iSCI.[4-9]

Balance control requires coordination of the center of mass (COM) relative to the base of support (BOS). During walking, the relation between the COM and BOS is typically modulated by a combination of the hip, ankle, and foot placement strategy.[10,11] Basically, the hip and ankle strategies involve adjustments to the COM by rotating the body around the respective joints.[10-12] The foot placement strategy involves adjustments to the BOS by controlling the location and timing of foot placement.[10,11] The foot placement strategy modulates the relation between the COM and BOS at relatively low actuation costs, because it only requires movement of the swing leg. Consequently, foot placement is the dominant mechanism to maintain balance in the mediolateral (ML) direction during walking in healthy subjects.[13,14]

Literature suggests that ML foot placement is based on COM kinematics.[15-19] This was first observed in simulations, where stable walking was achieved by positioning the foot at a fixed distance lateral to the extrapolated COM (i.e., the COM position adjusted for its velocity).[15] The relation between ML foot placement and COM kinematics was also observed in experiments investigating foot placement modulation in healthy subjects.[16-19] For example, in the work of Vlutters et al.,[18] healthy subjects showed foot placement adjustments proportional to the ML COM velocity when being perturbed in the ML direction during walking. Furthermore, Wang and Srinivasan[19] showed that ML foot placement can be predicted by the ML COM position and velocity, suggesting that the ML foot placement strategy comprises a strong relation between ML COM kinematics and ML foot placement.

Adjusting foot placement based on COM kinematics requires an adequate estimate of the COM state and sufficient ability to move the swing leg. The COM kinematics must be estimated using visual, vestibular, and proprioceptive information,[14] which inputs are used to control the placement of the swing leg, for instance, by modulating the activity of the hip abductor muscles to make step adjustments in the ML direction.[20] Because iSCI potentially affects the afference of sensory information as well as the conduct of efferent neural signals to the muscles,[1] it may easily impact the ML foot placement strategy. Indeed, impaired foot placement after iSCI has already been suggested by Day and colleagues.[4] Their results revealed higher variability in ML foot placement relative to the COM position in people with iSCI compared to healthy controls. Moreover, in the study of Arora et al.,[7] people with iSCI generated less soleus activation in the swing leg after slip perturbations, suggesting impaired muscle control in balance-challenging conditions. Cornwell et al.[6] examined the effect of walking speed on gait stability and concluded

4

that individuals with iSCI were able to maintain lateral stability when walking at a fast speed, even when their lateral balance was challenged. Furthermore, their results suggested a weaker coordination between COM state and lateral foot placement in people with iSCI compared to healthy controls, implying an impaired ML foot placement strategy. However, they instructed participants to maintain their COM within a narrow target lane, which may yield different results than unrestricted walking. Therefore, more research is necessary to evaluate the ML foot placement strategy in people with iSCI during regular straight walking.

The main purpose of this study was to determine if the ML foot placement strategy is impaired in people with iSCI compared to healthy controls. More specifically, this study investigated the relation between ML COM kinematics and ML foot placement during straight walking in both populations. We hypothesized that the ML foot placement strategy would be impaired in people with iSCI.[6]

Methods

Participants

Participants were people with iSCI that had been referred to GRAIL (Gait Real-time Analysis Interactive Lab) training by a rehabilitation physician to improve their gait capacity and dynamic balance. Inclusion criteria were: 1) a motor incomplete spinal cord injury with a traumatic or non-traumatic cause (American spinal injury association Impairment Scale (AIS) C or D), 2) six months post injury, 3) ability to walk in a self-paced mode on the GRAIL without using the handrails, and 4) age ≥ 18 years. Subjects were excluded if they had preinjury impairments of the nervous system, or lower limbs, or any other impairment that might affect balance control. Healthy controls were included if they were 18 years or older without a history of neurological or musculoskeletal problems. The study was approved by the regional medical ethics committee of Arnhem-Nijmegen (2019-5255). All participants provided written informed consent under the Declaration of Helsinki.

Data collection

Participants were tested on an instrumented split-belt treadmill (GRAIL, Motek Medical BV, the Netherlands). Kinematic data were acquired using an ten-camera motion capture system (VICON, Oxford, United Kingdom). Reflective markers were placed on 19 anatomical landmarks: 7th cervical vertebra and left and right acromion process, humeral lateral epicondyle, ulnar styloid process, Anterior Superior Iliac Spine (ASIS), Posterior Superior Iliac Spine (PSIS), femoral lateral epicondyle, lateral malleolus, metatarsal II, and calcaneus. Marker data were sampled at 100 Hz.

Protocol

All participants performed a 2-minute Walk Test (2mWT) at a self-paced speed on the treadmill. The participants with iSCI performed the 2mWT at the start of their first training session. The speed of the belt was adjusted in real-time to the anterior-posterior position and velocity of the pelvis to allow participants to walk at a self-selected walking speed (self-paced mode), which is a suitable alternative to fixed-speed treadmill walking in gait analysis.[21,22] In the self-paced mode, walking on the front part of the treadmill results in acceleration proportional to the difference between the pelvis position and middle of the belt, and to the velocity of the pelvis. Likewise, walking on the back part of the treadmill results in deceleration. The participants were instructed to walk at a comfortable walking speed. The healthy controls performed one extra 2mWT at a fixed speed equal to 50% of their mean self-paced walking speed (preferred speed) to analyze the effects of walking speed on their ML foot placement strategy, and because this speed was presumed to be similar to the preferred walking speed of the participants with iSCI.[23] A fixed speed was selected because walking in the self-paced mode at 50% of the preferred speed is challenging, and previous research found no significant differences between self-paced and fixed-speed walking.[21,22] Before the 2mWTs, participants performed one to four one-minute practice rounds to familiarize themselves with walking on the treadmill. To ensure safety, all participants wore a safety harness attached to a rail on the ceiling, without body weight support.

Data analysis

Data were processed using MATLAB (R2019b, MathWorks). The first 20 and last 5 seconds of each 2mWT were excluded from the analysis to remove the start and stop phases. Gaps in the ASIS and PSIS marker data were automatically filled using the rigid body method as previously described.[24] Cubic spline fill was used for the remaining markers when a gap was no more than 10 samples. Marker data were filtered with a 4th order zero-phase low-pass Butterworth filter with a cut-off frequency of 20 Hz.

Hip joint centers were estimated using the regression method reported by Dumas et al.[25] Marker data and hip joint centers were used to estimate the COM location of nine segments (torso and head, upper leg, lower leg and foot, upper arm, forearm and hand) as described by Tisserand et al.[26] Whole-body COM location was computed using a weighted sum of the segment COM locations. Gaps in the whole-body COM, resulting from gaps in the marker data, were filled using the pattern fill method as described by Camargo et al.[24] The average location of the ASIS and PSIS markers was used as the donor pattern.

Marker data of the feet were used to detect gait instances.[27] Heel strike was defined as the instant at which the anterior-posterior velocity of the calcaneus marker reversed with respect to the walking direction. Toe-off was defined as the instant at which the velocity of the metatarsal II marker reversed to the positive walking direction. Step width was defined as the distance between the left and right calcaneus marker at the instant of midstance.

To study the foot placement strategy of a participant, linear regression was used to predict the ML foot placement (FP) based on ML COM position and velocity at heel strike.[19,28-30] We used the following regression equation:

$$FP = \beta_{pos} \cdot COM + \beta_{vel} \cdot C\dot{O}M + \varepsilon$$

in which β_{pos} and β_{vel} are the regression coefficients of the COM position and velocity, respectively, and ε the model error. Foot placement was defined as the demeaned ML distance between the left and right calcaneus markers at midstance. The COM position was defined with respect to the calcaneus marker of the stance foot at mid stance, and both predictors were demeaned.

Outcome measures

The accuracy of the foot placement strategy was evaluated by the root mean square error (RMSE) between the predicted and actual foot placements. The RMSE was selected as primary outcome measure and referred to as foot placement deviation.

To confirm adherence to the foot placement strategy, the goodness of the fit of the linear regression model was evaluated with the coefficient of determination (R^2), here referred to as foot placement adherence. Substantial adherence to the foot placement strategy was considered when the coefficient of determination was larger than 0.26.[31] In addition, the within-subject standard deviation (SD) of actual foot placement was determined, because foot placement adherence is influenced by the dispersion of the actual ML foot placement.

Step width was selected as a secondary outcome measure, because wider steps have previously been linked to instability during walking[32,33] and a reduced foot placement strategy.[34]

Statistical analysis

Participant characteristics of both groups were compared with independent t-tests for continuous variables and Chi-square tests for nominal variables. Foot placement deviation of people with iSCI was compared with values obtained from healthy controls at different walking speeds using independent t-tests, whereas a difference in foot placement deviation between different walking speeds in healthy controls was tested with a dependent t-test. Likewise, group differences in foot placement adherence, in the SD of actual foot placement, and in step width were tested with independent t-tests, whereas differences between different walking speeds within the healthy control group were tested with dependent t-tests. We performed the Student's independent t-test when the assumption of homogeneity of variance was met and the Welch's independent t-test when this assumption was not met (resulting in fractional degrees of freedom). When the assumption of normality was violated, non-parametric equivalent tests were performed. The level of significance (α) was adjusted for the number of tests performed (3) and set at 0.017.

Results

Participants

In total, 30 people with iSCI and 19 healthy controls participated. Two persons with iSCI were not included in the analysis due to incomplete marker data resulting in 28 people with iSCI. Participant characteristics are reported in Table 1. No significant differences in sex and age were found between both groups. The weight and height of the iSCI group were higher compared to controls, but no significant difference in body mass index (BMI) was found between groups $(t(45) = 1.94, p = .058)$. Walking speed of the participants with iSCI was significantly lower compared to healthy controls walking in the self-paced (SP) condition $(t(41.7) = -7.35, p < .001)$, but not significantly different from their fixed-speed 50% (FS50) condition $(t(32.0) = 1.61, p = .116)$.

Table 1 Characteristics of participants with incomplete spinal cord injury (iSCI) and healthy controls (HC) (mean ± SD or median [range])

	iSCI	HC	p
N	28	19	
Demographic			
Sex (M/F)	18/10	9/10	.250
Age (yr)	58 ± 13	60 ± 9	.611
Weight (kg)	85 ± 13	75 ± 13	.010
Height (cm)	177 ± 7.9	172 ± 7.0	.034
BMI	27.2 ± 3.7	25.1 ± 3.3	.058
Walking speed			
Self-paced	0.85 ± 0.37	1.45 ± 0.18	.000
Fixed-speed 50%		0.74 ± 0.09	.116*
iSCI characteristics			
AIS (C/D)	2/26		
Level of injury	Thoracic 5 [Cervical 1 - Lumbar 4]		
Time post injury (month)	23 [6 - 212]		
Cause (traumatic/non-traumatic)	3/25		
FAC (3/4/5)	1/5/22		

BMI = Body Mass Index; AIS = American spinal injury association Impairment Scale; FAC = Functional Ambulation Categories. * Indicates the comparison between healthy controls walking in the fixed-speed 50% condition and people with iSCI walking in the self-paced condition.

4

4

Foot placement deviation

The actual ML foot placements and predicted ML foot placements of a representative participant from both groups are shown in Figure 1. At group level, foot placement deviation of people with iSCI walking in the self-paced condition was higher compared to healthy controls independent of walking speed (SP: t(45) = 5.21, p < .001; FS50: t(45) = 4.06, p < .001; Figure 2A, Table 2). Participants with iSCI exhibited 0.40 cm (51%) and 0.33 cm (38%) higher foot placement deviation compared to healthy controls walking in the self-paced and the FS50 condition, respectively. No significant difference in foot placement deviation was found between healthy controls walking in the self-paced and the FS50 condition (z = 2.01, p = .044).

Table 2 Foot placement deviation (RMSE), foot placement adherence (R²), standard deviation (SD) of the actual foot placement, and step width in people with incomplete spinal cord injury (iSCI) and healthy controls (HC) walking in the self-paced (SP) or fixed-speed 50% (FS50) condition (mean ± SD or median [range])

	iSCI SP	HC SP	HC FS50
Foot placement deviation (cm)	1.19 ± 0.30 *†	0.79 ± 0.18	0.86 ± 0.22
Foot placement adherence	0.85 [0.18-0.91] *	0.90 [0.78-0.94] ‡	0.78 [0.50-0.95]
SD actual foot placement (cm)	2.78 ± 0.88 †	2.37 ± 0.51 ‡	1.90 ± 0.62
Step width (cm)	18.17 ± 5.65 *†	12.59 ± 2.65	11.44 ± 2.73

Footnotes indicate significant differences (p < .017) between iSCI SP and HC SP (*), iSCI SP and HC FS50 (†), and HC SP and HC FS50 (‡).

Foot placement adherence

All participants except one iSCI participant showed substantial foot placement adherence (R² ≥ 0.26). At group level, foot placement adherence of people with iSCI was lower compared to healthy controls walking in the self-paced condition (z = 3.62, p < .001; Figure 2B, Table 2), but there was no longer a significant difference when people with iSCI were compared to controls in the FS50 condition (z =-1.19, p = .233). In addition, foot placement adherence was lower in healthy controls walking in the FS50 condition compared to walking in the self-paced condition (z =-3.67, p < .001).

Foot placement variability

No significant difference in the SD of actual foot placement was found between people with iSCI and healthy controls walking in the self-paced condition (t(44.0) = 1.99, p = .053; Figure 3A, Table 2). When compared to healthy controls walking in the FS50 condition, participants with iSCI exhibited 0.88 cm (46%) higher SD of actual foot placement (t(45) = 3.74, p < .001). Moreover, healthy controls walking in the self-paced condition exhibited 0.47 cm (25%) higher SD of actual foot placement compared to walking in the FS50 condition (t(18) = 4.18, p < .001).
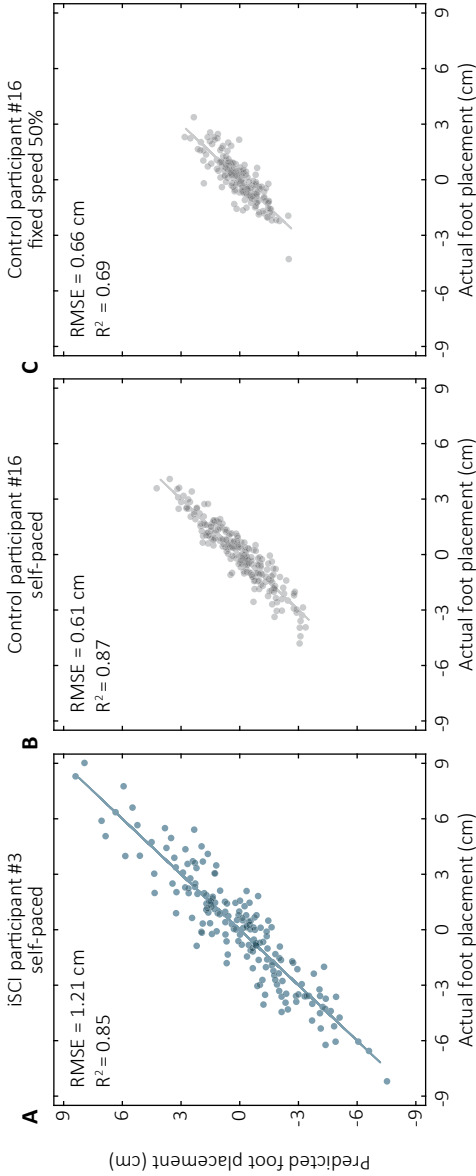
Figure 1 Actual mediolateral (ML) foot placement versus predicted ML foot placement of a person with incomplete spinal cord injury (iSCI) walking in the self-paced condition (A) and of a healthy control walking in the self-paced condition (B) and the fixed-speed 50% condition (C). RMSE indicates the root mean square error between the actual and predicted foot placements, referred to as foot placement deviation. R^2 indicates the coefficient of determination of the fit, referred to as foot placement adherence.
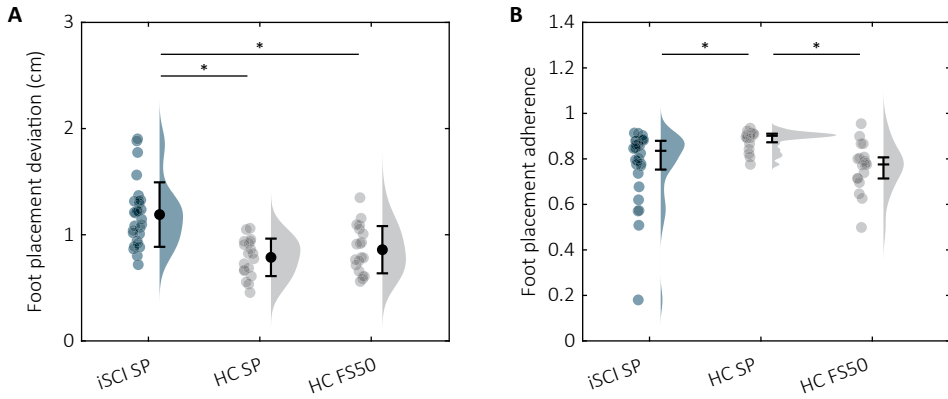
Figure 2 Raincloud plots of foot placement deviation (RMSE) (A) and foot placement adherence (R^2) (B) of people with incomplete spinal cord injury (iSCI) and healthy controls (HC) walking in the self-paced (SP) or fixed-speed 50% (FS50) condition. Dots represent the individual data points and bars the mean ± standard deviation (panel A) or median and 25th and 75th percentile (panel B). * p <.017.

Step width

Step width of people with iSCI was higher compared to healthy controls independent of walking speed (SP: t(40.9) = 5.45, p < .001; FS50: t(41.4) = 5.44, p < .001; Figure 3B, Table 2). Participants with iSCI walked with 5.59 cm (44%) and 6.73 cm (59%) wider steps compared to healthy controls walking in the self-paced and the FS50 condition, respectively. No significant difference in step width was found between healthy controls walking in the self-paced condition and the FS50 condition (t(18) = 2.33, p = .032).

Discussion

In the current study, we found that – independent of walking speed – the accuracy of the ML foot placement strategy during walking in people with iSCI was reduced compared to healthy controls.

Foot placement deviation

Congruent with our hypothesis, people with iSCI showed significantly higher foot placement deviation compared to healthy controls, indicating an impaired ML foot placement strategy. This finding is in line with the results of Cornwell et al.[6] and Day et al.,[4] who found indications of a weaker coordination between COM state and lateral foot placement in individuals with iSCI. An impaired ML foot placement strategy in people with iSCI could be explained by
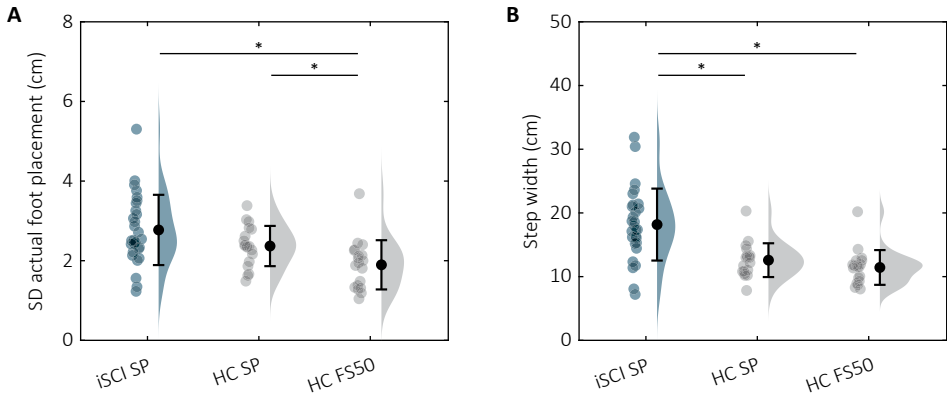
Figure 3 Raincloud plots of the standard deviation (SD) of the actual foot placement (A) and step width (B) of people with incomplete spinal cord injury (iSCI) and healthy controls (HC) walking in the self-paced (SP) or fixed-speed 50% (FS50) condition. Dots represent the individual data points and bars the mean ± standard deviation. * p < .017.

two important underlying mechanisms. The first mechanism is the impaired proprioceptive information from body structures below the lesion level[1] that could impede the estimation of the COM state and the spatial location of the feet. Indeed, changes in ML foot placement during walking have been observed in healthy subjects when proprioceptive information from muscle spindles was manipulated through muscle vibration.[35] The second mechanism is the decreased muscle coordination in people with iSCI,[1] which affects the ability to control the swing leg and therefore limits the coordination of foot placement. In line with this notion, previous research observed a smaller magnitude of soleus activation in the swing leg after slip perturbations in people with iSCI compared to healthy controls,[7] implying impaired muscle control in balance-challenging conditions. Moreover, decreased coordination of foot placement has been observed in people with stroke performing a hip abduction tracking task,[36] suggesting that reduced control of the swing leg may limit coordination between COM movement and foot placement. With the current study, we cannot determine to what extent impaired proprioceptive information and/or decreased muscle coordination underly the impaired foot placement strategy in people with iSCI. Therefore, future research should focus on disentangling the role of both mechanisms on the foot placement strategy, which can help design and optimize interventions for people with iSCI. Nevertheless, current interventions could focus on provoking more lateral COM excursion and velocity to specifically train the coordination between COM kinematics and ML foot placement. Examples of such interventions are perturbation-based balance training[37] or walking adaptability training.[38]

4

Foot placement adherence and variability

All participants except one participant with iSCI showed substantial adherence to the foot placement strategy, indicating that both people with iSCI and healthy controls use the foot placement strategy during walking. People with iSCI had significantly lower foot placement adherence compared to healthy controls walking at a self-paced speed. However, when corrected for walking speed, the significant group difference in foot placement adherence disappeared. It should be acknowledged that foot placement adherence is influenced by the within-subject SD of actual foot placement, i.e., a larger SD of actual foot placement results in larger foot placement adherence. In line with previous research,[4] participants with iSCI walking at a self-paced speed showed a significantly larger SD of actual foot placement compared to healthy controls walking at 50% of their preferred speed (see Figures 1 and 3). As a result, a valid comparison of foot placement adherence between both groups is hard to make.

Step width

Participants with iSCI had a larger step width compared to healthy controls. Increased step width has previously been linked to instability during walking.[32,33] Healthy subjects increased step width when perturbed in the ML direction[39] or while walking on a destabilizing surface.[40] In contrast, individuals with iSCI decreased step width when walking stability was increased by external lateral stabilization.[9] Moreover, healthy subjects decreased modulation of foot placement based on the COM state in response to an increased (imposed) step width.[34] These results suggest that wider steps increase postural stability and therefore reduce the demand for accurate foot placement modulation. Therefore, it is likely that people with iSCI increased their step width to improve postural stability, thereby compensating for a decreased foot placement strategy.

Effect of walking speed

The walking speed of the participants with iSCI was significantly lower compared to healthy controls walking in the self-paced condition. Therefore, an effect of walking speed on the foot placement strategy should be considered. Healthy controls showed similar foot placement deviation while walking at 50% of their preferred walking speed compared to walking at a self-paced (preferred) speed, suggesting no effect of walking speed on the ML foot placement strategy. In the literature, conflicting results regarding the effect of walking speed on the ML foot placement strategy have been reported. Wang and Srinivasan[19] found no effect of walking speed on the prediction of ML foot placement based on the upper body state. Likewise, Stimpson et al.[41] observed that speed-dependent differences in the ML foot placement strategy largely disappeared at the end of a step. In contrast, Cornwell et al.[6] and van Leeuwen et al.[30] found a stronger correlation between COM state and ML foot placement at fast walking speeds. Of note, all studies assessed foot placement adherence (R^2) to evaluate the foot placement strategy. As mentioned before, foot placement adherence is influenced by the within-subject SD of actual foot placement. Because this latter parameter increases at faster walking speeds,[6,41,42] the effect of walking speed on foot placement adherence is hard to extrapolate.

Limitations

Participants with iSCI were included if they were able to walk in a self-paced mode on the GRAIL without using the handrails. This resulted in a group of individuals who were mild to moderately affected. Therefore, the results cannot be generalized to all individuals with iSCI. As a higher impairment level in iSCI potentially affects their sensorimotor control more, it can be expected that the ML foot placement strategy is more severely impaired in individuals with a higher impairment level. Further research is necessary to evaluate the relation between the ML foot placement strategy and the level of impairment in people with iSCI.

Healthy controls walking in the FS50 condition exhibited 0.47 cm lower SD of actual foot placement compared to walking in the self-paced condition. This decrease in SD of actual foot placement when walking in the FS50 condition could be the result of a difference in treadmill mode (i.e., fixed speed versus self-paced). Yet, Sloot et al.[21] showed that step width variability increased with only 1 mm when walking in a fixed speed mode compared to a self-paced mode. Therefore, we anticipate that the treadmill mode itself had only little effect on the SD of actual foot placement.

Finally, the healthy controls in this study were not sex- or age-matched to the participants with iSCI. Nevertheless, we aimed to include healthy controls in a similar age category as the majority of people with iSCI (age ≥ 45 years).[43] Furthermore, we found no significant difference in age and sex between both groups.

Conclusion

This study found a higher foot placement deviation in people with iSCI compared to healthy controls independent of walking speed, indicative of an impaired ML foot placement strategy. Moreover, our results suggested that people with iSCI tended to compensate for this decreased foot placement strategy by increasing their step width. Future research should focus on improving the foot placement strategy by targeted balance training.

4

References

1. Wirz M, van Hedel HJA. Balance, gait, and falls in spinal cord injury. In: Handbook of Clinical Neurology.Vol 159. 3rd ed. Elsevier B.V.; 2018:367–384.

2. van Hedel HJA. Gait speed in relation to categories of functional ambulation after spinal cord injury. Neurorehabil Neural Repair. 2009;23:343–350.

3. Brotherton SS, Krause JS, Nietert PJ. Falls in individuals with incomplete spinal cord injury. Spinal Cord. 2007;45:37–40.

4. Day K v., Kautz SA, Wu SS, Suter SP, Behrman AL. Foot placement variability as a walking balance mechanism post-spinal cord injury. Clinical Biomechanics. 2012;27:145–150.

5. Lemay JF, Duclos C, Nadeau S, Gagnon D, Desrosiers É. Postural and dynamic balance while walking in adults with incomplete spinal cord injury. Journal of Electromyography and Kinesiology. 2014;24:739–746.

6. Cornwell T, Woodward J, Ochs W, Gordon KE. Stabilization Strategies for Fast Walking in Challenging Environments With Incomplete Spinal Cord Injury. Frontiers in Rehabilitation Sciences. 2021;2:1–14.

7. Arora T, Musselman KE, Lanovaz JL, et al. Reactive balance responses to an unexpected slip perturbation in individuals with incomplete spinal cord injury. Clinical Biomechanics. 2020;78:105099.

8. Ochs WL, Woodward J, Cornwell T, Gordon KE. Meaningful measurements of maneuvers: People with incomplete spinal cord injury 'step up' to the challenges of altered stability requirements. J Neuroeng Rehabil. 2021;18:1–13.

9. Matsubara JH, Wu M, Gordon KE. Metabolic cost of lateral stabilization during walking in people with incomplete spinal cord injury. Gait Posture. 2015;41:646–651.

10. Reimann H, Fettrow TD, Thompson ED, Agada P, McFadyen BJ, Jeka JJ. Complementary mechanisms for upright balance during walking. PLoS One. 2017;12:1–16.

11. Reimann H, Fettrow T, Jeka JJ. Strategies for the control of balance during locomotion. Kinesiology Review. 2018;7:18–25.

12. Blenkinsop GM, Pain MTG, Hiley MJ. Balance control strategies during perturbed and unperturbed balance in standing and handstand. R Soc Open Sci. 2017;4:1–12.

13. Winter DA. Human balance and posture control during standing and walking. Gait Posture. 1995;3:193–214.

14. Bruijn SM, Van Dieën JH. Control of human gait stability through foot placement. J R Soc Interface. 2018;15:1–11.

15. Hof AL. The "extrapolated center of mass" concept suggests a simple control of balance in walking. Hum Mov Sci. 2008;27:112–125.

16. Hof AL, Vermerris SM, Gjaltema WA. Balance responses to lateral perturbations in human treadmill walking. Journal of Experimental Biology. 2010;213:2655–2664.

17. Hof AL, van Bockel RM, Schoppen T, Postema K. Control of lateral balance in walking. Experimental findings in normal subjects and above-knee amputees. Gait Posture. 2007;25:250–258.

18. Vlutters M, van Asseldonk EHF, van der Kooij H. Center of mass velocity-based predictions in balance recovery following pelvis perturbations during human walking. Journal of Experimental Biology. 2016;219:1514–1523.

19. Wang Y, Srinivasan M. 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;10:1–5.

20. Rankin BL, Buffo SK, Dean JC. A neuromechanical strategy for mediolateral foot placement in walking humans. J Neurophysiol. 2014;112:374–383.

21. Sloot LH, van der Krogt MM, Harlaar J. Self-paced versus fixed speed treadmill walking. Gait Posture. 2014;39:478–484.

22. Theunissen K, van Hooren B, Plasqui G, Meijer K. Self-paced and fixed speed treadmill walking yield similar energetics and biomechanics across different speeds. Gait Posture. 2022;92:2–7.

23. Lapointe R, Lajoie Y, Serresse O, Barbeau H. Functional community ambulation requirements in incomplete spinal cord injured subjects. Spinal Cord. 2001;39:327–335.

24. Camargo J, Ramanathan A, Csomay-Shanklin N, Young A. Automated gap-filling for marker-based biomechanical motion capture data. Comput Methods Biomech Biomed Engin. 2020;23:1180–1189.

25. Dumas R, Chèze L, Verriest JP. Adjustments to McConville et al. and Young et al. body segment inertial parameters. J Biomech. 2007;40:543–553.

26. Tisserand R, Robert T, Dumas R, Chèze L. A simplified marker set to define the center of mass for stability analysis in dynamic situations. Gait Posture. 2016;48:64–67.

27. Zeni JA, Richards JG, Higginson JS. Two simple methods for determining gait events during treadmill and overground walking using kinematic data. Gait Posture. 2008;27:710–714.

28. Mahaki M, Bruijn SM, van Dieën JH. The effect of external lateral stabilization on the use of foot placement to control mediolateral stability in walking and running. PeerJ. 2019;7:e7939:1–15.

29. Hoogstad LA, van Leeuwen AM, van Dieën JH, Bruijn SM. Can foot placement during gait be trained? Adaptations in stability control when ankle moments are constrained. J Biomech. 2022;134:1–7.

30. van Leeuwen AM, van Dieën JH, Daffertshofer A, Bruijn SM. Active foot placement control ensures stable gait: Effect of constraints on foot placement and ankle moments. PLoS One. 2020;15:1–19.

31. Cohen J. Multiple regression and correlation analysis. In: Statistical power analysis for the behavioral sciences. 2nd ed. New York: Lawrence Erlbaum Associates; 1988:407–465.

32. van Vugt Y, Stinear J, Claire Davies T, Zhang Y. Postural stability during gait for adults with hereditary spastic paraparesis. J Biomech. 2019;88:12–17.

33. Hak L, Houdijk H, van der Wurff P, et al. Stepping strategies used by post-stroke individuals to maintain margins of stability during walking. Clinical Biomechanics. 2013;28:1041–1048.

34. Perry JA, Srinivasan M. Walking with wider steps changes foot placement control, increases kinematic variability and does not improve linear stability. R Soc Open Sci. 2017;4:1–9.

35. Roden-Reynolds DC, Walker MH, Wasserman CR, Dean JC. Hip proprioceptive feedback influences the control of mediolateral stability during human walking. J Neurophysiol. 2015;114:2220–2229.

36. Dean JC, Embry AE, Stimpson KH, Perry LA, Kautz SA. Effects of hip abduction and adduction accuracy on post-stroke gait. Clinical Biomechanics. 2017;44:14–20.

37. Unger J, Chan K, Lee JW, et al. The Effect of Perturbation-Based Balance Training and Conventional Intensive Balance Training on Reactive Stepping Ability in Individuals With Incomplete Spinal Cord Injury or Disease: A Randomized Clinical Trial. Front Neurol. 2021;12:1–13.

38. van Dijsseldonk RB, de Jong LAF, Groen BE, Vos-van der Hulst M, Geurts ACH, Keijsers NLW. Gait stability training in a virtual environment improves gait and dynamic balance capacity in incomplete spinal cord injury patients. Front Neurol. 2018;9:963.

4

39.   Hak L, Houdijk H, Steenbrink F, et al. Speeding up or slowing down?: Gait adaptations to preserve gait stability in response to balance perturbations. Gait Posture. 2012;36:260–264.

40.   Onushko T, Boerger T, Van Dehy J, Schmit BD. Dynamic stability and stepping strategies of young healthy adults walking on an oscillating treadmill. PLoS One. 2019;14:1–12.

41.   Stimpson KH, Heitkamp LN, Horne JS, Dean JC. Effects of walking speed on the step-by-step control of step width. J Biomech. 2018;68:78–83.

42.   Wu AR, Simpson CS, van Asseldonk EHF, van der Kooij H, Ijspeert AJ. Mechanics of very slow human walking. Sci Rep. 2019;9:1–10.

43.   Toda M, Nakatani E, Omae K, Fukushima M, Chin T. Age-specific characterization of spinal cord injuries over a 19-year period at a Japanese rehabilitation center. PLoS One. 2018;13.

4

4

Part II

Rehabilitation approaches to improve walking capacity after motor **complete** spinal cord injury

Chapter 5

The effect of limited sensory information on exoskeleton performance in people with complete spinal cord injury

Eline Zwijgers

Bart Nienhuis

Hennie Rijken

Ilse J.W. van Nes

Alexander C.H. Geurts

Noël L.W. Keijsers

5

Abstract

Background

Despite the absence of somatosensory information from the lower extremities, people with complete spinal cord injury (SCI) can maintain postural stability in an exoskeleton. This is partly because humans are able to reweigh the relative dependence on each of the senses. However, when the sensory environment is changed, people with complete SCI are limited in their ability to reweigh their sensory organization towards more dependence on somatosensory information. The aim of this study was to investigate the effect of limited visual and/or auditory information on exoskeleton performance in people with complete SCI.

Methods

Three experienced exoskeleton users performed twelve walking trials in the ReWalk Exoskeleton. In each trial, the presence or absence of visual and/or auditory information was varied. Exoskeleton performance was operationalized as the walking distance covered and the amount of crutch loading.

Results

In one participant, the distance covered decreased when visual information was limited. The other two participants did not show substantial differences in distance covered between sensory conditions. Two participants decreased crutch loading when visual information was restricted, and one participant decreased crutch loading when auditory information was limited.

Conclusion

The current study suggests a limited influence of the presence or absence of visual and auditory information on the distance covered in people with complete SCI walking in an exoskeleton. Interestingly, crutch loading seemed to decrease rather than increase when visual or auditory information was limited.

Background

People with complete spinal cord injury (SCI) lack motor function below their lesion level and are, thus, wheelchair dependent. In recent years, wearable exoskeletons have emerged as potential mobility devices for this population. They enable people with complete SCI to support their standing and walking ability in and outside the clinical setting.[1,2]

Although exoskeletons generate the basic motions for ambulation (i.e., standing, walking, sit to stand transfers), postural stability must be maintained by the user. Postural stability, also referred to as 'balance', is the ability to control the body's center of mass in relation to the base of support.[3] It is a complex task derived from the interaction of multiple sensorimotor processes.[4] In people with complete paraplegic SCI, the disruption of the sensorimotor loop results not only in a lack of motor function but also in the absence of somatosensory information coming from the lower extremities. As somatosensory perception is essential for postural stability,[5] the ability of people with complete SCI to maintain postural stability is affected.[6] Hence, maintaining balance in an exoskeleton is demanding and crutches are necessary.

Nevertheless, people with complete SCI can successfully stand and walk in an exoskeleton despite the absence of somatosensory information. This is partly because humans are able to reweigh the relative dependence on each of the senses when the sensory environment is changed[5,7] or one of the senses is affected.[8-13] As people with SCI miss important somatosensory information, they need a higher contribution of visual input to maintain postural stability compared to healthy subjects.[8-10] Moreover, experienced exoskeleton users with complete SCI indicated that the sound of the exoskeleton was helpful during training.[6,14]

Due to the absence of somatosensation, people with complete SCI are limited in their ability to reweigh their sensory organization towards more dependence on somatosensory information when the sensory environment is changed. Therefore, it was hypothesized that a reduction of sensory information would affect exoskeleton performance in people with complete SCI. The aim of this study was to investigate the effect of limited visual and/or auditory information on exoskeleton performance in people with complete SCI. Exoskeleton performance was operationalized as the walking distance covered and the amount of crutch loading. Limited sensory information was expected to decrease walking distance covered and increase crutch loading.

Methods

Participants

Participants were people with SCI that previously participated in the exoskeleton training program of the Sint Maartenskliniek (i.e., twenty-four training sessions of 1.5-hour over an eight-week period). Participants were included if they had 1) a motor complete SCI (American

spinal injury association Impairment Scale (AIS) A or B), 2) an injury level between T1 and L1, 3) the ability to walk in the ReWalk Exoskeleton without assistance of a physiotherapist, and 4) age ≥ 18 years old. Participants were excluded if they had visual or auditory problems that could not be resolved with glasses or a hearing device. The study was approved by the regional medical ethics committee of Arnhem-Nijmegen (2020-6868). All participants provided written informed consent under the Declaration of Helsinki.

Exoskeleton performance

The ReWalk Exoskeleton (ReWalk™; Argo Medical Technologies, Inc, Marlborough, MA, USA) has a fixed preset step length and step duration. However, the distance covered within a certain time may be affected by involuntary stops due to incorrect exoskeleton use (i.e., insufficient weight shift during the loading response causing high resistance during the initial swing and subsequently interruption of gait). Exoskeleton performance can therefore be quantified as the walking distance covered within a fixed time frame.[1] Moreover, the performance level of participants using an exoskeleton has been associated with the amount of ground reaction force underneath the feet.[15] Lower ground reaction forces in less-skilled participants were attributed to higher crutch loading, presumably to increase postural stability. This was also observed in elderly people using walkers,[16] who increased their leaning onto the walker to move the combined center of pressure (of the user and the walker) forward within the (enlarged) base of support to improve postural stability. Therefore, in this study, exoskeleton performance was evaluated both with walking distance covered and crutch loading (i.e., the amount of force applied onto the crutches).

Instrumented crutches

Two forearm crutches were instrumented with a 6-component force-torque sensor (Sensix, Biopôle, France). The force-torque sensors were each connected to a 16-Bit A/D converter (USB-1608FS, Measurement Computing Corporation, Norton, MA, USA). The A/D converters were synchronized to provide simultaneous sampling at 100 Hz. In addition, the A/D converters were connected to a laptop for data storage.

Protocol

Participants performed twelve walking trials in the ReWalk. They walked without human assistance, but for safety reasons, a physiotherapist walked behind them to provide support when necessary. Each trial consisted of straight walking for 50 seconds. During the trials, the presence or absence of visual and auditory information varied. A headphone playing white noise was used to limit auditory information and a dribble goggle, blocking downward vision, was used to limit visual information from the exoskeleton and the lower limbs. In total, there were four sensory conditions, i.e., visual and auditory information available (Control); auditory and limited visual information available (LV); visual and limited auditory information available (LA); and limited visual and limited auditory information available (LV&LA). Each sensory condition was repeated three times and the order of conditions was based on block randomization (3 blocks).

Data analysis

The walking distance covered was defined as the distance between the rear heel in the starting position and after 50 seconds. Force data were processed using Matlab (R2019b, MathWorks). For each trial, a zero adjustment for each crutch was automatically performed. The algorithm determined consecutive time frames when a crutch was unloaded (i.e., no force applied on the crutch) and removed the first and last 10% of each period. Subsequently, the mean value during these time periods was used as the offset to perform the zero adjustment. Force data were filtered with a 4th order zero-phase low-pass Butterworth filter with a cut-off frequency of 10 Hz. The total force was obtained from the summation of the force on both crutches. A step was defined as the period where the total force was above 20 N. The first and last two steps and involuntary stops were excluded from the analysis. Thereafter, the mean force per step was determined and normalized to the percentage of body weight (% BW) for each participant.

Statistical analysis

The walking distance covered was analyzed with descriptive statistics. Differences in the mean force applied on the crutches between steps were analyzed using a two-way independent ANOVA for each participant ($\alpha = 0.05$), with the availability of visual information and the availability of auditory information as independent variables.

Results

Participants

Three participants were included in the study. Participant 3 performed only 1 block (4 trials) due to fatigue. Individual participant characteristics are reported in Table 1. All participants had complete paraplegia with injury onset ranging from 11 to 30 years ago.

Distance covered

The walking distance covered in the different sensory conditions for all three participants is shown in Figure 1. Participants 1 and 3 did not show substantial differences in walking distance covered between the different sensory conditions, while in participant 2 it decreased in the condition with limited visual information.

Crutch loading

The time course of the total force applied on both crutches of a single participant is shown in Figure 2. The mean force applied on both crutches ranged from 10 to 50 % BW. The mean force per step in the four sensory conditions for all three participants is shown in Figure 3. For participant 1 there were no significant main or interaction effects. For participant 2, there was a significant main effect for the presence of visual information ($F(1,328) = 36.97$, $p < 0.01$) and the presence of auditory information ($F(1,328) = 11.92$, $p < 0.01$). The mean force on the

crutches was higher in the conditions in which visual information was available (Control and LA) compared to the conditions in which visual information was limited (LV and LV&LA). The same effect was found for auditory information as the mean force on the crutches was higher in the conditions in which auditory information was available (Control and LV) compared to the conditions in which auditory information was limited (LA and LV&LA). For participant 3, there was a significant main effect for the presence of visual information ($F(1,126) = 7.35$, $p < 0.01$). Specifically, the mean force on the crutches was higher in the conditions in which visual information was available compared to the conditions in which visual information was limited.

Table 1 Participant characteristics

	P1	P2	P3
Demographic			
Sex	M	F	M
Age (yr)	31	51	48
Weight (kg)	95	70	85
Height (cm)	183	180	193
Injury-related			
AIS	A	A	A
Level of injury	T9	T6	T6
Time post injury (yr)	11	30	13

AIS = American spinal injury association Impairment Scale; T = thoracic vertebral level.

Discussion

This study investigated the effect of limited visual and/or auditory information on exoskeleton performance in people with complete SCI. Exoskeleton performance was operationalized as the walking distance covered and the amount of crutch loading. Two out of three participants did not show considerable changes in the walking distance covered when visual and/or auditory information was limited. In the other participant, the walking distance covered decreased when visual information was restricted. With respect to crutch loading, two participants decreased loading when visual information was limited, and one participant decreased crutch loading when auditory information was limited.

Distance covered

To maintain balance, humans can rely on somatosensory, visual, and vestibular information.[5] People with complete SCI indicated that they also used the rhythmic sounds of the exoskeleton as
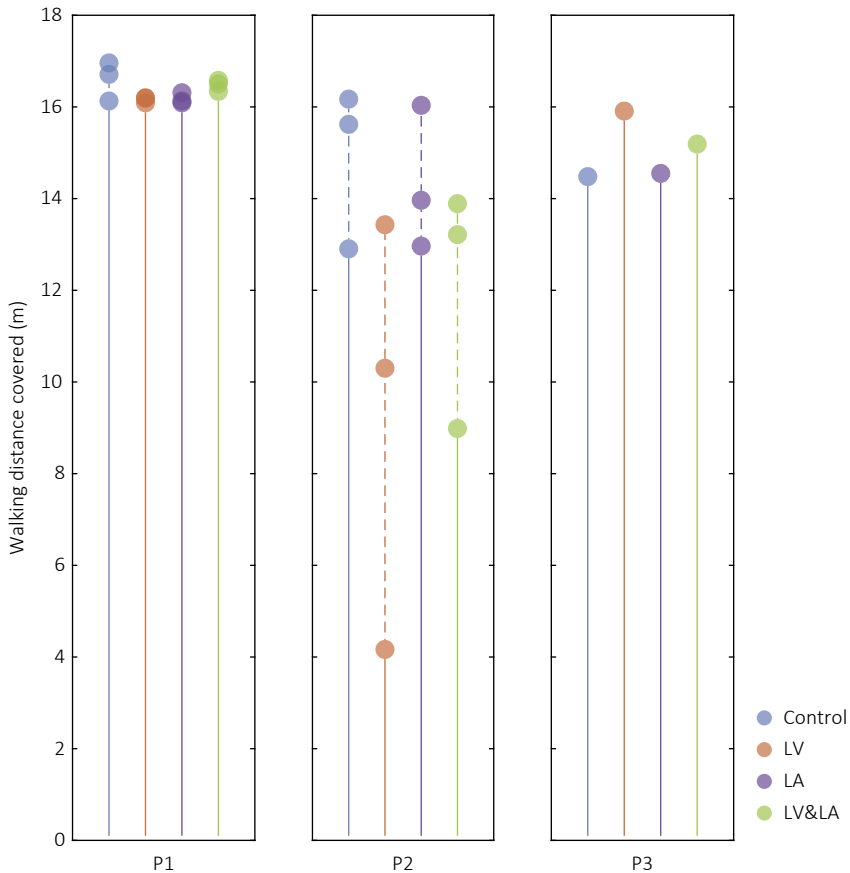
Figure 1 Walking distance covered in 50 seconds in the four sensory conditions, i.e., auditory and visual information available (Control), auditory and limited visual information available (LV), visual and limited auditory information available (LA), and limited visual and limited auditory information available (LV&LA). Dots represent a single trial.

a source of information to maintain balance.[6] As people with SCI miss important somatosensory information, they need a higher contribution of visual[8-10] and auditory[6] information to maintain postural stability. Therefore, it was expected that a reduction of sensory information would significantly affect the distance covered when walking in an exoskeleton. Surprisingly, our results suggest a limited influence of visual and auditory deprivation. This implies that the available somatosensation from segments above the spinal lesion (i.e., shoulders, arms, and partly the trunk) and the vestibulum, remain the most important sources of information to maintain balance. This is in line with healthy subjects who rely predominantly on somatosensory (70%) and vestibular (20%) information for postural stability.[5,7]
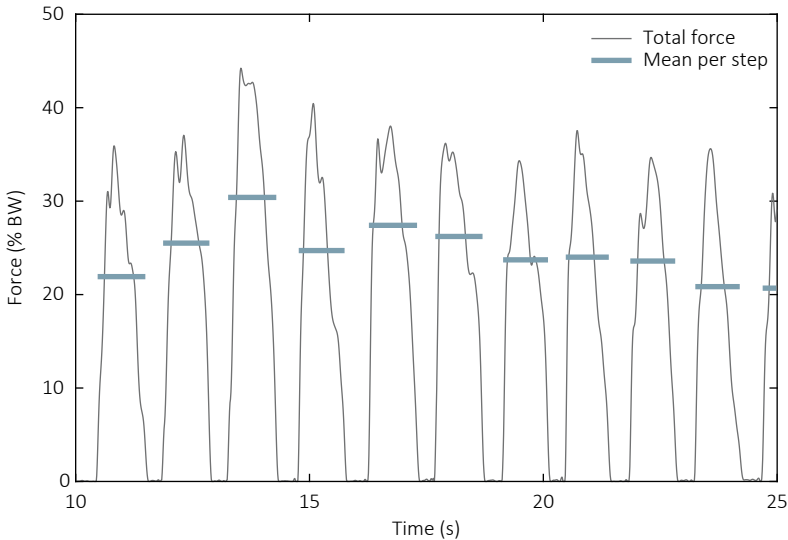
5

Figure 2 Example of a recording of the total force applied on the crutches during walking expressed as the percentage of body weight (% BW). The mean force per step was determined when the force was higher than 20 N.

Crutch loading

In addition to the walking distance covered, crutch loading was used as a measure of exoskeleton performance. Previous research found a lower amount of ground reaction force underneath the feet in less-skilled exoskeleton users and suggested that more crutch loading was used to increase postural stability.[15] Thus, it was expected that limited sensory information would result in increased crutch loading to achieve more postural stability. However, unexpectedly, two out of three participants showed decreased crutch loading when visual or auditory information was limited. A possible explanation of this decreased crutch loading might be attributed to an impaired perception of body orientation (i.e., the perception of body parts with respect to each other).

While using exoskeletons, the velocity-adjusted (or 'extrapolated') center of mass of the whole system (user, exoskeleton, and crutches) is generally located closer to the posterior border of the base of support, making users more prone to lose stability in the backward direction. When visual and auditory information was available, participants were aware of arising backward instability and presumably acted upon this by increasing the load on the crutches. On the contrary, limited sensory information may have reduced the perception of body orientation, resulting in a poorer estimation of the extrapolated center of mass with respect to the base of support and therefore unawareness of increased instability in the backward direction.
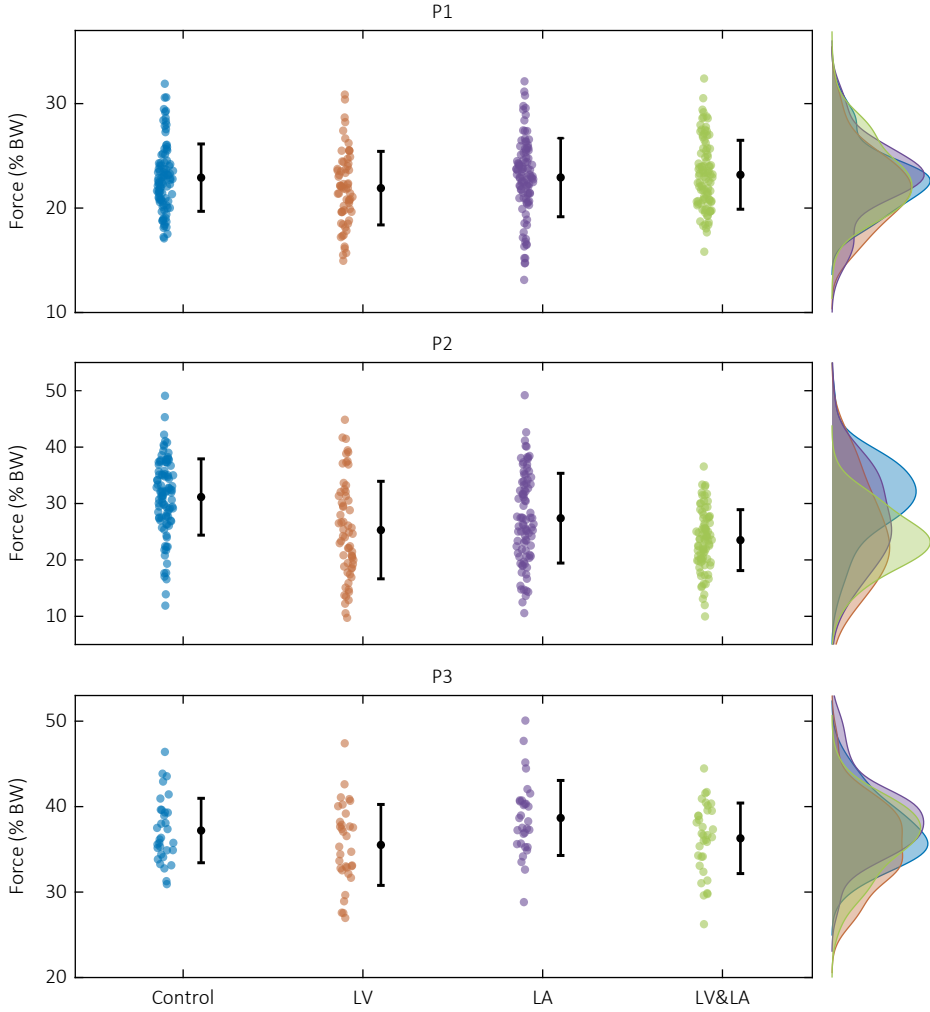
Figure 3 Raincloud plots of the mean force per step expressed as the percentage of body weight (% BW), applied on the crutches in the four sensory conditions, i.e., auditory and visual information available (Control), auditory and limited visual information available (LV), visual and limited auditory information available (LA), and limited visual and limited auditory information available (LV&LA). Dots represent the individual steps and bars the mean ± standard deviation.

5

Because the participants were unaware of increased instability in backward direction, they presumably did not increase the load on the crutches. However, this poorer estimation of the extrapolated center of mass appeared small enough not to significantly influence the walking distance covered.

The decrease in crutch loading as a result of restricted visual information could also be attributed to a change in posture. When visual information is available, exoskeleton users tend to look downwards and bend more forward to visually monitor the spatial orientation of the exoskeleton and their lower limbs. When visual information is limited, looking down becomes ineffective and people may tend to optimize their remaining sensory input by walking more upright. Finally, participants were aware that exoskeleton performance might be affected by limiting visual and auditory information. Hence, they might have disproportionately focused on their somatosensory information above the lesion when walking with restricted visual and auditory information, causing an overperformance compared to the situation where all sensory information was available.

Limitations

There are several limitations of this study. The sample size was small (n = 3), and all participants had a high spinal lesion. Future research is necessary to learn if the results apply to a larger population and whether lesion level is of influence. In addition, our participants were all experienced exoskeleton users who may have learned to quickly reweigh their sensory organization, but exoskeleton performance of unexperienced users may rely more on visual and auditory information and less on somatosensory information above the lesion. Furthermore, a physiotherapist was continuously walking behind the exoskeleton user to provide support when necessary. This may have reduced the fear of falling causing less prominent effects of limited sensory information.

Conclusion

The current study suggests a limited influence of the presence or absence of visual and auditory information on distance covered in people with complete SCI walking in an exoskeleton. Remarkably, crutch loading seemed to decrease rather than increase when visual or auditory information was limited. However, more research is needed to learn if the results apply to a larger population.

References

1. van Dijsseldonk RB, Rijken H, Nes IJW van, Meent H van de, Keijsers NLW. A framework for measuring the progress in exoskeleton skills in people with complete spinal cord injury. Front Neurosci. 2017;11:1–12.

2. van Dijsseldonk RB, van Nes IJW, Geurts ACH, Keijsers NLW. Exoskeleton home and community use in people with complete spinal cord injury. Sci Rep. 2020;10:1–8.

3. Shumway-Cook A, Woollacott MH. Motor Control: Translating Research Into Clinical Practice. Lippincott Williams & Wilkins; 2007.

4. Horak FB, Macpherson JM. Postural orientation and equilibrium. In: Rowell LB, Stepherd JT, eds. Handbook of Physiology: Section 12, Exercise Regulation and Integration of Multiple Systems. New York: Oxford University Press; 1996:255–292.

5. Peterka RJ. Sensorimotor integration in human postural control. J Neurophysiol. 2002;88:1097–1118.

6. Muijzer-Witteveen H, Sibum N, van Dijsseldonk RB, Keijsers NLW, van Asseldonk E. Questionnaire results of user experiences with wearable exoskeletons and their preferences for sensory feedback. J Neuroeng Rehabil. 2018;15:1–8.

7. Horak FB. Postural orientation and equilibrium: What do we need to know about neural control of balance to prevent falls? Age Ageing. 2006;35:7–11.

8. Ionta S, Villiger M, Jutzeler CR, Freund P, Curt A, Gassert R. Spinal cord injury affects the interplay between visual and sensorimotor representations of the body. Sci Rep. 2016;6.

9. Lee GE, Bae H, Yoon TS, Kim JS, Yi TI, Park JS. Factors that influence quiet standing balance of patients with incomplete cervical spinal cord injuries. Ann Rehabil Med. 2012;36:530–537.

10. Lemay JF, Gagnon D, Duclos C, Grangeon M, Gauthier C, Nadeau S. Influence of visual inputs on quasi-static standing postural steadiness in individuals with spinal cord injury. Gait Posture. 2013;38:357–360.

11. Lin IS, Lai DM, Ding JJ, et al. Reweighting of the sensory inputs for postural control in patients with cervical spondylotic myelopathy after surgery. J Neuroeng Rehabil. 2019;16:1–12.

12. Camicioli R, Panzer VP, Kaye J. Balance in the Healthy Elderly. Arch Neurol. 1997;54:976–981.

13. Bonan I V., Marquer A, Eskiizmirliler S, Yelnik AP, Vidal PP. Sensory reweighting in controls and stroke patients. Clinical Neurophysiology. 2013;124:713–722.

14. Gagnon DH, Vermette M, Duclos C, Aubertin-Leheudre M, Ahmed S, Kairy D. Satisfaction and perceptions of long-term manual wheelchair users with a spinal cord injury upon completion of a locomotor training program with an overground robotic exoskeleton. Disabil Rehabil Assist Technol. 2019;14:138–145.

15. Fineberg DB, Asselin P, Harel NY, et al. Vertical ground reaction force-based analysis of powered exoskeleton-assisted walking in persons with motor-complete paraplegia. Journal of Spinal Cord Medicine. 2013;36:313–321.

16. Costamagna E, Thies SB, Kenney LPJ, et al. Objective measures of rollator user stability and device loading during different walking scenarios. PLoS One. 2019;14:1–13.

5

Chapter 6

Sensory substitution in exoskeletons
for people with motor
complete spinal cord injury:
Should we implement
vibrotactile feedback?

Eline Zwijgers
Joan Lobo-Prat
Patrick P.S.J. Koomen
Ilse J.W. van Nes
Alexander C.H. Geurts
Katlin Kreamer-Tonin
Noël L.W. Keijsers

6

Abstract

Background

Over the past decade, wearable exoskeletons have emerged as promising powered assistive devices for individuals with motor complete spinal cord injury (SCI). Yet, exoskeleton motor learning and motor control are challenging, notably due to somatosensory loss below the injury level. The objective of this study was to investigate the impact of discrete vibrotactile feedback related to weight shift and step initiation on exoskeleton motor learning and motor control under both normal and sensory-deprived conditions in individuals with motor complete SCI.

Methods

Individuals with motor complete SCI underwent five training sessions and one evaluation session with the ABLE Exoskeleton. After the first introductory training session, two training sessions included feedback, and two were without. Progress during the training sessions was assessed with three 50-second walking trials without feedback. In the evaluation session, participants completed 24 50-second walking trials in four sensory conditions: 1) control, 2) limited visual, 3) limited auditory, and 4) limited visual and auditory. Half of these trials included feedback. The primary outcome measure was walking distance covered. Secondary measures focused on the center of mass trajectory in the double support phase: 1) reach path ratio and 2) reach time. User experience with vibrotactile feedback was assessed through questionnaires.

Results

Participants increased their walking distance by an average of 27% during the training sessions. Five out of six participants showed no clear indication of larger improvements during training with vibrotactile feedback compared to training without feedback. Furthermore, no clear discernible effect of vibrotactile feedback was observed in three out of the four sensory conditions. Only in the limited auditory condition, four out of six participants demonstrated a meaningful improvement on two or more outcome measures with vibrotactile feedback. The questionnaires indicated that most participants found the vibrotactile feedback beneficial during their training.

Conclusion

Discrete vibrotactile feedback related to weight shift and step initiation may not significantly enhance exoskeleton motor learning or motor control in individuals with motor complete SCI. However, individuals with motor complete SCI were generally positive about the vibrotactile feedback, particularly regarding its use during the training phase.

Background

Motor complete spinal cord injury (SCI) leads to a loss of motor, sensory, and autonomic functions below the injury level, resulting in lower-limb paralysis and subsequent reliance on wheelchair mobility. Over the past decade, wearable exoskeletons have emerged as promising powered assistive devices for this population, offering the ability to stand and walk, both within the clinical setting and in daily life.[1-7] However, individuals with motor complete SCI require an intensive training period to effectively control an exoskeleton[2,8,9] and, even after training, walking with an exoskeleton remains a challenging task.

The challenge in exoskeleton motor learning and motor control lies in maintaining dynamic stability. While exoskeletons compensate for compromised leg motor control, most cannot respond to postural instability, thus requiring users to rely on additional support such as crutches or a walker.[2,10] Moreover, maintaining dynamic stability relies on processing sensory input from the visual, vestibular, and somatosensory systems.[11] Yet, individuals with motor complete SCI experience partial to complete loss of somatosensory information below the injury level, which complicates balance maintenance. Additionally, the loss of somatosensory information may intensify reliance on other sensory modalities, such as visual inputs[12-14] or auditory cues from the exoskeleton.[15,16] In noisy or busy environments, visual and/or auditory information may not be readily available, presenting additional challenges for exoskeleton walking.

When sensory information from a specific system is lost, one potential solution is to compensate for this loss by providing extrinsic feedback through another sensory modality, a concept known as sensory substitution. Sensory substitution has been the subject of extensive investigation among diverse patient groups who miss essential sensory information aiming at improving motor control. For instance, studies have demonstrated that vibrotactile feedback can enhance motor control in users of leg prostheses[17,18] and arm prostheses.[19] Furthermore, individuals with severe vestibular deficits showed improved balance control when provided with extrinsic feedback in the form of vibrotactile, visual, or auditory cues.[20-25] Individuals with motor incomplete SCI experienced improved posture and reduced dependency on visual input in the presence of electrotactile feedback.[26] Similarly, individuals with motor incomplete SCI performed a more efficient spatiotemporal gait pattern when extrinsic feedback was provided.[27] Therefore, it has been hypothesized that sensory substitution could enhance exoskeleton motor control in individuals with motor complete SCI.[28] Additionally, extrinsic feedback has been recognized as a significant contributor to motor learning,[29-32] suggesting that the incorporation of sensory substitution could also enhance motor learning in exoskeletons.

When implementing sensory substitution into exoskeleton walking, the selection of the type of extrinsic feedback is paramount. A qualitative study[15] highlighted that individuals with motor complete SCI considered feedback of mediolateral (ML) and anteroposterior (AP) weight shift and step initiation as potentially beneficial. Furthermore, preferences leaned towards the

use of vibrotactile feedback over auditory and visual cues, as well as discrete feedback over continuous feedback.

The primary objective of this study was to investigate the impact of providing discrete vibrotactile feedback related to weight shift and step initiation on exoskeleton use in individuals with motor complete SCI. Our specific objectives were to evaluate the impact of vibrotactile feedback on two key aspects: 1) exoskeleton motor learning, and 2) exoskeleton motor control under both normal and sensory-deprived conditions. We incorporated sensory-deprived conditions to enhance the difficulty of exoskeleton walking by limiting the sensory inputs that participants typically rely on. Furthermore, we assessed the user experience with vibrotactile feedback during exoskeleton walking. Based on the proven effectiveness of extrinsic feedback on motor learning[29-32] and motor control,[17-27] we hypothesized that providing vibrotactile feedback would enhance exoskeleton motor learning and motor control in individuals with motor complete SCI.

Methods

The study was conducted at the Sint Maartenskliniek (the Netherlands) and received ethical approval from both the regional medical ethics committee Oost-Nederland (NL82999.091.22) and the internal review board of the Sint Maartenskliniek. Prior to participation, all individuals provided written informed consent in accordance with the Declaration of Helsinki.

The exoskeleton and vibrotactile feedback

In this study, we used the ABLE Exoskeleton (ABLE Human Motion, Barcelona, Spain), a wearable powered lower-limb exoskeleton.[33] To initiate a step with this exoskeleton, users must shift their center of mass (COM) from the trailing leg to the leading leg in both AP and ML directions during the double-support phase. A step is triggered once predetermined thresholds for AP and ML are exceeded.

Participants wore a vibrotactile feedback belt around their chest to receive real-time feedback during the double-support phase. This belt includes three tactors positioned on the sternum and beneath the right and left armpits. Each tactor has a dimension of 70 by 50 mm and encapsulates a vibration motor (VZ6DL2B0055211, Vybronics Inc., China), providing vibration with an acceleration of 22 m/s^2 at a frequency of 55 Hz. During the double-support phase, when the COM exceeds the AP threshold, the sternum tactor initiates vibrating. Similarly, when the COM exceeds the ML threshold, the corresponding tactor under the armpit is activated. When a step is initiated, the tactors cease vibrating. See Figure 1 for a visual representation of the vibrotactile feedback belt and the activation pattern.

Participants

The participants in this study had previously taken part in the ReWalk Exoskeleton training program at the Sint Maartenskliniek, conducted from 2016 to 2019.[2] We targeted individuals
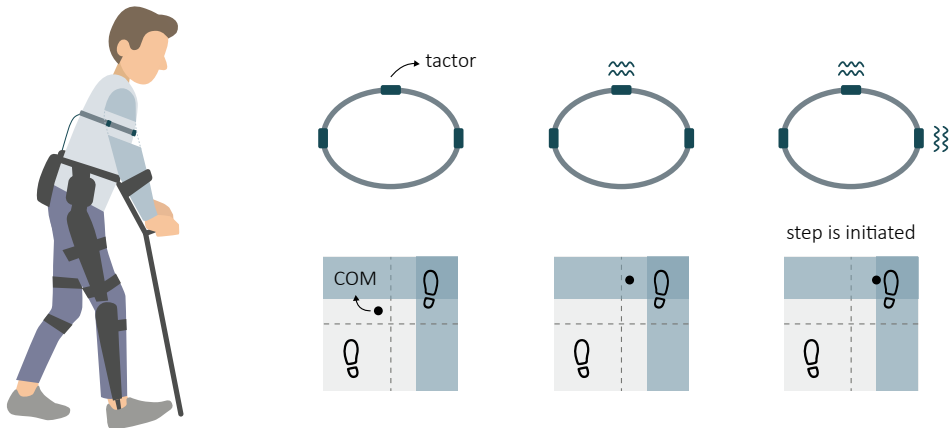
Figure 1 Vibrotactile feedback belt. Left: A schematic depiction of the user wearing the vibrotactile feedback belt. Right: A schematic representation of the vibrotactile feedback belt, consisting of three tactors (vibrating motors) with one positioned on the sternum and two beneath the armpits, along with an overview of the belt activation pattern. When the center of mass (COM) exceeds the anteroposterior threshold, the sternum-based tactor initiates vibrations. Similarly, when the COM exceeds the mediolateral threshold, the corresponding tactor beneath the armpit is activated. Once the COM has exceeded both thresholds, a step is initiated, and both tactors cease vibrating.

with prior experience using a different exoskeleton to focus on improving walking skills. Typically, exoskeleton training begins with standing skills and progresses to walking skills.[2] Given the presumed transferability of standing skills across various exoskeletons, including participants with previous experience using a different exoskeleton enabled us to bypass the initial standing skill acquisition. With the distinctive control mechanisms for walking between the ReWalk Exoskeleton, where the device continues stepping upon initiating a stop, and the ABLE Exoskeleton, where users must initiate each step individually, we anticipated limited transference of walking skills across these devices.

The inclusion criteria for the present study were: 1) being diagnosed with motor complete spinal cord injury from a traumatic or non-traumatic non-progressive origin (American spinal injury association Impairment Scale (AIS) A or B), 2) minimally six months post injury, 3) prior experience with the ReWalk Exoskeleton (ReWalk Robotics, Marlborough, USA) demonstrating the ability to walk independently in the ReWalk Exoskeleton, 4) age ≥ 18 years. Exclusion criteria were: 1) pre-existing somatosensory problems, 2) visual or auditory issues that could not be corrected with glasses or a hearing device, 3) no sensation at the level of the tactors, 4) insufficient understanding or mastery of the Dutch language, and 5) contraindications related to the ABLE Exoskeleton, such as severe spasticity (Modified Ashworth Scale = 4), height > 190 cm or < 150 cm, body weight > 100 kg, orthostatic hypotension, or restricted

range of motion in the lower extremities that might interfere with 'normal gait'. Participant characteristics, including demographic and injury-related data, were registered at the time of inclusion. Demographic characteristics included sex, age, weight, and height, while injury-related characteristics included the AIS classification, level and cause of injury, and time post injury.

Protocol

The study protocol included six sessions of 90 minutes spread over three weeks (two sessions per week with a minimum of 24 hours between sessions). All sessions were supervised by a physiotherapist certified to use the ABLE Exoskeleton, and took place in the sports hall of the Sint Maartenskliniek. The first five sessions were dedicated to training to assess the effect of vibrotactile feedback on exoskeleton motor learning (i.e., training sessions). The last session assessed the effect of vibrotactile feedback on exoskeleton motor control (i.e., evaluation session). See Appendix 1 for a schematic overview of the study design.

Training sessions

The goal of the training sessions was to enable participants to independently walk with the exoskeleton. The first session served as an introductory phase, involving customization of the exoskeleton to each user's body characteristics (i.e., height, weight, limb length) and their initial experience of standing up and taking steps with it. In this session, physiotherapists had the option to adjust the predetermined thresholds for AP and ML COM movements to initiate a step, if deemed necessary. This introductory session did not yet involve vibrotactile feedback.

During the subsequent four training sessions, we implemented a structured approach that alternated between sessions with feedback (FB) and sessions with no feedback (NFB). Participants were divided into two groups: one group received vibrotactile feedback in the second and fourth sessions (sequence: NFB – FB – NFB – FB – NFB), whereas the other group received vibrotactile feedback in the third and fifth sessions (sequence: NFB – NFB – FB – NFB – FB). This approach was adopted to mitigate the impact of a non-linear learning curve.[2] Therapists were permitted to give verbal instructions to the participants, as this is a common practice during exoskeleton training, but were instructed to provide approximately the same amount of verbal content across all training sessions.

At the start of sessions two to six, a standardized assessment was conducted to evaluate the participants' progress with the exoskeleton. This assessment involved three walking trials with the exoskeleton, without vibrotactile feedback. Each trial consisted of straight walking for a duration of 50 seconds. Participants commenced each trial in a parallel stance and were instructed to initiate a first step when the timer began. They were then directed to stop walking after a duration of 50 seconds by refraining from initiating a subsequent step. To ensure safety, the physiotherapist stood nearby, but refrained from direct assistance or verbal instructions. Prior to the assessments, participants received five minutes of practice.

Evaluation session

The sixth session was a final evaluation session, comprising 24 walking trials divided into three blocks of eight trials. In each walking trial, participants walked straight for a duration of 50 seconds, similar as described before.

Within each block, participants were tested in four distinct sensory conditions: 1) the control condition, 2) the limited visual condition, 3) the limited auditory condition, and 4) the limited visual and auditory condition. To limit visual information, participants wore dribble goggles that restricted their downward-oriented vision of their legs and the exoskeleton. For auditory restriction, participants wore headphones that played white noise. Each sensory condition was repeated twice within a block, once with vibrotactile feedback and once without. The order of the sensory conditions and the presence or absence of feedback were randomized according to a specific randomization protocol designed to mitigate the potential impact of fatigue (see Appendix 2).

Outcome measures

Exoskeleton performance

The primary outcome measure was walking distance covered during a 50-second walking trial, defined as the distance between the starting heel position and the trailing heel position after the 50-second interval.

For a more detailed analysis of exoskeleton control, we included two secondary outcome measures related to the COM-trajectory in the double support phase: 1) the reach path ratio, and 2) the reach time. The COM trajectories were extracted from the ABLE Exoskeleton. The reach path ratio for each step was determined by dividing the total distance covered by the COM during the double-support phase by the length of a direct path from the COM position at the onset of the double-support phase to the COM position at the end of that phase. A reach path ratio equal to one represents a straight path, while a ratio greater than one represents a more curved path. The reach time represents the time spent in double-support phase. A lower reach path ratio and time was considered indicative of better exoskeleton control.

User experience

To assess user experience with the vibrotactile feedback, we administered three questionnaires immediately after the final session, focusing on the system's usability and user satisfaction. The first questionnaire was customized to assess the specific user experience with the system, considering key aspects related to exoskeleton motor learning and motor control. This questionnaire comprised five visual analogue questions employing a 5-point scale, ranging from 'strongly disagree' to 'strongly agree' (see top panel of Figure 7A).

The second questionnaire was the Dutch version of the Quebec User Evaluation of Satisfaction with assistive Technology (D-QUEST), only including the eight items related to user satisfaction with the assistive device.[34] Ratings are assigned on a scale of one to five, with higher scores indicating greater satisfaction. The third questionnaire was the Dutch System Usability Scale (D-SUS).[35] This scale ranges from 0 to 100, with scores above 70 being considered acceptable usability.[36]

Analysis

Training

To assess participants' activities during the training sessions, we extracted data from the ABLE Exoskeleton on two key metrics: the percentage of time spent walking out of the total upright time and the number of steps taken during a session.

Effect of vibrotactile feedback on exoskeleton motor learning

To evaluate the effect of vibrotactile feedback on exoskeleton motor learning, we used descriptive statistics. Specifically, we calculated the changes (delta values) in walking distance, reach path ratio, and reach time between subsequent sessions. For walking distance, we averaged the results of the three trials conducted within each session. As for the reach path ratio and reach time, we determined the median values across all steps taken during the three trials within a session, given that both outcomes displayed non-normal distributions. To mitigate the influence of start and stop phases in each trial, we excluded the first double-support phase following the first step and the last double-support phase before the last step of each 50-second walking trial. To assess the effect of vibrotactile feedback on exoskeleton motor learning, we compared the delta values between sessions with feedback and those without feedback. We considered a positive effect of vibrotactile feedback when both sessions with feedback demonstrated a larger delta compared to both sessions without it. Conversely, we considered a negative effect of vibrotactile feedback when both sessions without feedback showed a larger delta compared to both sessions with feedback.

Effect of vibrotactile feedback on exoskeleton motor control

We conducted a descriptive comparative analysis of walking distance, reach path ratio, and reach time across the four distinct sensory conditions, comparing the presence and absence of vibrotactile feedback. Walking distances were averaged across trials with identical sensory conditions and feedback presence. For the reach path ratio and reach time, we computed the median values across all steps within trials with identical sensory conditions and feedback presence. Again, we excluded the initial and final double-support phases of each trial. We considered a change to be meaningful if the difference between the sensory condition with feedback and the same condition without feedback exceeded 10% of the mean value across all participants in each condition. In the case of the reach path ratio, we subtracted one to account for the lowest possible score.

Results

Participants

Participant enrollment commenced January 2023, and the last participant completed the study protocol in June 2023. In total, seven participants were included, whose characteristics are presented in Table 1. Participant 4 was excluded from the training data analysis due to an illness that prevented him from participating for more than two weeks between sessions 4 and 5. Therefore, data from six participants (participants 1, 2, 3, 5, 6, 7) were analyzed for the training phase. Additionally, participant 5 was excluded from the evaluation data analysis due to exoskeleton motor overheating issues, resulting in analysis of six participants (participants 1, 2, 3, 4, 6, 7) for the evaluation phase. Three out of six participants were unable to complete the full 24 trials during the evaluation session due to fatigue. Specifically, participants 2, 4, and 6 completed trials up to the 20th, 18th, and 16th, respectively.

Table 1 Participant characteristics

	P1	P2	P3	P4	P5	P6	P7
Demographic							
Sex	F	F	M	M	M	M	F
Age (yr)	47	33	30	33	31	47	55
Weight (kg)	52	75	62	70	77	86	60
Height (cm)	164	180	176	180	186	186	167
Injury-related							
AIS	A	A	B [1]	A	A	A	A
Level of injury	T9	T4	T4	T12	T5	T12	T4
Time post injury (yr)	23	7	14	7	6	13	12
Cause	TR	TR	TR	TR	TR	TR	TR

[1] Pain and touch sensation absent from thoracic vertebral level (T) 7 to sacral vertebral level 3. AIS = American spinal injury association Impairment Scale; TR = Traumatic.

Training

During training sessions two to five, participants spent an average of 58 ± 13 minutes upright in the exoskeleton, with 36 ± 10% of this time walking (Figure 2A), taking an average of 450 ± 237 steps (Figure 2B). Participants 2 and 6 demonstrated trends of increased walking distances during the 50-second walking trials, with respective increases of 47% and 84% from session 2 to session 6, as illustrated in Figure 3A. In contrast, the remaining four participants demonstrated limited or negligible progress in walking distance throughout the training sessions (-1 − 16%).
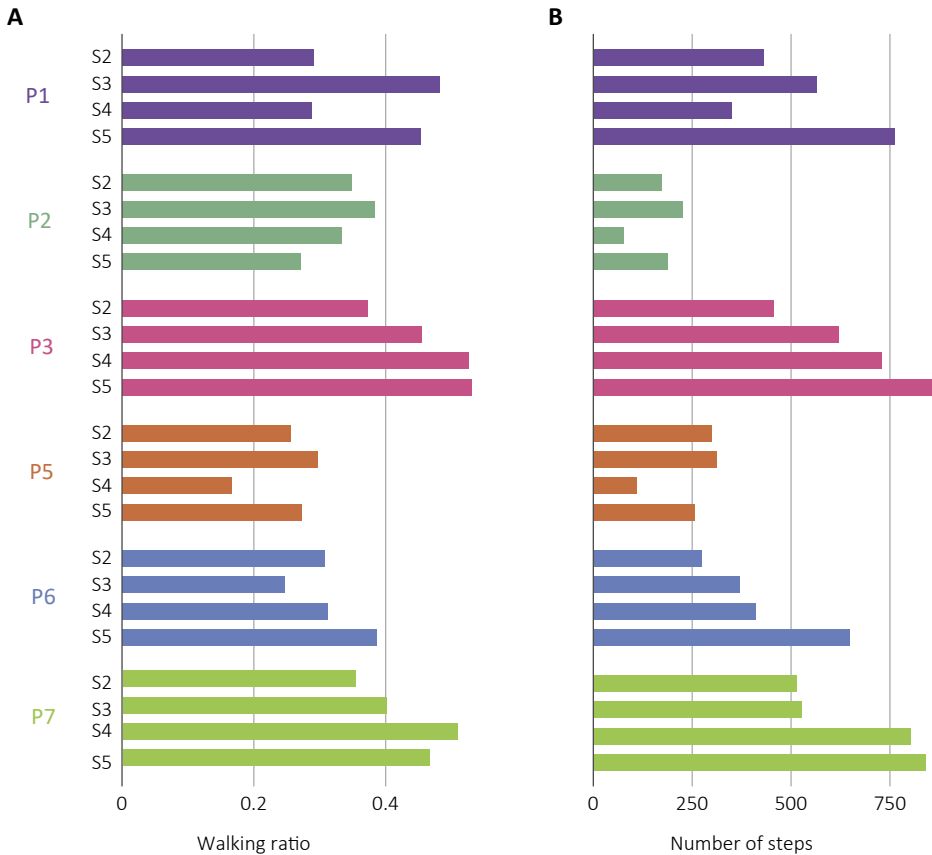
Figure 2 Training session (S) characteristics for each participant (P). **A** Walking ratio defined as walking time divided by walking and standing time. **B** Number of steps.

Improvements in reach path ratio and reach time during the training sessions were also limited or negligible across participants (Figure 4A and 5A, respectively). However, it should be noted that the majority of participants already had a reach path ratio close to one during session 2, indicating limited room for further improvement.

Effect of vibrotactile feedback on exoskeleton motor learning

Participants 1 and 2 demonstrated larger improvements in walking distance after both sessions with feedback compared to both sessions without, suggesting a positive effect of feedback (Figure 3B). However, the other four participants did not show a discernible effect of vibrotactile feedback on the improvement of walking distance.

Participant 2 was the only person who showed a positive effect of vibrotactile feedback on the improvement of reach path ratio (Figure 4B). For reach time, participants 1 and 5 displayed a negative effect on the improvement of reach time with vibrotactile feedback. For the remaining participants, no effect of vibrotactile feedback on the improvement of reach path ratio or reach time during the training sessions was identified.

Effect of vibrotactile feedback on exoskeleton motor control

Figure 6 shows the walking distance, reach path ratio, and reach time across the four sensory conditions with and without vibrotactile feedback. In the limited auditory condition, four out of six participants demonstrated a meaningful improvement of walking distance with the vibrotactile feedback. However, across the other three conditions, clear results regarding the effect of vibrotactile feedback on walking distance was not evident.

All participants experiencing meaningful improvements in walking distance with the vibrotactile feedback in the limited auditory condition also showed improvements in reach path ratio and/or reach time. Conversely, across the other three conditions, clear results regarding the effect of vibrotactile feedback on reach path ratio and reach time were not evident.

User experience

Most participants found the vibrotactile feedback beneficial during training and did not perceive it as disruptive or distracting (Figure 7A). Additionally, the majority expressed a preference for training sessions that included vibrotactile feedback. However, four out of seven participants were reluctant to continue using the feedback after the training. The average satisfaction with the sensory feedback system was rated at 3.8 ± 0.5 out of 5.0 on the D-QUEST device subscale (Figure 7B) and the system received an average usability of 75 ± 14 out of 100 on the D-SUS (Figure 7C).

6

6
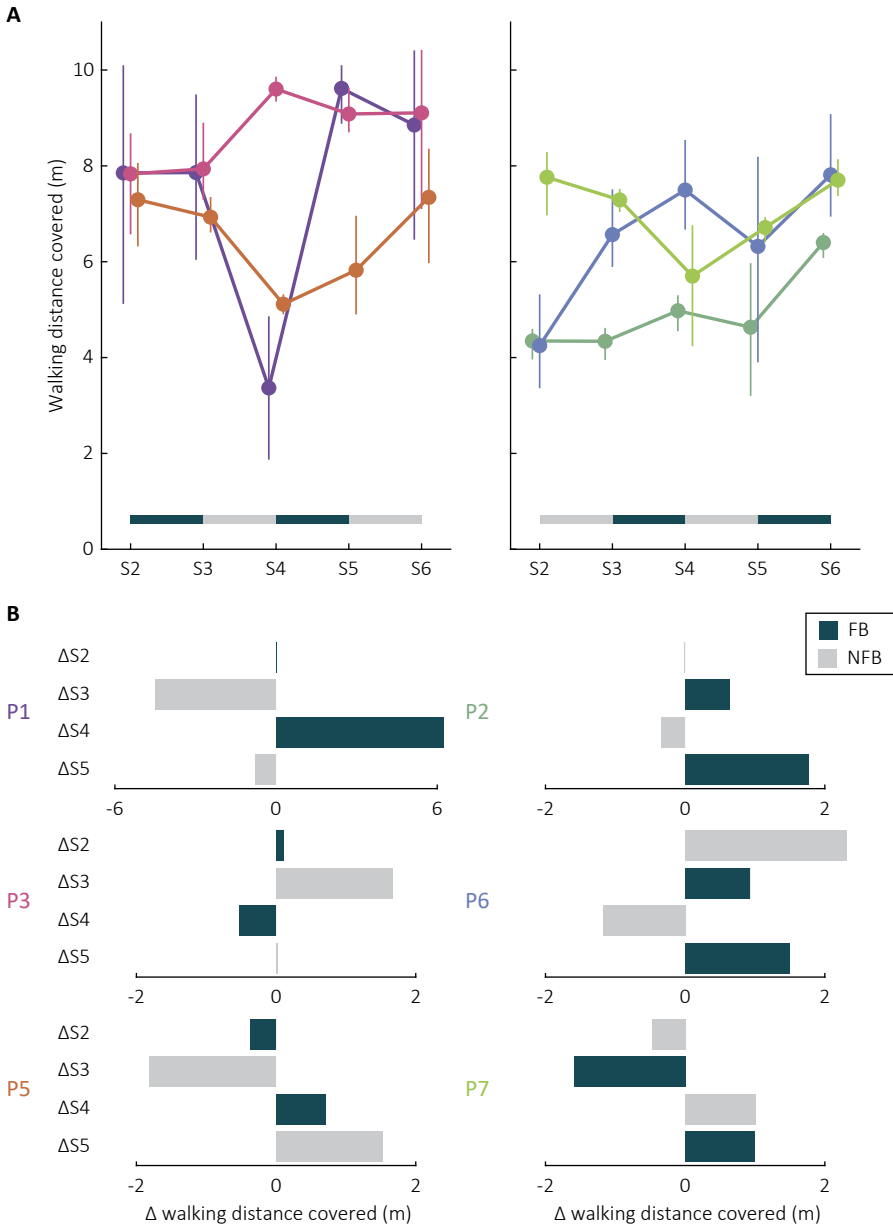
Figure 3 A Walking distance covered over time. Each dot represents the mean value, with bars indicating the range from the minimum to maximum distance achieved. **B** Change in walking distance covered across sessions (S). The figures on the left include participants (P) who trained with feedback in S2 and S4, while the figures on the right include participants who trained with feedback in S3 and S5. FB = feedback; NFB = no feedback.
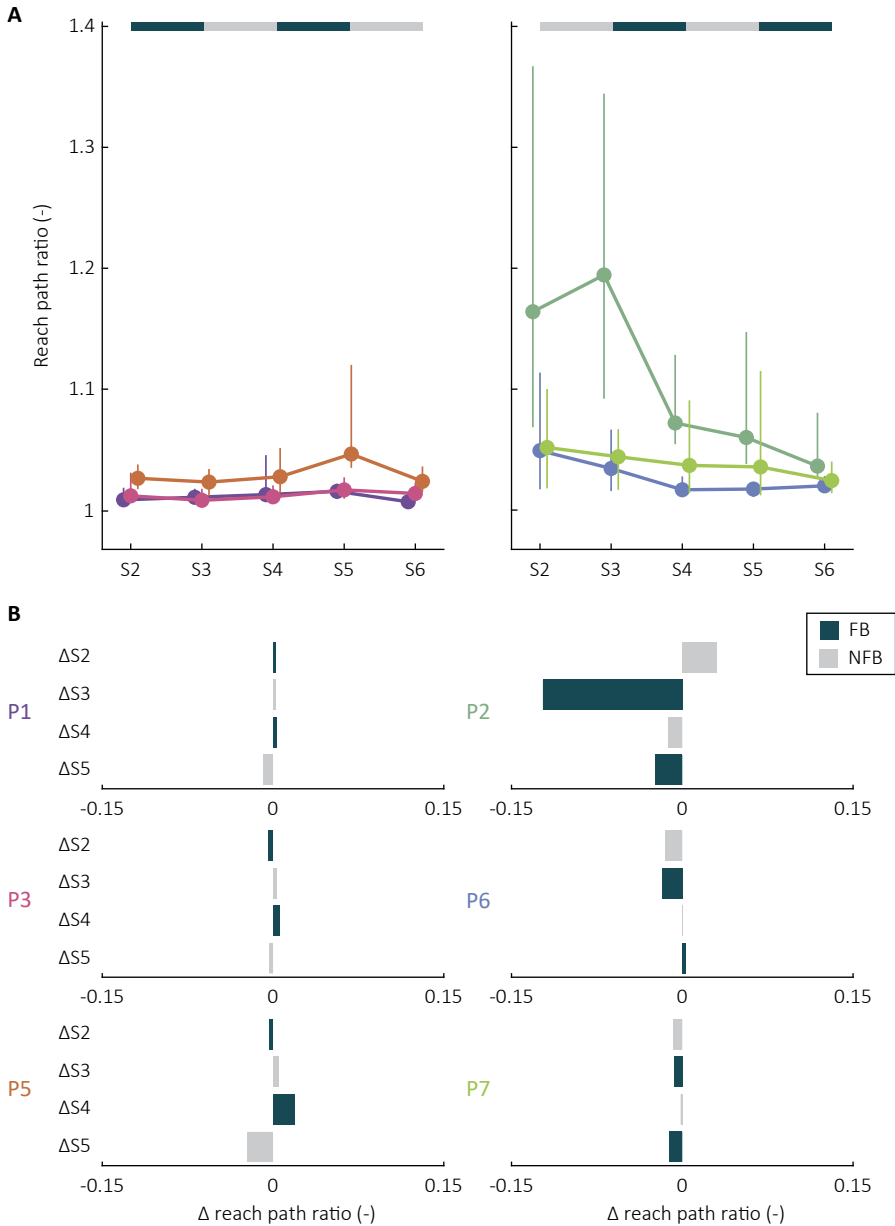
Figure 4 A Reach path ratio over time. Each dot represents the median value, with bars indicating the interquartile range. **B** Change in reach path ratio across sessions (S). The figures on the left include participants (P) who trained with feedback in S2 and S4, while the figures on the right include participants who trained with feedback in S3 and S5. FB = feedback; NFB = no feedback.

6
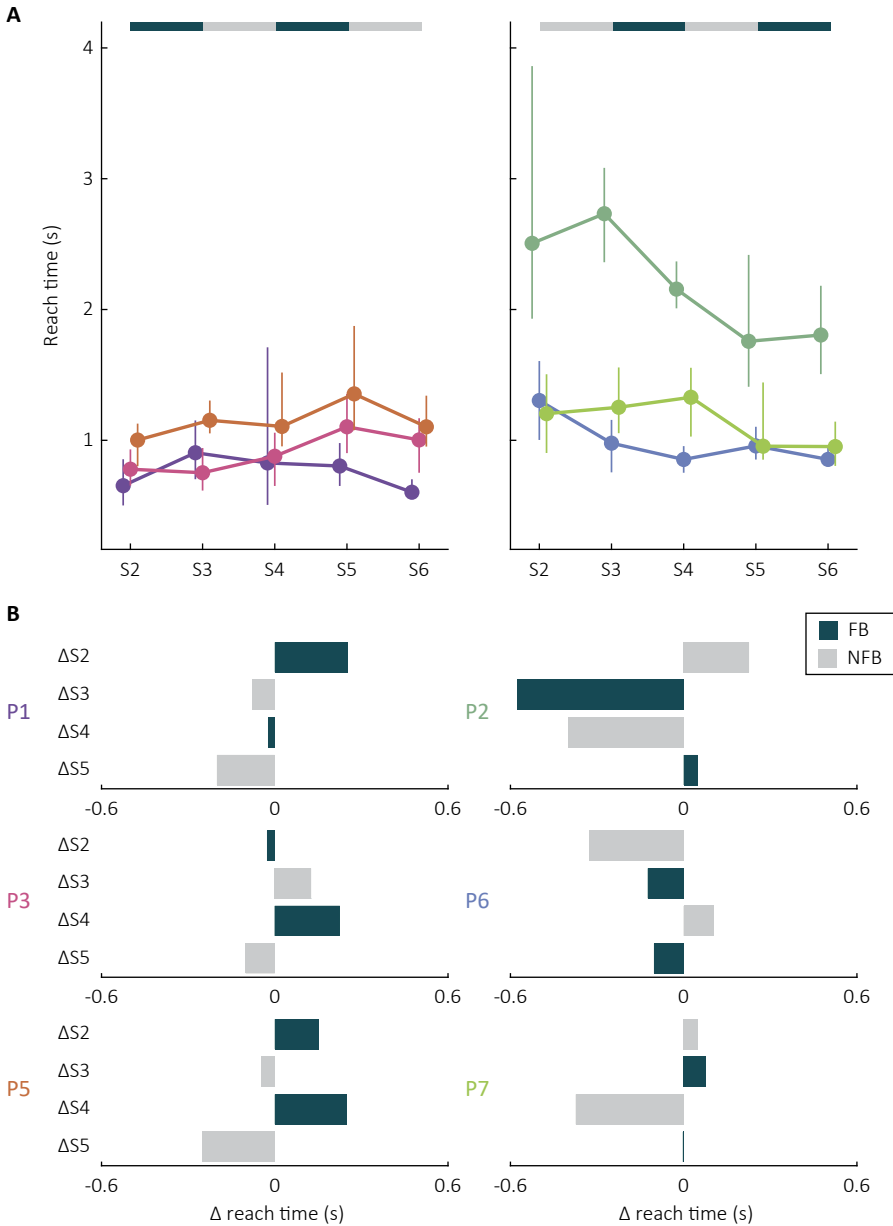
Figure 5 A Reach time over time. Each dot represents the median value, with bars indicating the interquartile range. **B** Change in reach time across sessions (S). The figures on the left include participants (P) who trained with feedback in S2 and S4, while the figures on the right include participants who trained with feedback in S3 and S5. FB = feedback; NFB = no feedback.
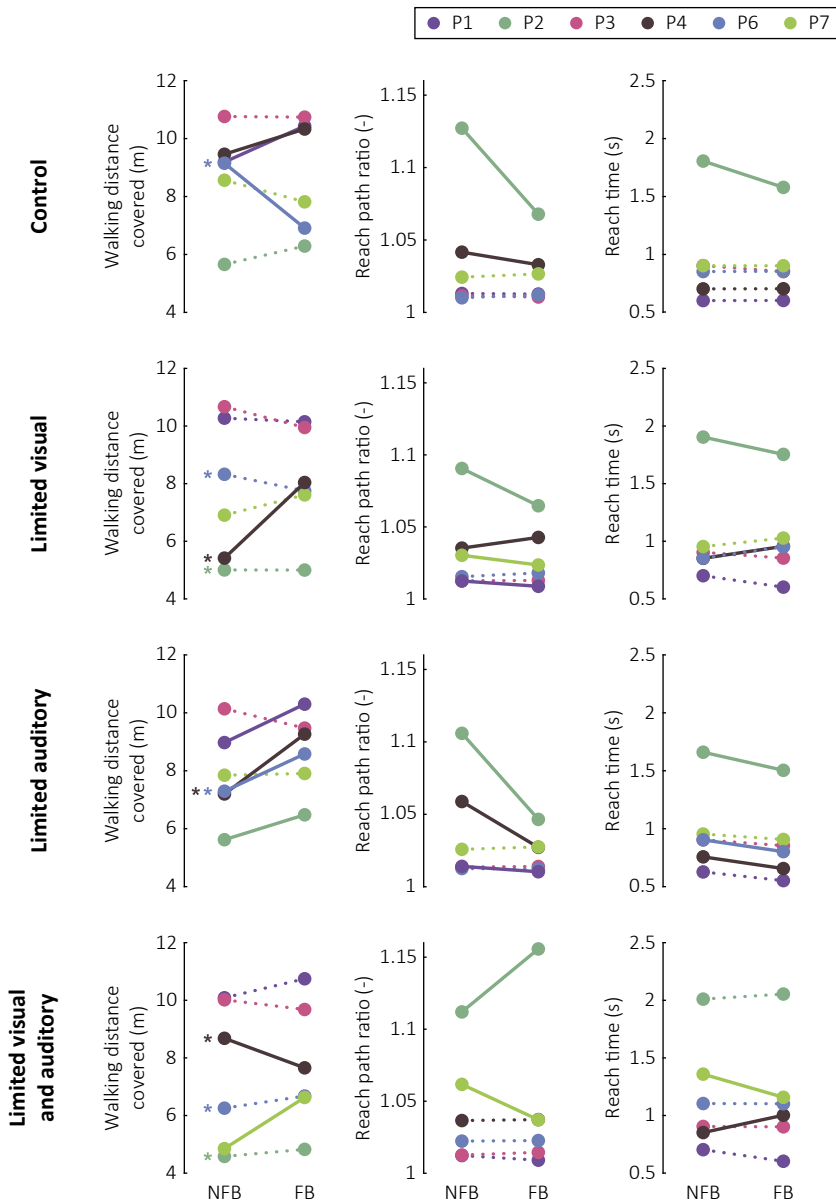
Figure 6 Walking distance covered, reach path ratio, and reach time in the four sensory conditions. For walking distance covered, the dots represent the mean of all trials with the same condition. For reach path ratio and reach time, the dots represent the median across all steps of trials with the same condition. FB = feedback; NFB = no feedback. Solid lines indicate a meaningful change between NFB and FB while dashed lines indicate no meaningful change between NFB and FB. The asterisk (*) denotes that a participant performed 2 trials in both the NFB and FB conditions, rather than the expected 3 trials.

6
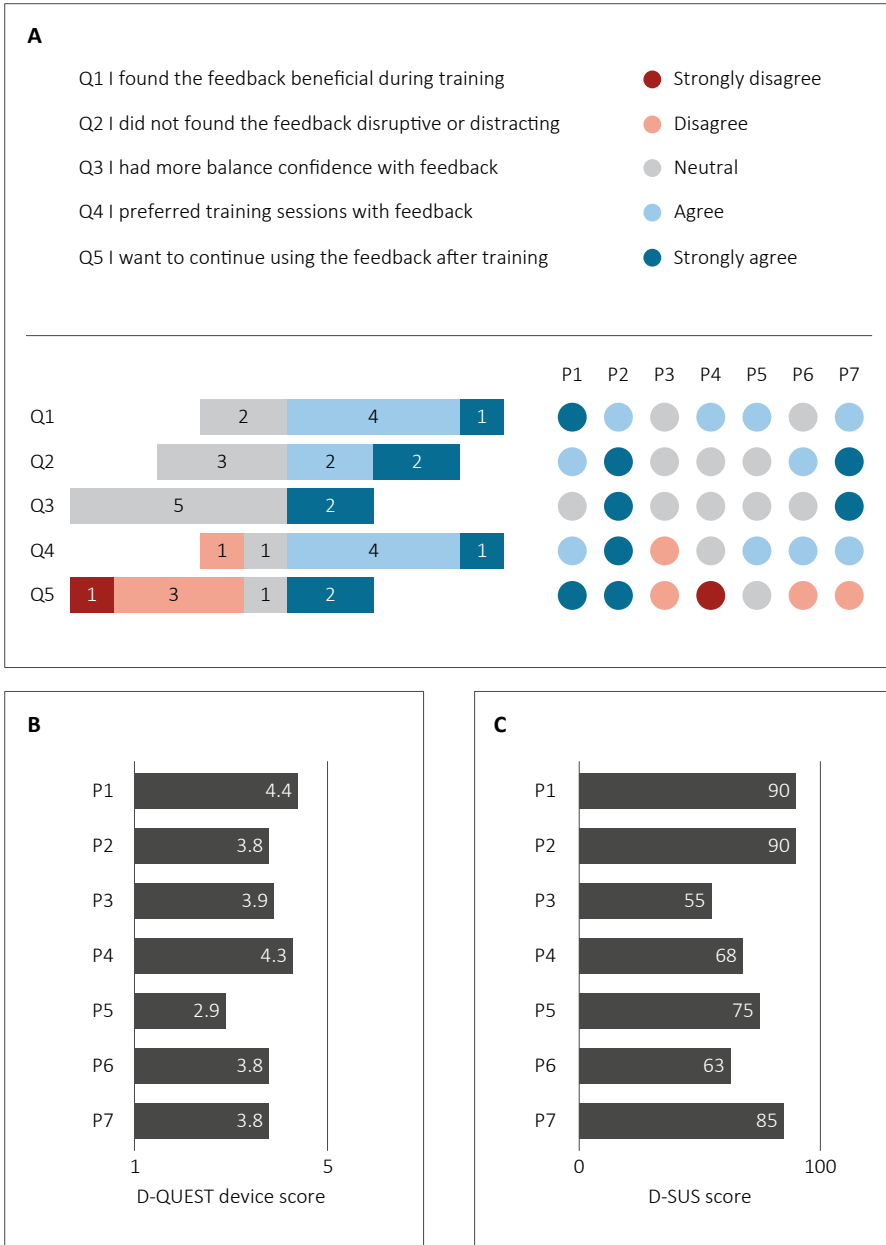
Figure 7 User experience with the vibrotactile feedback system. **A** Custom questionnaire comprising five visual analog questions. The top panel presents the questions and answer options. The bottom left panel displays distributions of the answers, while the bottom right panel displays individual responses. **B** Dutch version of the Quebec User Evaluation of Satisfaction with assistive Technology (D-QUEST) device score. **C** Dutch System Usability Scale (D-SUS) score.

Discussion

The objective of this study was to investigate the impact of providing discrete vibrotactile feedback related to weight shift and step initiation on exoskeleton motor learning and motor control in individuals with motor complete SCI. Five out of six participants showed no clear indication of greater improvements during training with vibrotactile feedback. This suggests that the provided feedback did not significantly contribute to exoskeleton motor learning.

Regarding the impact of vibrotactile feedback on exoskeleton motor control, we also observed no clear discernible effect when normal visual and auditory information was present, nor in the conditions involving limited visual information, or limited visual and auditory information. Notably, in the condition with limited auditory information, vibrotactile feedback appeared beneficial. However, given the absence of a clear discernible effect in the condition with both limited visual and auditory information, it is possible that the observed effect in the limited auditory condition was coincidental. Another factor to consider is that, in the condition with both limited visual and auditory information, participants may have directed greater attention to the task of walking in the exoskeleton compared to the condition with only limited auditory information. This heightened focus on their own sensory information could have imposed a higher cognitive load. Additionally, previous research has highlighted that vibrotactile feedback can introduce an extra cognitive burden.[37-39] Therefore, it is possible that during the condition with both limited visual and auditory information, participants reached their maximal cognitive capacity, making it challenging for them to allocate cognitive resources effectively for the processing of the vibrotactile feedback. Nevertheless, given the vibrotactile feedback's effect in only one of the four sensory conditions and the possibility of this effect being coincidental, our findings suggest that the provided vibrotactile feedback did not significantly contribute to exoskeleton motor control.

Our findings are in contrast to previous research suggesting that extrinsic feedback enhances motor learning among both healthy and disabled individuals[30-32,40,41] and improves motor control across various patient groups that lack essential sensory information.[17-27] The goal of sensory substitution is to compensate for the loss of specific sensory information to enhance motor performance. However, when sufficient sensory cues are available or when the extrinsic feedback conveys identical information as the existing sensory cues, substitution of sensory information may become redundant. This notion finds support in Guémann's study,[42] which demonstrated that while vibrotactile feedback improved myoelectric control of a virtual arm in situations devoid of visual information, its addition alongside visual cues did not notably enhance myoelectric control. In our study, it is plausible that somatosensory information above the lesion level, particularly from the arms in contact with the ground surface via the crutches or walker, along with inputs from other sensory modalities such as visual, vestibular, and auditory systems, adequately provide the necessary information for effective weight shifting and step initiation with the exoskeleton, making the extrinsic vibrotactile feedback redundant. Therefore, we incorporated sensory-deprived conditions to enhance the difficulty

of exoskeleton walking by limiting the sensory inputs that participants typically rely on. However, only with limited auditory information, vibrotactile feedback appeared effective, which might suggest that in the absence of auditory cues, vibrotactile feedback might have substituted for the sound of the exoskeleton, thereby enhancing exoskeleton control. This aligns with previous research indicating that experienced exoskeleton users with motor complete SCI found the exoskeleton's sound beneficial during walking.[15,16] However, our observation of no clear effect in the limited auditory and visual condition leaves unanswered whether vibrotactile feedback loses its redundancy when auditory information is limited.

Another potential explanation for the absence of a clear effect of vibrotactile feedback on exoskeleton motor learning could be the limited or negligible improvement demonstrated by most participants during training, indicating restricted overall motor learning. We anticipated limited transfer of walking skills due to the different control mechanisms for walking between both exoskeletons and because our subjects had not walked in an exoskeleton for at least three years since their participation in the ReWalk Exoskeleton training program. However, participants in our study managed to cover a mean walking distance of four meters or more unassisted within 50 seconds at the beginning of the second session. In contrast, previous studies showed that most individuals with SCI new to exoskeleton use achieve unassisted walking after multiple training sessions.[2,9] These discrepancies suggest a certain degree of transferability of walking skills between different exoskeleton devices, reducing the necessity for extensive exoskeleton motor learning when transitioning between devices. Further research is essential to better comprehend the potential impact of vibrotactile feedback among inexperienced exoskeleton users with motor complete SCI.

Contrary to the limited effectiveness of vibrotactile feedback, the overall user experience was largely positive. The majority of participants favored training with feedback, highlighting its perceived value in the learning process. The positive user experience findings were further supported by the results of the D-QUEST and D-SUS assessments, indicating an overall high level of satisfaction and usability, respectively. Nevertheless, it is noteworthy that our system received a lower D-SUS score (75) than two vibrotactile feedback systems designed for users of leg prostheses, which achieved a mean D-SUS score above 80.[17,18] Furthermore, the majority of participants expressed reluctance to continue using feedback after training, suggesting limited perceived value of the feedback after the learning phase.

To the best of our knowledge, this is the first study exploring the effects of sensory substitution in exoskeleton use in individuals with motor complete SCI. Given its exploratory nature, we chose a small sample size, under the premise that a clear feedback effect would likely manifest even within such a limited group, consistent with previous studies exploring extrinsic feedback in prosthetic users or individuals with spinal cord injuries, which also had small sample sizes ranging from 3 to 6.[17,18,26] Furthermore, we only studied the effect of vibrotactile feedback related to weight shifting and step initiation. It is crucial to recognize that the absence of a clear effect on these aspects of exoskeleton walking does not exclude the possibility that feedback

related to other control aspects could be effective. Exploring alternative feedback parameters might uncover aspects where vibrotactile feedback could have a more pronounced influence on exoskeleton use.

Conclusion

Our study suggests that discrete vibrotactile feedback related to weight shifting and step initiation does not significantly enhance exoskeleton motor learning or motor control under both normal and sensory-deprived conditions in individuals with motor complete SCI. Still, individuals with motor complete SCI were generally positive about the vibrotactile feedback, particularly during the training phase.

6

References

1. Benson I, Hart K, Tussler D, Van Middendorp JJ. Lower-limb exoskeletons for individuals with chronic spinal cord injury: findings from a feasibility study Article. Clin Rehabil. 2016;30:73–84.

2. van Dijsseldonk RB, Rijken H, Nes IJW van, Meent H van de, Keijsers NLW. A framework for measuring the progress in exoskeleton skills in people with complete spinal cord injury. Front Neurosci. 2017;11:1–12.

3. van Dijsseldonk RB, van Nes IJW, Geurts ACH, Keijsers NLW. Exoskeleton home and community use in people with complete spinal cord injury. Sci Rep. 2020;10:1–8.

4. Bach Baunsgaard C, Vig Nissen U, Katrin Brust A, et al. Gait training after spinal cord injury: safety, feasibility and gait function following 8 weeks of training with the exoskeletons from Ekso Bionics. Spinal Cord. 2018;56:106–116.

5. Tefertiller C, Hays K, Jones J, et al. Initial Outcomes from a Multicenter Study Utilizing the Indego Powered Exoskeleton in Spinal Cord Injury. Top Spinal Cord Inj Rehabil. 2018;24:78–85.

6. Guanziroli E, Cazzaniga M, Colombo L, Basilico S, Legnani G, Molteni F. Assistive powered exoskeleton for complete spinal cord injury: Correlations between walking ability and exoskeleton control. Eur J Phys Rehabil Med. 2019;55:209–216.

7. Lee H, Ferguson PW, Rosen J. Lower limb exoskeleton systems-overview. In: Wearable Robotics: Systems and Applications. INC; 2020:207–229.

8. Kozlowski AJ, Bryce TN, Dijkers MP. Time and Effort Required by Persons with Spinal Cord Injury to Learn to Use a Powered Exoskeleton for Assisted Walking. Top Spinal Cord Inj Rehabil. 2015;21:110–121.

9. Platz T, Gillner A, Borgwaldt N, Kroll S, Roschka S. Device-Training for Individuals with Thoracic and Lumbar Spinal Cord Injury Using a Powered Exoskeleton for Technically Assisted Mobility: Achievements and User Satisfaction. Biomed Res Int. 2016;2016.

10. Asselin PK, Avedissian M, Knezevic S, Kornfeld S, Spungen AM. Training persons with spinal cord injury to ambulate using a powered exoskeleton. Journal of Visualized Experiments. 2016;2016.

11. Bruijn SM, Van Dieën JH. Control of human gait stability through foot placement. J R Soc Interface. 2018;15:1–11.

12. Ionta S, Villiger M, Jutzeler CR, Freund P, Curt A, Gassert R. Spinal cord injury affects the interplay between visual and sensorimotor representations of the body. Sci Rep. 2016;6.

13. Lee GE, Bae H, Yoon TS, Kim JS, Yi TI, Park JS. Factors that influence quiet standing balance of patients with incomplete cervical spinal cord injuries. Ann Rehabil Med. 2012;36:530–537.

14. Lemay JF, Gagnon D, Duclos C, Grangeon M, Gauthier C, Nadeau S. Influence of visual inputs on quasi-static standing postural steadiness in individuals with spinal cord injury. Gait Posture. 2013;38:357–360.

15. Muijzer-Witteveen H, Sibum N, van Dijsseldonk RB, Keijsers NLW, van Asseldonk E. Questionnaire results of user experiences with wearable exoskeletons and their preferences for sensory feedback. J Neuroeng Rehabil. 2018;15:1–8.

16. Gagnon DH, Vermette M, Duclos C, Aubertin-Leheudre M, Ahmed S, Kairy D. Satisfaction and perceptions of long-term manual wheelchair users with a spinal cord injury upon completion of a locomotor training program with an overground robotic exoskeleton. Disabil Rehabil Assist Technol. 2019;14:138–145.

17. Crea S, Edin BB, Knaepen K, Meeusen R, Vitiello N. Time-Discrete Vibrotactile Feedback Contributes to Improved Gait Symmetry in Patients With Lower Limb Amputations: Case Series. Phys Ther. 2017;97:198–207.

18. Vimal AK, Godiyal AK, Singh U, Bhasin S, Joshi D. Transfemoral amputee's limit of stability and sway analysis during weight shifting exercise with a vibrotactile feedback system. Somatosens Mot Res. 2019;36:31–41.

19. Raveh E, Friedman J, Portnoy S. Evaluation of the effects of adding vibrotactile feedback to myoelectric prosthesis users on performance and visual attention in a dual-task paradigm. Clin Rehabil. 2018;32:1308–1316.

20. Wall C, Kentala E. Control of sway using vibrotactile feedback of body tilt in patients with moderate and severe postural control deficits. J Vestib Res. 2005;15:313–325.

21. Dozza M, Chiari L, Horak FB. Audio-biofeedback improves balance in patients with bilateral vestibular loss. Arch Phys Med Rehabil. 2005;86:1401–1403.

22. Chiari L, Dozza M, Cappello A, Horak FB, Macellari V, Giansanti D. Audio-biofeedback for balance improvement: An accelerometry-based system. IEEE Trans Biomed Eng. 2005;52:2108–2111.

23. Dozza M, Wall C, Peterka RJ, Chiari L, Horak FB. Effects of practicing tandem gait with and without vibrotactile biofeedback in subjects with unilateral vestibular loss. J Vestib Res. 2007;17:195–204.

24. Asseman F, Bronstein AM, Gresty MA. Using vibrotactile feedback of instability to trigger a forward compensatory stepping response. J Neurol. 2007;254:1555–1561.

25. Kingma H, Felipe L, Gerards MC, et al. Vibrotactile feedback improves balance and mobility in patients with severe bilateral vestibular loss. J Neurol. 2019;266:19–26.

26. De Castro MCF, Cliquet A. Artificial sensorimotor integration in spinal cord injured subjects through neuromuscular and electrotactile stimulation. Artif Organs. 2000;24:710–717.

27. Amatachaya S, Keawsutthi M, Amatachaya P, Manimmanakorn N. Effects of external cues on gait performance in independent ambulatory incomplete spinal cord injury patients. Spinal Cord. 2009;47:668–673.

28. Muijzer-Witteveen HJB, Nataletti S, Agnello M, Casadio M, Van Asseldonk EHF. Vibrotactile feedback to control the amount of weight shift during walking- A first step towards better control of an exoskeleton for spinal cord injury subjects. IEEE International Conference on Rehabilitation Robotics. 2017:1482–1487.

29. Moinuddin A, Goel A, Sethi Y. The Role of Augmented Feedback on Motor Learning: A Systematic Review. Cureus. 2021;13.

30. Subramanian SK, Massie CL, Malcolm MP, Levin MF. Does provision of extrinsic feedback result in improved motor learning in the upper limb poststroke? a systematic review of the evidence. Neurorehabil Neural Repair. 2010;24:113–124.

31. Jung KS, Bang H, In TS, Cho HY. Gait training with auditory feedback improves trunk control, muscle activation and dynamic balance in patients with hemiparetic stroke: A randomized controlled pilot study. J Back Musculoskelet Rehabil. 2020;33:1–6.

32. Schmidt RA, Lee TD. Motor learning and performance: from principles to application. 5th ed. Human Kinetics; 2013.

33. Wright MA, Herzog F, Mas-Vinyals A, et al. Multicentric investigation on the safety, feasibility and usability of the ABLE lower-limb robotic exoskeleton for individuals with spinal cord injury: a framework towards the standardisation of clinical evaluations. J Neuroeng Rehabil. 2023;20:1–18.

34. Wessels RD, De Witte LP. Reliability and validity of the Dutch version of QUEST 2.0 with users of various types of assistive devices. Disabil Rehabil. 2003;25:267–272.

35. Ensink CJ, Keijsers NLW, Groen BE. Translation and validation of the System Usability Scale to a Dutch version: D-SUS. Disabil Rehabil. 2022;0:1–6.

36. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. Int J Hum Comput Interact. 2008;24:574–594.

6

37. Lin C-C, Whitney SL, Loughlin PJ, et al. The use of vibrotactile feedback during dual-task standing balance conditions in people with unilateral vestibular hypofunction. Otology & Neurotology. 2018;39:349–356.

38. Lin CC, Whitney SL, Loughlin PJ, et al. The effect of age on postural and cognitive task performance while using vibrotactile feedback. J Neurophysiol. 2015;113:2127–2136.

39. Haggerty S, Jiang LT, Galecki A, Sienko KH. Effects of biofeedback on secondary-task response time and postural stability in older adults. Gait Posture. 2012;35:523–528.

40. Huang H, Wolf SL, He J. Recent developments in biofeedback for neuromotor rehabilitation. 2006;12:1–12.

41. Moinuddin A, Goel A, Sethi Y. The Role of Augmented Feedback on Motor Learning: A Systematic Review. Cureus. 2021;14:271–275.

42. Guémann M, Halgand C, Bastier A, et al. Sensory substitution of elbow proprioception to improve myoelectric control of upper limb prosthesis: experiment on healthy subjects and amputees. J Neuroeng Rehabil. 2022;19:1–12.

6

Appendix 1 – Study design
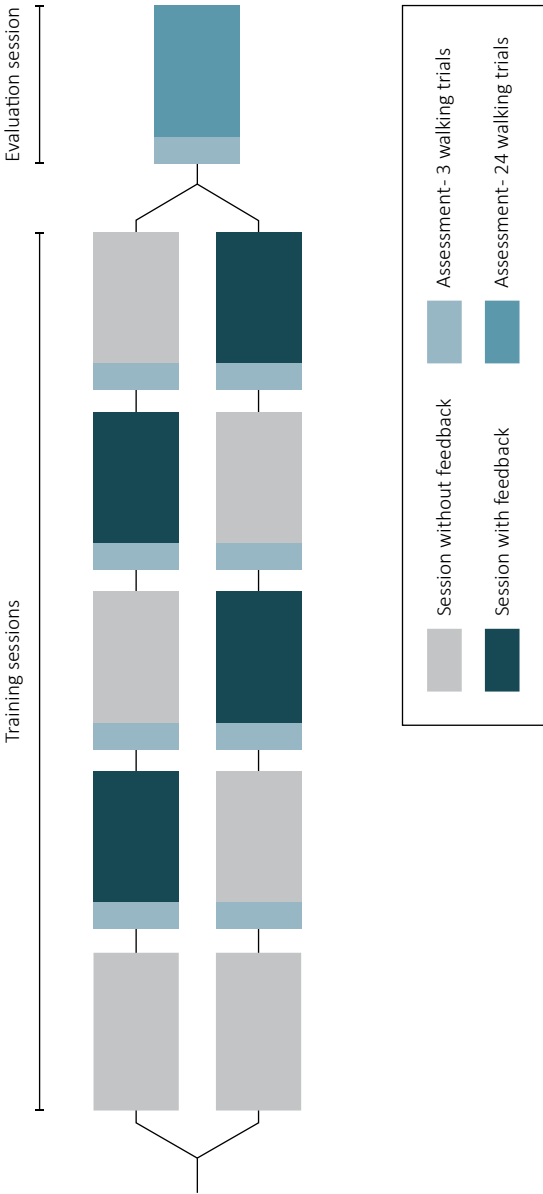
Appendix 2 - Randomization protocol of the evaluation session

The evaluation session consisted of 24 walking trials, organized into three blocks of eight trials. Within each block, participants were tested in four distinct sensory conditions.

In the first block, the order of the four sensory conditions was randomized, and each condition was repeated twice: once with vibrotactile feedback and once without it. The order of the presence or absence of feedback was randomized within each sensory condition.

In the second block, the order of the sensory conditions was shifted by one position compared to the first block. Additionally, the order of feedback presence or absence for each sensory condition was reversed from what participants experienced in the first block.

In the third block, the order of the sensory conditions was shifted by two positions compared to the first block. Similar to the first block, the order of the presence or absence of feedback within each sensory condition was randomized. See the table below for an example of the randomization protocol.

	Block 1		Block 2		Block 3	
Trial 1	LA	FB	LV&LA	NFB	C	FB
Trial 2	LA	NFB	LV&LA	FB	C	NFB
Trial 3	LV&LA	FB	C	FB	LV	NFB
Trial 4	LV&LA	NFB	C	NFB	LV	FB
Trial 5	C	NFB	LV	FB	LA	FB
Trial 6	C	FB	LV	NFB	LA	NFB
Trial 7	LV	NFB	LA	NFB	LV&LA	NFB
Trial 8	LV	FB	LA	FB	LV&LA	FB

C = control condition; LA = limited auditory condition; LV = limited visual condition; LV&LA = limited visual and limited auditory condition; F = feedback; NFB = no feedback.

6

Chapter 7

Summary and
general discussion

7

Summary

The aim of this thesis was to explore possibilities for improving walking capacity in individuals with spinal cord injury (SCI). The thesis comprises two distinct parts: the first part targets individuals with motor *incomplete* SCI, whereas the second part concentrates on those with motor *complete* SCI.

Part I Rehabilitation approaches to improve walking capacity after motor *incomplete* spinal cord injury

To improve walking capacity in individuals with motor incomplete SCI, multiple rehabilitation interventions are available. In **chapter 2**, I investigated the efficacy of walking adaptability training (WA) compared to conventional locomotor and strength training (CLS) for improving walking capacity, functional ambulation, balance confidence, and participation among ambulatory individuals with motor incomplete SCI. Conducting a two-center, parallel-group, pragmatic randomized controlled trial (RCT), 41 participants were randomly assigned to either six weeks of WA or CLS. The findings demonstrated similar improvements in walking capacity (maximal walking speed measured with an overground 2-minute Walk Test (2mWT)), functional ambulation (Spinal Cord Injury-Functional Ambulation Profile (SCI-FAP)), balance confidence (Activities-specific Balance Confidence (ABC) scale), and participation (Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P)) at six weeks follow-up for both training approaches. I concluded that WA did not outperform CLS in enhancing these parameters among ambulatory individuals with motor incomplete SCI.

In **chapter 3**, I presented the follow-up findings of the RCT reported in chapter 2, as it was a priori designed as a two-armed cross-over study. This design allowed us to explore the efficacy of two intervention sequences — CLS followed by WA or vice versa — to improve walking capacity, functional ambulation, balance confidence, and participation in ambulatory individuals with motor incomplete SCI. The findings revealed similar improvements in walking capacity (maximal walking speed measured with an overground 2mWT) and functional ambulation (SCI-FAP) regardless of the intervention sequence. However, the CLS-WA sequence exhibited superior effects in enhancing balance confidence (ABC scale) and reducing participation restrictions (USER-P restrictions) compared to the WA-CLS sequence.

Successful walking in everyday life requires an optimal level of walking capacity. Walking capacity refers to a person's ability to walk and comprises three fundamental elements: stepping, dynamic stability, and walking adaptability. Chapters 2 and 3 addressed two fundamental elements for enhancing walking capacity: 'stepping' and 'walking adaptability'. However, to comprehensively improve walking capacity, understanding 'dynamic stability' and how it is affected in individuals with motor incomplete SCI is imperative. Therefore, in **chapter 4**, I explored the mediolateral (ML) foot placement strategy, a fundamental mechanism for maintaining dynamic stability during walking, by comparing individuals with motor incomplete SCI to healthy controls. The study involved a 2mWT on an instrumented

7

treadmill, during which we analyzed foot placement deviation, specifically the error between predicted ML foot placement, based on the center of mass position and velocity, and the actual ML foot placement. The findings revealed that individuals with motor incomplete SCI demonstrated significantly larger foot placement deviation, indicative of an impaired ML foot placement strategy compared to healthy controls.

Part II Rehabilitation approaches to improve walking capacity after motor complete spinal cord injury

In recent years, wearable exoskeletons have emerged as promising assistive mobility devices for individuals with motor complete SCI, offering the ability to regain walking capacity. However, learning to use and control an exoskeleton poses challenges, notably due to the loss of somatosensory information below the level of injury. Given the absence of essential somatosensory information from the lower part of their body, individuals with motor complete SCI must rely more on visual, vestibular, and auditory cues to effectively control an exoskeleton. Therefore, **chapter 5** delved into the impact of limited visual and/or auditory information on exoskeleton control among experienced exoskeleton users with motor complete SCI. Exoskeleton control was assessed by the walking distance covered during a 50-second Walk Test (50sWT) and crutch loading. Our findings revealed that the presence or absence of visual and auditory information had minimal influence on the walking distance of individuals using an exoskeleton. Intriguingly, we observed a decrease rather than an increase in crutch loading when visual or auditory information was limited.

When sensory information from a specific system is lost, one potential solution is to compensate for this loss by providing extrinsic feedback through another sensory modality. In **chapter 6**, I explored the impact of providing discrete vibrotactile feedback related to weight shift and step initiation on exoskeleton motor learning and motor control in individuals with motor complete SCI. Participants had six sessions, structured into one introduction session, followed by four training sessions (either with or without vibrotactile feedback), and ending with one evaluation session. The training sessions assessed the efficacy of vibrotactile feedback on exoskeleton motor learning by comparing individuals' progress between sessions with and without feedback. The evaluation session assessed the efficacy of vibrotactile feedback on exoskeleton motor control under both normal and sensory-deprived conditions when the training protocol was finished. The study findings suggested that, in individuals with motor complete SCI, the vibrotactile feedback did not significantly enhance exoskeleton motor learning or motor control, as assessed by the walking distance covered during a 50sWT, and two outcomes related to the center of mass trajectory during the double support phase: reach path ratio and reach time. User experience with vibrotactile feedback was assessed using three questionnaires: a customized visual analogue scale consisting of five items, the Dutch version of the Quebec User Evaluation of Satisfaction with Assistive Technology (D-QUEST), and the Dutch System Usability Scale (D-SUS). The questionnaires revealed that participants were generally positive about the vibrotactile feedback, especially regarding its use during the training phase.

General discussion

In this subchapter, I will introduce a theoretical framework that describes the recovery of walking capacity in people with SCI. Subsequently, I will explore different approaches, clinical implications, and future directions for enhancing walking capacity after both motor *incomplete* and motor *complete* SCI.

A framework describing walking capacity in spinal cord injury

Successful walking in everyday life necessitates an optimal level of walking capacity which, according to the tripartite model of Balasubramanian introduced in chapter 1, encompasses three fundamental elements: stepping, dynamic stability, and walking adaptability.[1] While this model provides a valuable distinction of the fundamental elements of walking, it lacks the specification of the determinants that are necessary to recover these fundamental elements after neurological injury. Furthermore, the heterogeneity within the SCI population, stemming from variable lesion heights and completeness levels, underscores the necessity for a more comprehensive model tailored specifically to people with SCI. Such a model helps to select interventions aimed to enhance walking capacity in this diverse population. Therefore, I introduce a theoretical framework describing walking capacity in persons with SCI, encompassing the fundamental elements for an optimal level of walking capacity along with the specific determinants to restore these elements after SCI (see Figure 1).

A comparable theoretical framework already exists for individuals post stroke, proposed by van Duijnhoven,[2] to guide clinical decision-making. Van Duijnhoven's model builds upon Balasubramanian's framework and integrates the three fundamental elements essential for successful walking in everyday life —formulated as walking independence, walking pattern, and walking adaptability— along with the specific determinants of these elements. Despite both stroke and SCI being neurological conditions, the framework tailored to the stroke population proves inadequate for SCI, primarily due to the bilateral nature of SCI, involving the loss of both limb and trunk control on both sides, as opposed to the unilateral presentation of most types of stroke. Therefore, in my theoretical framework outlining the recovery of walking capacity after SCI, the foundations of van Duijnhoven's framework served as the starting point while the determinants were specifically adjusted to suit SCI.

To relearn walking under predictable and stable circumstances, walking independence and a basic walking pattern are essential. Walking independence refers to the capacity to ambulate independently, either unaided or with the assistance of a walking aid, without reliance on another person for support or supervision.[3,4] Previous studies found a high correlation between walking independence and steady-state balance control, which involves maintaining a stable equilibrium during static or steady-state conditions, such as standing or walking on level ground.[5,6] In these studies, walking independence was assessed with the Walking Index for Spinal Cord Injury, while steady-state balance control was evaluated with the Berg Balance Scale. The observed high correlation between walking independence and steady-state
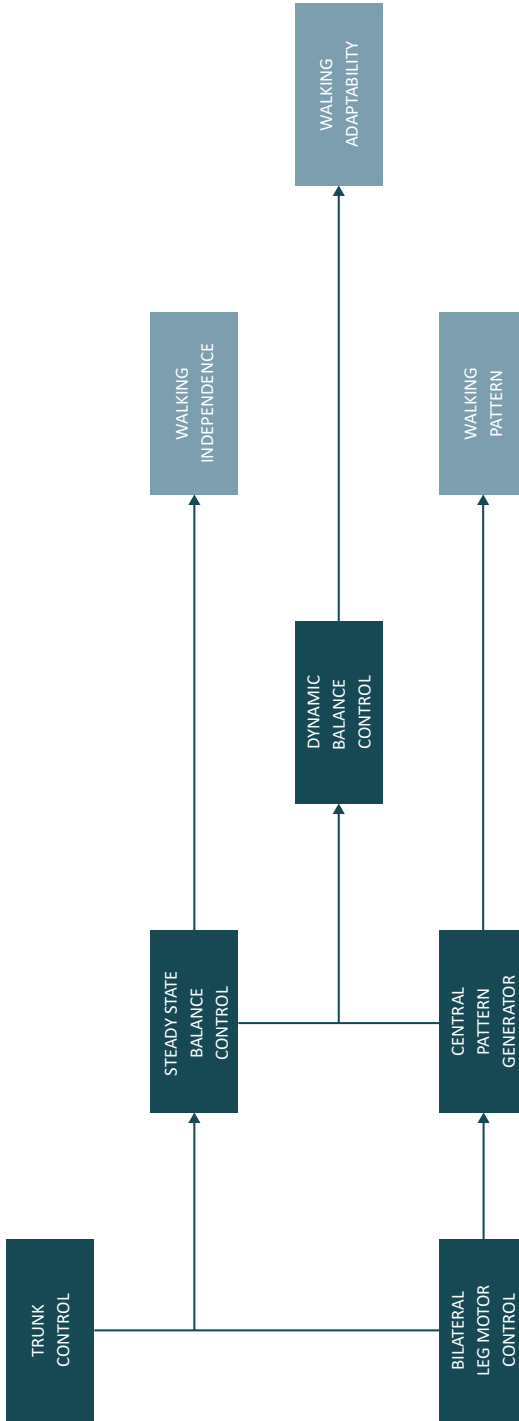
7

Figure 1 Theoretical framework describing the recovery of walking capacity after spinal cord injury. The light blue blocks encompass the three fundamental elements necessary for an optimal level of walking capacity, while the dark blue blocks reflect the specific determinants of these fundamental elements.

balance control suggests that, similar to the context of stroke, steady-state balance control is a prerequisite for regaining walking independence after SCI. In the case of stroke, steady-state balance control is mainly determined by sufficient trunk control and compensatory motor control through the non-paretic leg.[2,7] The notion that steady-state balance control after stroke does not require refined motor control of the non-paretic and paretic leg stems from the observation that the severity of hemiparesis does not reliably predict the recovery of walking capacity.[8] Moreover, several posturographic studies have shown that balance recovery after stroke takes place independent of motor recovery of the paretic leg,[7,9,10] just like many individuals with a lower-limb amputation achieve walking independence using a passive lower-limb prosthesis. SCI, on the other hand, generally affects both sides of the body and the trunk, which implies that there is no 'unaffected side' that is able to compensate for the 'affected side'. Hence, it is anticipated that steady-state balance control after SCI requires the integration of trunk control and motor control of both legs. This perspective is supported by previous studies highlighting the significance of bilateral leg motor control, especially lower extremity motor scores, as the primary determinant of walking independence after SCI.[3,4,11,12] Trunk control as a prerequisite for steady-state balance control has been less explored in the context of SCI, yet one study identified trunk control as a predictor of walking independence after SCI.[13] Therefore, we assume that in people with SCI trunk control is a determinant of walking independence through its effect on steady-state balance control, although further research is necessary to solidify this assumption.

The walking pattern refers to the ability to generate a sequence of repetitive movements of both legs in interaction with the trunk and arms. These rhythmic movements are orchestrated by the spinal central pattern generator (CPG) for walking.[14] The CPG consists of neuronal networks in the spinal cord that generate the fundamental patterned motor outputs essential for locomotion, operating to some extent independently of modulation from the brain or sensory feedback.[14] Indeed, research has demonstrated that individuals with SCI, lacking the ability to generate voluntary lower limb muscle activity, can exhibit involuntary myoclonic rhythmic movements of the lower limbs when placed on a treadmill[15] or when in a supine position.[16-18] However, while the CPG plays a fundamental role in generating rhythmic and coordinated movements at a spinal level, the CPG alone is insufficient for producing a truly effective walking pattern in humans. The generation of an adequate walking pattern in humans requires sufficient leg motor control, incorporating supraspinal neural processes, sensory feedback, and muscle strength.[19]

Steady-state balance control leading to independent walking and generating a basic walking pattern may be sufficient requirements for ambulating under predictable and fixed circumstances. However, in daily life, individuals regularly encounter unpredictable and changing circumstances that demand the modification of the walking pattern in response to environmental challenges (i.e., walking adaptability). This requires adaptive balance control, involving both proactive and reactive adaptations.[20] Examples of proactive adaptations in response to visual stimuli include stepping over an obstacle, precisely placing the foot when

navigating rough terrain, or making a turn around a corner. Reactive adaptations entail responses to mechanical perturbations, such as stumbling over a doorstep or slipping on a muddy surface. Dynamic balance control during walking requires the integration of both steady-state balance control and adequate leg movement coordination by the spinal CPG.[19]

Motor *incomplete* spinal cord injury

Around 80% of the individuals with motor incomplete SCI achieve walking independence.[4] However, their walking pattern may be significantly affected, for example characterized by inadequate hip extension, limited hip flexion, limited knee flexion, excess of ankle plantar flexion, and impaired foot contact.[21] Furthermore, walking adaptability is often compromised,[22] resulting in an increased risk of falling.[23-25]

Approaches to improve walking capacity

Improving walking capacity for individuals with motor incomplete SCI can be achieved through assistive devices, training interventions or a combination of both. Examples of assistive devices include mobility aids or lower-limb orthoses. Mobility aids such as canes, crutches, or walkers broaden the base of support, facilitating hip stability, trunk control and steady-state balance control, thereby promoting walking independence.[26] Additionally, they alleviate stress on the legs by allowing the transfer of some body weight onto the device and facilitating propulsive forces.[27] This may require less lower limb muscle strength for walking, which may improve the walking pattern to some extent. Lower-limb orthoses are externally worn medical devices that compensate for loss of function and prevent unwanted movements. They can be either passive (e.g., ankle-foot orthoses or knee-ankle-foot orthoses) or active (e.g., wearable exoskeletons[28], soft exosuits[29] or powered knee orthoses[30]). Orthoses support leg motor control, thereby promoting walking independence,[26] the walking pattern,[31-33] and/or walking adaptability.[34]

Training interventions aimed at improving walking capacity in individuals with motor incomplete SCI can be classified into two primary categories: steady-state gait training and dynamic gait training. Steady-state gait training involves walking under predominantly predictable and stable circumstances, employing methods such as overground, treadmill-based, or robot-assisted gait training.[35-38] Such training focuses on walking independence and refining the quality of the walking pattern. In contrast, dynamic gait training focuses on walking under unpredictable and changing conditions, using approaches such as overground or virtual-reality-based adaptability training, as well as perturbation-based balance training.[39,40] These interventions primarily aim to enhance walking adaptability.

Despite their distinct emphases, both steady-state and dynamic gait training have demonstrated effectiveness in improving walking capacity among individuals with motor incomplete SCI.[35,36,41] Furthermore, emerging evidence (including findings presented in chapter 2 of this thesis) suggests non-differential effects between steady-state and dynamic gait training to enhance walking in everyday life for individuals with motor incomplete SCI[39] and other neurological conditions.[42] This can be understood using the proposed theoretical

framework. While dynamic gait training specifically targets dynamic balance control through exposure to variable walking conditions, steady-state gait training indirectly enhances aspects of dynamic balance control by promoting determinants such as leg motor control and steady-state balance control. Conversely, dynamic gait training may indirectly enhance walking independence and refine the walking pattern by promoting steady-state balance control and stimulating the CPG.

To comprehend how assistive devices and training interventions enhance walking capacity, it is essential to grasp the underlying mechanisms of functional recovery. Functional recovery typically occurs through either 'restitution' or 'substitution' of function. Restitution of function involves the recovery of sensorimotor functions comparable to pre-injury movement patterns,[43] facilitated by repair mechanisms like remyelination/regeneration and reconnection of damaged spinal tract fibers, alongside neural plasticity fostering the reorganization of neuronal circuits.[44] Conversely, substitution of function involves acquiring new sensorimotor strategies to accomplish tasks in an adapted manner.[43] Assistive devices enhance walking capacity through substitution of function as they enable individuals to compensate for impaired or lost abilities by providing alternative means to perform tasks or activities. For training interventions, the underlying mechanism can be attributed to both restitution and substitution of function. In the (sub)acute phase both mechanisms may play an important role as spontaneous neurological recovery still occurs and may be promoted by intensive gait training. However, during the chronic phase, further functional recovery is primarily dependent on substitution of function as the neurological recovery has mostly plateaued.[45] Consequently, steady-state and dynamic gait training in the chronic phase may be effective by promoting substitution of function. For instance, increasing one's step width to compensate for reduced balance represents a form of substitution of function that could be promoted by training interventions. Growing evidence (including chapter 4 of this thesis) suggests an impaired coordination between the center of mass state and lateral foot placement in individuals with motor incomplete SCI.[46,47] To compensate, individuals could widen their steps to enhance postural stability and decrease the demand for precise foot placement modulation. Another form of substitution of function, which could be developed during both steady-state and dynamic gait training, could be the increased reliance on visual input to control gait to compensate for proprioceptive deficits.[48-50]

While substitution of function is most likely the underlying mechanism of functional recovery in the chronic phase, recent research has shown that some restitution of function is still possible during this period. For example, Donati and colleagues demonstrated that individuals with chronic SCI improved sensorimotor functions after a twelve-month intensive multi-stage brain-machine-interfaces-based gait neurorehabilitation intervention.[51] They hypothesized that recovery of function occurred as a result of cortical and spinal plasticity that changed and modulated neurological circuits in the preserved area around the lesion. Thus, if neuroplasticity is still possible during the chronic phase, steady-state and dynamic gait training might also promote restitution of function in this phase to some extent, but further research is required to substantiate this notion.

7

Other underlying mechanisms contributing to the enhanced walking capacity observed after gait training may involve the general effects of training, namely increase in muscle mass and improvements in cardiorespiratory fitness. Individuals with motor incomplete SCI often exhibit low levels of physical activity compared to their non-SCI counterparts,[52,53] potentially leading to muscle disuse atrophy and diminished cardiorespiratory endurance. Therefore, various types of gait training interventions have the potential to enhance both muscle mass and cardiorespiratory fitness. This assertion finds support in prior research demonstrating that locomotor training can effectively increase muscle mass and fiber size in individuals with chronic motor incomplete SCI.[54-56] Additionally, a comprehensive review cautiously concluded that locomotor training may reach the minimum threshold of 'moderate intensity' necessary for cardiovascular fitness benefits.[57]

Clinical implications and future directions

The recently published Integral Care Agreement (Integraal Zorg Akkoord / IZA) in the Netherlands propagates a transition from hospital-based healthcare to community-based healthcare. This shift is driven by the recognition that community-based healthcare offers several advantages, including proximity to citizens, shorter waiting times, and lower costs. These advantages closely align with IZA's vision of future healthcare, which emphasizes not only high quality care, but also its accessibility and affordability.

When considering interventions aimed at improving walking capacity in individuals with motor incomplete SCI, I believe that steady-state gait training is the most feasible option for implementation in the community care system, as opposed to dynamic gait training. In terms of effectiveness, findings from chapter 2 suggest no significant differences between steady-state and dynamic gait training. Yet, steady-state gait training demands minimal resources, requiring only a flat surface (or a treadmill) for overground (or treadmill-based) training, both of which are commonly available in community-based physiotherapy practices. In contrast, dynamic gait training requires an environment with unpredictable and changing circumstances, such as dynamic obstacles, stepping stones, and perturbations, either in the real world or within a virtual reality setting. Such resources are less commonly available in community-based practices. Therefore, I recommend steady-state gait training in the community care system for individuals with motor incomplete SCI that aim to improve their walking capacity.

Additionally, subsequent to steady-state gait training, I recommend dynamic gait training in specialized clinical settings for people with motor incomplete SCI with higher training goals aimed at outdoor walking. Chapter 3 suggests that commencing with steady-state gait training before dynamic gait training yields superior outcomes in enhancing balance confidence and reducing participation restrictions compared to the reverse intervention sequence. This notion finds support in the theoretical framework describing the recovery of walking capacity after SCI. Specifically, steady-state gait training focuses on improving walking independence and refining the walking pattern by addressing determinants such as steady-state balance control and leg motor control. In contrast, dynamic gait training focuses on dynamic balance

control to improve walking adaptability. Effective dynamic balance control requires sufficient steady-state balance control and leg motor control. Therefore, I believe that a sequential approach, beginning with steady-state gait training followed by dynamic gait training, may offer the greatest potential for improvement of walking capacity in those individuals with motor incomplete SCI capable of outdoor walking.

To enhance future accessibility of dynamic gait training methods in community-based physiotherapy practices, innovative approaches are required. One such example is the HoloLens developed by the Microsoft Corporation (Redmond, WA, USA). The HoloLens is a headset using mixed reality, enabling individuals to interact with both physical objects in the real world and convincing virtual objects.[58] Previous research has already demonstrated the potential of the HoloLens for dynamic gait training.[59] However, further research is needed to determine its effectiveness and safety for individuals with motor incomplete SCI to improve their walking capacity.

Motor *complete* spinal cord injury

Individuals with motor complete SCI rarely achieve walking independence,[4,45,60] leading to a dependency on wheelchairs for independent mobility. However, a lifetime of predominant sitting is associated with multiple secondary health problems. Therefore, regaining walking capacity can play a crucial role in mitigating some of these secondary complications.

Approaches to improve walking capacity

Individuals with motor complete SCI currently face limited prospects of functional recovery, making training interventions aimed at improving walking capacity ineffective. However, they can use assistive devices to regain some walking capacity. Among these devices are passive lower-limb orthoses like hip-knee-ankle-foot orthoses or knee-ankle-foot orthoses.[45] Although these aids can partially restore walking capacity, they typically come with a significant energy expenditure,[61,62] thereby limiting the duration and distance of walking. A more promising assistive device is a wearable exoskeleton, which serves as a motorized orthosis, enabling individuals with motor complete SCI to stand and walk. By providing external support and assistance for leg movements, wearable exoskeletons effectively compensate for compromised leg motor control resulting from SCI. In this way, wearable exoskeletons enhance walking capacity through substitution of function.

Wearable exoskeletons for individuals with motor complete SCI are intended to serve as assistive mobility devices. However, previous research demonstrated that individuals with motor complete SCI primarily use these exoskeletons for exercise and specific social interaction, with minimal usage during regular daily activities.[63] This observation aligns with the general notion that while current exoskeletons hold great potential for exercise and social engagement at eye level, they offer limited support for most daily activities.[64,65] One key factor contributing to this limitation is the user's responsibility for maintaining steady-state balance control.[66] While exoskeletons compensate for compromised leg motor control, most lack the ability to detect

7

and respond to postural instability. Individuals with motor complete SCI can contribute partially to steady-state balance control through trunk movements. However, reliance on trunk control alone proves insufficient for maintaining steady-state balance. Therefore, additional support from crutches or a walker is necessary. This need for postural support through the upper extremities restricts people in using their arms for other activities, like bringing a coffee cup from the kitchen to the table or carrying groceries.

Another reason for the postural challenge in steady-state balance control after motor complete SCI is the absence of essential somatosensory information from below the lesion level. In chapter 6, I aimed to enhance steady-state balance control by compensating for the loss of proprioceptive information through sensory substitution. However, the findings indicated that incorporating vibrotactile feedback did not significantly enhance exoskeleton motor learning or motor control. It is plausible that somatosensory information above the lesion level, particularly from the arms that are in contact with the ground surface via the crutches or walker, along with inputs from other sensory modalities such as the vestibular and visual system, provide the necessary information to maintain steady-state balance, making extrinsic vibrotactile feedback redundant. In chapter 5, I observed that proprioception from above the lesion level is likely the most important form of sensory information when using an exoskeleton. Therefore, I believe that the challenge in achieving steady-state balance control with a wearable exoskeleton is not due to individuals with motor complete SCI lacking the ability to perceive postural instability adequately. Instead, their limitation lies in their incapacity to respond effectively. This limitation primarily arises from the absence of leg motor control necessary for crucial balance strategies. Furthermore, they can only partially compensate by trunk motor control. Hence, they strongly rely on the mechanical and sensory support from a walker or crutches.

Another reason why the use of wearable exoskeletons is limited in many daily life activities is the very low walking speed. Current exoskeletons maintain an average walking speed of 0.26 m/s (ranging from 0.03 to 0.71 m/s),[67] whereas healthy able-bodied individuals prefer walking speeds between 1.0 and 1.5 m/s.[68] Moreover, when the comfortable walking speed falls below 0.6 m/s, individuals with SCI typically prefer using a wheelchair for their daily mobility needs.[69] In addition to walking speed, other factors contributing to the limited use of wearable exoskeletons for daily life activities include the need for a buddy,[65,70] issues with transportability[64,65] and comfort,[71,72] concerns about weight,[64,72] and limited battery life.[65]

Clinical implications and future directions

Individuals with motor complete SCI primarily use wearable exoskeletons for exercise,[63] suggesting that current exoskeletons are most suitable for exercise training. When exoskeletons are regularly used as a training device, they have the potential to enhance quality of life.[73] This is because exoskeletons can positively impact secondary health complications resulting from reduced weight-bearing activity post SCI. Studies have shown improvements in bladder and bowel function,[74,75] reduced spasticity[74,76] and neuropathic pain severity,[76,77] increased bone

mineral density,[78] and enhanced joint mobility[79] among exoskeleton users. Beyond physical health benefits, the social implications of exoskeleton use are profound. By enabling individuals with motor complete SCI to engage with peers at eye level, exoskeletons facilitate invaluable social interaction and promote psychological well-being.[80] Considering the IZA, it would be advantageous to offer the option of exercise training with wearable exoskeletons either at home or in community-based physiotherapy practices. As a prerequisite for using a wearable exoskeleton in either of these settings, individuals should have successfully completed a training program with an experienced physical therapist in a specialized clinical setting. This ensures that a basic skill level is achieved, allowing the exoskeleton to be safely used under the supervision of a buddy, whether at home or in community-based physiotherapy practices.

In their current state, wearable exoskeletons are not yet ready to serve as assistive mobility devices capable of replacing wheelchairs. Therefore, significant improvements are required. In my view, the primary focus for improvement should be on shifting balance control from the user to the exoskeleton, thereby freeing the user from reliance on a walker or crutches for postural stability. This enhancement should be achieved without compromising the exoskeleton's weight, ensuring ease of transportability. Some progress has already been made in this regard. For instance, previous research has demonstrated the successful implementation of a momentum-based balance controller in a wearable exoskeleton, enabling it to effectively counteract perturbations and maintain self-balance without external assistance during stance, without a user wearing the exoskeleton.[81] This development holds promise for enabling wearable exoskeletons to autonomously maintain balance during standing, and possibly during walking, when used by individuals with motor complete SCI.

Another crucial area for improvement is the development of an exoskeleton that is capable of walking adaptability. Currently, exoskeletons operate on predetermined trajectories initiated by users,[66] thereby limiting their ability to respond to environmental challenges in everyday scenarios. A first step would involve empowering users, through a control device, to adjust step length, height, and/or timing to accommodate various situations, such as ascending a sidewalk, navigating obstacles, or slowing down to avoid collisions with cyclists.

While wearable exoskeletons are promising as assistive mobility devices, the optimal direction for SCI rehabilitation would be to focus on restoring leg motor control, thereby enabling individuals with motor complete SCI to regain the ability to walk without the need for orthoses. One potential strategy to achieve this goal is through neuromodulation of the lumbar spinal cord. Previous research demonstrated that neuromodulation of the lumbar spinal cord results in significant improvement in lower-limb motor control in both animal models[82,83] and humans[84] with motor complete SCI. This suggests that neuromodulation could play a pivotal role in restoring walking independence in this population. Moreover, a recent breakthrough has been achieved: researchers successfully restored natural control over lower limb movements through the use of a brain-spine interface (BSI), reinstating communication between the brain and the spinal cord.[85] This BSI enabled a paralyzed individual to walk

7

on complex terrains solely through thinking about the activity at stake. Furthermore, the neurological improvements mediated by this BSI persisted even after deactivation, suggesting potential for functional recovery after SCI. Although this study was a case report involving only one paralyzed individual with motor incomplete SCI, the authors suggest that this approach holds potential for a wide population of individuals with paralysis, including motor complete SCI. It is important to note, however, that before effectively using a BSI, extensive gait training is necessary. In this context, there could be a role for the wearable exoskeleton to assist in the initial BSI training, gradually tapering off the support and use of the exoskeleton as the individual becomes proficient with the BSI technology. Therefore, the role of gait training with or without robot assistance will remain significant in functional recovery after SCI, emphasizing the importance of tailored rehabilitation programs.

7

References

1. Balasubramanian CK, Clark DJ, Fox EJ. Walking Adaptability after a Stroke and Its Assessment in Clinical Settings. Stroke Res Treat. 2014;2014:591013.

2. Duijnhoven H van. The challenges of dynamic balance & gait for people after stroke (dissertation). Nijmegen (NL): Donders Institute for Brain, Cognition and Behaviour, Radboud Univerisity Medical Center; 2019.

3. Van Middendorp JJ, Hosman AJ, Donders ART, et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: A longitudinal cohort study. The Lancet. 2011;377:1004–1010.

4. Hicks KE, Zhao Y, Fallah N, et al. A simplified clinical prediction rule for prognosticating independent walking after spinal cord injury: a prospective study from a Canadian multicentre spinal cord injury registry. Spine Journal. 2017;17:1383–1392.

5. Scivoletto G, Romanelli A, Mariotti A, et al. Clinical factors that affect walking level and performance in chronic spinal cord lesion patients. Spine (Phila Pa 1976). 2008;33:259–264.

6. Lemay JF, Nadeau S. Standing balance assessment in ASIA D paraplegic and tetraplegic participants: Concurrent validity of the Berg Balance Scale. Spinal Cord. 2010;48:245–250.

7. De Haart M, Geurts AC, Huidekoper SC, Fasotti L, Van Limbeek J. Recovery of standing balance in postacute stroke patients: A rehabilitation cohort study. Arch Phys Med Rehabil. 2004;85:886–895.

8. Kollen B, Van De Port I, Lindeman E, Twisk J, Kwakkel G. Predicting improvement in gait after stroke a longitudinal prospective study. Stroke. 2005;36:2676–2680.

9. Schröder J, Saeys W, Embrechts E, et al. Recovery of Quiet Standing Balance and Lower Limb Motor Impairment Early Poststroke: How Are They Related? Neurorehabil Neural Repair. 2023;37:530–544.

10. Roerdink M, Geurts ACH, De Haart M, Beek PJ. On the relative contribution of the paretic leg to the control of posture after stroke. Neurorehabil Neural Repair. 2009;23:267–274.

11. Moon J, Yu J, Choi J, Kim MY, Min K. Degree of contribution of motor and sensory scores to predict gait ability in patients with incomplete spinal cord injury. Ann Rehabil Med. 2017;41:969–978.

12. Waters RL, Adkins RH, Yakura JS, Sie I. Motor and Sensory Recovery Following Incomplete Paraplegia. Arch Phys Med Rehabil. 1994;75:67–72.

13. Quinzaños-Fresnedo J, Fratini-Escobar PC, Almaguer-Benavides KM, et al. Prognostic validity of a clinical trunk control test for independence and walking in individuals with spinal cord injury. Journal of Spinal Cord Medicine. 2020;43:331–338.

14. Klarner T, Zehr EP. Sherlock Holmes and the curious case of the human locomotor central pattern generator. J Neurophysiol. 2018;120:53–77.

15. Bussel B, Roby-Bram A, Azouvi PH, Biraben A, Yakovleff A, Held JP. Myoclonus in a Patient With Spinal Cord Transection. Brain. 1988;111:1235–1245.

16. Calancie B, Needham-shropshire B, Jacobs P, Willer K, Zych G, Green BA. Involuntary stepping after chronic spinal cord injury: Evidence for a central rhythm generator for locomotion in man. Brain. 1994;117:1143–1159.

17. Calancie B. Spinal myoclonus after spinal cord injury. Journal of Spinal Cord Medicine. 2006;29:413–424.

18. Nadeau S, Jacquemin G, Fournier C, Lamarre Y, Rossignol S. Spontaneous motor rhythms of the back and legs in a patient with a complete spinal cord transection. Neurorehabil Neural Repair. 2010;24:377–383.

19. MacKay-Lyons M. Central pattern generation of locomotion: A review of the evidence. Phys Ther. 2002;82:69–83.

20. Weerdesteyn V, Hollands KL, Hollands MA. Gait adaptability. 1st ed. Elsevier B.V.; 2018.

7

21.   van der Salm A, Nene A V., Maxwell DJ, Veltink PH, Hermens HJ, Ijzerman MJ. Gait impairments in a group of patients with incomplete spinal cord injury and their relevance regarding therapeutic approaches using functional electrical stimulation. Artif Organs. 2005;29:8–14.

22.   Mohammadzada F, Zipser CM, Easthope CA, et al. Mind your step: Target walking task reveals gait disturbance in individuals with incomplete spinal cord injury. J Neuroeng Rehabil. 2022;19:36.

23.   Brotherton SS, Krause JS, Nietert PJ. Falls in individuals with incomplete spinal cord injury. Spinal Cord. 2007;45:37–40.

24.   Phonthee S, Saengsuwan J, Siritaratiwat W, Amatachaya S. Incidence and factors associated with falls in independent ambulatory individuals with spinal cord injury: A 6-month prospective study. Phys Ther. 2013;93:1061–1072.

25.   Khan A, Pujol C, Laylor M, et al. Falls after spinal cord injury: a systematic review and meta-analysis of incidence proportion and contributing factors. Spinal Cord. 2019;57:526–539.

26.   Ditunno JF, Ditunno PL, Graziani V, et al. Walking index for spinal cord injury (WISCI): An international multicenter validity and reliability study. Spinal Cord. 2000;38:234–243.

27.   Melis EH, Torres-Moreno R, Barbeau B, Lemaire ED. Analysis of assisted-gait characteristics in persons with incomplete spinal cord injury. Spinal Cord. 1999;37:430–439.

28.   Wright MA, Herzog F, Mas-Vinyals A, et al. Multicentric investigation on the safety, feasibility and usability of the ABLE lower-limb robotic exoskeleton for individuals with spinal cord injury: a framework towards the standardisation of clinical evaluations. J Neuroeng Rehabil. 2023;20:1–18.

29.   Haufe FL, Kober AM, Schmidt K, et al. User-driven walking assistance: first experimental results using the MyoSuit. In: 2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR). IEEE; 2019:944–949.

30.   McGibbon CA, Sexton A, Jayaraman A, et al. Evaluation of the Keeogo exoskeleton for assisting ambulatory activities in people with multiple sclerosis: An open-label, randomized, cross-over trial. J Neuroeng Rehabil. 2018;15:1–14.

31.   Beekman C, Perry J, Boyd LA, Newsam CJ, Mulroy SJ. The effects of a dorsiflexion-stopped ankle-foot orthosis on walking in individuals with incomplete spinal cord injury. Top Spinal Cord Inj Rehabil. 2000;5:54–62.

32.   Kim CM, Eng JJ, Whittaker MW, Eng J. Effects of a simple functional electrical system and/or a hinged AFO on walking in individuals with incomplete spinal cord injury. Arch Phys Med Rehabil. 2004;60606:1718–1723.

33.   Arazpour M, Tajik HR, Aminian G, Bani MA, Ghomshe FT, Hutchins SW. Comparison of the effects of solid versus hinged ankle foot orthoses on select temporal gait parameters in patients with incomplete spinal cord injury during treadmill walking. Prosthet Orthot Int. 2013;37:70–75.

34.   Cikajlo I, Osrečki K, Burger H. The effects of different types of ankle-foot orthoses on postural responses in individuals with walking impairments. International Journal of Rehabilitation Research. 2016;39:313–319.

35.   Morawietz C, Moffat F. Effects of locomotor training after incomplete spinal cord injury: A systematic review. Arch Phys Med Rehabil. 2013;94:2297–2308.

36.   Mehrholz J, Harvey LA, Thomas S, Elsner B. Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. Spinal Cord. 2017;55:722–729.

37.   Nam KY, Kim HJ, Kwon BS, Park JW, Lee HJ, Yoo A. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. J Neuroeng Rehabil. 2017;14:1–13.

7

38.   Gil-Agudo Á, Megía-García Á, Pons JL, et al. Exoskeleton-based training improves walking independence in incomplete spinal cord injury patients: results from a randomized controlled trial. J Neuroeng Rehabil. 2023;20:1–11.

39.   Yang JF, Musselman KE, Livingstone D, et al. Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial. Neurorehabil Neural Repair. 2014;28:314–324.

40.   Unger J, Chan K, Lee JW, et al. The Effect of Perturbation-Based Balance Training and Conventional Intensive Balance Training on Reactive Stepping Ability in Individuals With Incomplete Spinal Cord Injury or Disease: A Randomized Clinical Trial. Front Neurol. 2021;12:1–13.

41.   van Dijsseldonk RB, de Jong LAF, Groen BE, Vos-van der Hulst M, Geurts ACH, Keijsers NLW. Gait stability training in a virtual environment improves gait and dynamic balance capacity in incomplete spinal cord injury patients. Front Neurol. 2018;9:963.

42.   de Rooij IJM, van de Port IGL, Visser-Meily JMA, Meijer JWG. Virtual reality gait training versus non-virtual reality gait training for improving participation in subacute stroke survivors: Study protocol of the ViRTAS randomized controlled trial. Trials. 2019;20:1–10.

43.   Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensationg" mean in patients following stroke? Neurorehabil Neural Repair. 2009;23:313–319.

44.   Curt A, Van Hedel HJA, Klaus D, Dietz V. Recovery from a spinal cord injury: Significance of compensation, neural plasticity, and repair. J Neurotrauma. 2008;25:677–685.

45.   Burns AS, Marino RJ, Flanders AE, Flett H. Clinical diagnosis and prognosis following spinal cord injury. In: Handbook of Clinical Neurology.Vol 109. 1st ed. Elsevier B.V.; 2012:47–62.

46.   Day K V., Kautz SA, Wu SS, Suter SP, Behrman AL. Foot placement variability as a walking balance mechanism post-spinal cord injury. Clinical Biomechanics. 2012;23:1–7.

47.   Cornwell T, Woodward J, Ochs W, Gordon KE. Stabilization Strategies for Fast Walking in Challenging Environments With Incomplete Spinal Cord Injury. Frontiers in Rehabilitation Sciences. 2021;2:1–14.

48.   Ionta S, Villiger M, Jutzeler CR, Freund P, Curt A, Gassert R. Spinal cord injury affects the interplay between visual and sensorimotor representations of the body. Sci Rep. 2016;6.

49.   Lee GE, Bae H, Yoon TS, Kim JS, Yi TI, Park JS. Factors that influence quiet standing balance of patients with incomplete cervical spinal cord injuries. Ann Rehabil Med. 2012;36:530–537.

50.   Lemay JF, Gagnon D, Duclos C, Grangeon M, Gauthier C, Nadeau S. Influence of visual inputs on quasi-static standing postural steadiness in individuals with spinal cord injury. Gait Posture. 2013;38:357–360.

51.   Donati ARC, Shokur S, Morya E, et al. Long-Term Training with a Brain-Machine Interface-Based Gait Protocol Induces Partial Neurological Recovery in Paraplegic Patients. Sci Rep. 2016;6:1–16.

52.   Buchholz AC, McGillivray CF, Pencharz PB. Physical activity levels are low in free-living adults with chronic paraplegia. Obes Res. 2003;11:563–570.

53.   van den Berg-Emons RJ, Bussmann JB, Haisma JA, et al. A Prospective Study on Physical Activity Levels After Spinal Cord Injury During Inpatient Rehabilitation and the Year After Discharge. Arch Phys Med Rehabil. 2008;89:2094–2101.

54.   Giangregorio LM, Webber CE, Phillips SM, et al. Can body weight supported treadmill training increase bone mass and reverse muscle atrophy in individuals with chronic incomplete spinal cord injury? Applied Physiology, Nutrition and Metabolism. 2006;31:283–291.

7

55. Stewart BG, Tarnopolsky MA, Hicks AL, et al. Treadmill training-induced adaptations in muscle phenotype in persons with incomplete spinal cord injury. Muscle Nerve. 2004;30:61–68.

56. Jayaraman A, Shah P, Gregory C, et al. Locomotor training and muscle function after incomplete spinal cord injury: Case series. Journal of Spinal Cord Medicine. 2008;31:185–193.

57. Hicks AL. Locomotor training in people with spinal cord injury: is this exercise? Spinal Cord. 2021;59:9–16.

58. Brigham TJ. Reality Check: Basics of Augmented, Virtual, and Mixed Reality. Med Ref Serv Q. 2017;36:171–178.

59. Coolen B, Beek PJ, Geerse DJ, Roerdink M. Avoiding 3D obstacles in mixed reality: Does it differ from negotiating real obstacles? Sensors (Switzerland). 2020;20.

60. Kay ED, Deutsch A, Wuermser LA. Predicting Walking at Discharge From Inpatient Rehabilitation After a Traumatic Spinal Cord Injury. Arch Phys Med Rehabil. 2007;88:745–750.

61. Bowker P, Messenger N, Ogilvie C, Rowley DI. Energetics of paraplegic walking. J Biomed Eng. 1992;14:344–350.

62. Arazpour M, Samadian M, Ebrahimzadeh K, Ahmadi Bani M, Hutchins SW. The influence of orthosis options on walking parameters in spinal cord-injured patients: A literature review. Spinal Cord. 2016;54:412–422.

63. van Dijsseldonk RB, van Nes IJW, Geurts ACH, Keijsers NLW. Exoskeleton home and community use in people with complete spinal cord injury. Sci Rep. 2020;10:1–8.

64. Fritz H, Patzer D, Galen SS. Robotic exoskeletons for reengaging in everyday activities: promises, pitfalls, and opportunities. Disabil Rehabil. 2019;41:560–563.

65. Kandilakis C, Sasso-Lance E. Exoskeletons for Personal Use After Spinal Cord Injury. Arch Phys Med Rehabil. 2021;102:331–337.

66. Lee H, Ferguson PW, Rosen J. Lower limb exoskeleton systems-overview. In: Wearable Robotics: Systems and Applications. INC; 2020:207–229.

67. Louie DR, Eng JJ, Lam T. Gait speed using powered robotic exoskeletons after spinal cord injury: A systematic review and correlational study. J Neuroeng Rehabil. 2015;12:1–10.

68. Fukuchi CA, Fukuchi RK, Duarte M. Effects of walking speed on gait biomechanics in healthy participants: A systematic review and meta-analysis. Syst Rev. 2019;8:1–11.

69. Van Silfhout L, Hosman AJF, Bartels RHMA, et al. Ten Meters Walking Speed in Spinal Cord-Injured Patients: Does Speed Predict Who Walks and Who Rolls? Neurorehabil Neural Repair. 2017;31:842–850.

70. Gorgey AS. Robotic exoskeletons: The current pros and cons. World J Orthop. 2018;9:112–119.

71. Bhatnagar T, Ben Mortensen W, Mattie J, Wolff J, Parker C, Borisoff J. A survey of stakeholder perspectives on a proposed combined exoskeleton-wheelchair technology. IEEE International Conference on Rehabilitation Robotics. 2017;11:1574–1579.

72. van Dijsseldonk RB, Vriezekolk JE, Keijsers NLW, Geurts ACH, van Nes IJW. Needs and wishes for the future lower limb exoskeleton: an interview study among people with spinal cord injury with community-based exoskeleton experience. Disabil Rehabil. 2023;45:1139–1146.

73. van Nes IJW, van Dijsseldonk RB, van Herpen FHM, Rijken H, Geurts ACH, Keijsers NLW. Improvement of quality of life after 2-month exoskeleton training in patients with chronic spinal cord injury. Journal of Spinal Cord Medicine. 2022;0:1–7.

74. Miller LE, Zimmermann AK, Herbert WG. Clinical effectiveness and safety of powered exoskeleton-assisted walking in patients with spinal cord injury: Systematic review with meta-analysis. Medical Devices: Evidence and Research. 2016;9:455–466.

75. Chun A, Asselin PK, Knezevic S, et al. Changes in Bowel Function Following Exoskeletal-Assisted Walking in Persons with Spinal Cord Injury: An Observational Pilot Study. Spinal Cord. 2020;58:459–466.

76. Baunsgaard CB, Nissen UV, Brust AK, et al. Exoskeleton gait training after spinal cord injury: An exploratory study on secondary health conditions. J Rehabil Med. 2018;50:806–813.

77. Kressler J, Thomas CK, Field-Fote EC, et al. Understanding therapeutic benefits of overground bionic ambulation: Exploratory case series in persons with chronic, complete spinal cord injury. Arch Phys Med Rehabil. 2014;95:1878-1887.e4.

78. Karelis AD, Carvalho LP, Castillo MJE, Gagnon DH, Aubertin-Leheudre M. Effect on body composition and bone mineral density of walking with a robotic exoskeleton in adults with chronic spinal cord injury. J Rehabil Med. 2017;49:84–87.

79. White H, Hayes S, White M. The Effect of Using a Powered Exoskeleton Training Programme on Joint Range of Motion on Spinal Injured Individuals: A Pilot Study. International Journal of Physical Therapy & Rehabilitation. 2015;1:1–5.

80. Cahill A, Ginley OM, Bertrand C, Lennon O. Gym-based exoskeleton walking: A preliminary exploration of non-ambulatory end-user perspectives. Disabil Health J. 2018;11:478–485.

81. Vallinas A, Keemink A, Bayon C, Van Asseldonk E, Van Der Kooij H. Momentum-Based Balance Control of a Lower-Limb Exoskeleton During Stance. IEEE International Conference on Rehabilitation Robotics. 2023.

82. Wenger N, Moraud EM, Gandar J, et al. Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury. Nat Med. 2016;22:138–145.

83. Wenger N, Moraud EM, Raspopovic S, et al. Closed-loop neuromodulation of spinal sensorimotor circuits controls refined locomotion after complete spinal cord injury. Sci Transl Med. 2014;6.

84. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain. 2014;137:1394–1409.

85. Lorach H, Galvez A, Spagnolo V, et al. Walking naturally after spinal cord injury using a brain–spine interface. Nature. 2023;618:126–133.

7

Chapter 8

Nederlandse samenvatting
Summary in Dutch

8

Nederlandse samenvatting

Mensen met een dwarslaesie hebben geen of een verminderde loopvaardigheid, afhankelijk van de ernst en de hoogte van de laesie. Dit proefschrift behandelt mogelijkheden om de loopvaardigheid van mensen met een dwarslaesie te verbeteren. Het eerste deel richt zich op personen met een *verminderde* loopvaardigheid als gevolg van een motorisch *incomplete* dwarslaesie. Het tweede deel richt zich op personen *zonder* loopvaardigheid als gevolg van een motorisch *complete* dwarslaesie.

Deel I: Motorisch *incomplete* dwarslaesie

Voor het verbeteren van de loopvaardigheid van mensen met een motorisch incomplete dwarslaesie zijn verschillende interventies beschikbaar. In **hoofdstuk 2** heb ik middels een pragmatische, gerandomiseerd gecontroleerde studie (RCT) de effectiviteit van twee interventies vergeleken. De interventies werden beoordeeld op hun vermogen om de loopvaardigheid, functioneel lopen, vertrouwen in balansvaardigheid en maatschappelijke participatie te verbeteren. De ene interventie bestond uit een training gericht op het verbeteren van het loopaanpassingsvermogen (WA), terwijl de andere interventie bestond uit conventionele loop- en krachttraining (CLS). Het onderzoek werd uitgevoerd in twee centra, waarbij 41 deelnemers willekeurig werden toegewezen aan zes weken WA of CLS. De loopvaardigheid werd gemeten met een twee minuten looptest (2mWT), functioneel lopen met de Spinal Cord Injury Functional Ambulation Profile (SCI-FAP), het vertrouwen in balansvaardigheid met de Activities-specific Balance Confidence (ABC) schaal en de maatschappelijke participatie met de Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P). Beide groepen toonden vergelijkbare verbeteringen in alle uitkomstmaten zes weken na het voltooien van de interventies. Hieruit concludeerde ik dat WA niet superieur is aan CLS in het verbeteren van de loopvaardigheid, functioneel lopen, vertrouwen in balansvaardigheid of maatschappelijke participatie bij mensen met een motorisch incomplete dwarslaesie.

In **hoofdstuk 3** presenteerde ik de bevindingen van de vervolgstudie van de RCT. De RCT was oorspronkelijk ontworpen als een cross-over studie, waardoor ik de effectiviteit van twee verschillende interventievolgordes (CLS gevolgd door WA en vice versa) kon onderzoeken bij mensen met een motorisch incomplete dwarslaesie. De resultaten van de studie toonden vergelijkbare verbeteringen in de loopvaardigheid (gemeten met een 2mWT) en functioneel lopen (gemeten met de SCI-FAP). Echter, de volgorde CLS-WA vertoonde superieure effecten bij het verbeteren van het vertrouwen in de balansvaardigheid (gemeten met de ABC schaal) en de maatschappelijke participatie (gemeten met de USER-P) in vergelijking met de WA-CLS volgorde.

Naast het evalueren van verschillende interventies is het belangrijk om inzicht te krijgen in de onderliggende oorzaken van een verminderde loopvaardigheid als gevolg van een dwarslaesie. Daarom heb ik in **hoofdstuk 4** het gebruik van de belangrijkste balansstrategie (zijwaartse voetplaatsingsstrategie) tijdens het lopen bij mensen met een motorisch incomplete dwarslaesie

8

onderzocht. Volgens de zijwaartse voetplaatsingsstrategie wordt de voetplaatsing tijdens het lopen bepaald op basis van de positie en snelheid van het massazwaartepunt. Voor deze studie heb ik mensen met een motorisch incomplete dwarslaesie en een gezonde controlegroep op een geïnstrumenteerde loopband laten lopen. Vervolgens heb ik de voetplaatsingsstrategie in beide groepen geanalyseerd door de voetplaatsingsfout te evalueren. De voetplaatsingsfout is het verschil tussen de voorspelde zijwaartse voetplaatsing op basis van de positie en snelheid van het massazwaartepunt en de daadwerkelijke zijwaartse voetplaatsing. De resultaten toonden aan dat mensen met een motorisch incomplete dwarslaesie significant grotere voetplaatsingsfouten vertoonden in vergelijking met de gezonde controlegroep, wat wijst op een verminderd gebruik van de zijwaartse voetplaatsingsstrategie.

Deel II: Motorisch *complete* dwarslaesie

Mensen met een motorisch complete dwarslaesie kunnen niet zelfstandig lopen en zijn afhankelijk van een rolstoel. Een mogelijkheid om toch te kunnen lopen is door gebruik te maken van een exoskelet. Lopen met een exoskelet is echter uitdagend voor mensen met een dwarslaesie vanwege verminderde somatosensorische informatie als gevolg van de laesie. Door het ontbreken van deze essentiële informatie vertrouwen mensen met een dwarslaesie vermoedelijk meer op visuele, vestibulaire en auditieve informatie tijdens lopen met een exoskelet. In **hoofdstuk 5** onderzocht ik daarom wat het effect is van verminderde visuele en/of auditieve informatie op lopen met een exoskelet bij mensen met een motorisch complete dwarslaesie. Lopen met het exoskelet werd geëvalueerd aan de hand van de afstand die werd afgelegd en de hoeveelheid krukbelasting tijdens een 50-seconden looptest (50sWT). De resultaten van de studie toonden aan dat het verminderen van visuele en auditieve informatie slechts minimale invloed had op de afstand die werd afgelegd met het exoskelet. Wel was opvallend dat de hoeveelheid krukbelasting toenam wanneer visuele of auditieve informatie beperkt was.

Wanneer sensorische informatie van een zintuig ontbreekt, kan dit gecompenseerd worden door feedback te geven via een ander zintuig. In **hoofdstuk 6** onderzocht ik het effect van feedback op het lopen en leren lopen met een exoskelet bij mensen met een motorisch complete dwarslaesie. De feedback betrof informatie over de voor- en zijwaartse gewichtsverplaatsing tijdens de dubbele steunfase van het lopen en de initiatie van een stap. De feedback werd geleverd door middel van trillingen op het bovenlichaam. Deelnemers volgden zes sessies, bestaande uit één introductiesessie, gevolgd door vier trainingssessies (twee met en twee zonder feedback), en eindigend met één evaluatiesessie. De trainingssessies waren bedoeld om het effect van de feedback op het leren lopen met het exoskelet te beoordelen door de vooruitgang van de deelnemers te vergelijken tussen sessies mét en zonder feedback. De evaluatiesessie beoordeelde de effectiviteit van de feedback op het lopen met het exoskelet onder verschillende omstandigheden, waaronder normale omstandigheden, alsook situaties waarin het zicht en gehoor beperkt waren. Lopen in het exoskelet werd geëvalueerd aan de hand van de afgelegde afstand tijdens een 50sWT en twee uitkomstmaten gerelateerd aan het traject dat het massazwaartepunt aflegt tijdens de dubbele steunfase van het lopen: de

optimaliteit van het traject en de duur ervan. Daarnaast, werd de gebruikerservaring met de feedback beoordeeld aan de hand van drie vragenlijsten: een visueel analoge schaal bestaande uit vijf items, de Nederlandse versie van de Quebec User Evaluation of Satisfaction with Assistive Technology (D-QUEST) en de Nederlandse System Usability Scale (D-SUS). De resultaten toonden aan dat feedback geen significant effect heeft op het lopen en leren lopen met een exoskelet bij mensen met een motorisch complete dwarslaesie. Deelnemers waren over het algemeen positief over de feedback, vooral wat betreft het gebruik ervan tijdens de trainingsfase.

In **hoofdstuk 7** heb ik een theoretisch kader geïntroduceerd dat het herstel van de loopvaardigheid bij mensen met een dwarslaesie beschrijft. Dit kader belicht de fundamentele elementen die nodig zijn voor een optimale loopvaardigheid, namelijk: onafhankelijk kunnen lopen, een basaal looppatroon en loopaanpassingsvermogen, met daarbij de specifieke determinanten van deze fundamentele elementen.

8

Appendices

Acknowledgments

First, I would like to extend my gratitude to all the study participants who dedicated their time and effort to this research. Your involvement has been essential to the success of this project.

I would like to thank my PhD supervisors and co-supervisor for their guidance, collaboration, and contributions. Your insight and commitment have been fundamental to the development of this research.

I would also like to express my gratitude to the doctoral examination board for their thorough evaluation of my work.

Finally, I would like to thank everyone who offered their assistance, advice, or support along the way. Whether through professional contributions or personal encouragement, your help has been indispensable in completing this PhD.

About the author

Eline Zwijgers was born on September 24, 1995, in Utrecht. Driven by a passion for the intersection of technology and healthcare, she went on to study Technical Medicine at the University of Twente in Enschede, earning her bachelor's degree in 2016.

Between completing her bachelor's and beginning her master's, Eline organized the University of Twente's 2017 introduction program, Kick-In. As publication manager, she played a key role in managing communications and publications, ensuring the successful integration of over 2,000 new students into the university community.

Eline then pursued her master's in Biomedical Engineering at the University of Twente, where her interests shifted toward human-human and human-robot interactions. This interest led her to an internship at Imperial College London, where she worked under the supervision of prof. dr. Etienne Burdet. Her research focused on target estimation in human-robot interaction through sensory augmentation in a dual-wrist robotic interface.

For her master's thesis, Eline returned to the University of Twente to study how partner performance affects arm impedance modulation during haptic human-human interactions. Under the guidance of dr. Edwin van Asseldonk, she explored the nuances of motor control in collaborative settings, deepening her understanding of human adaptability in response to external factors.

In 2019, Eline earned her master's degree and shortly thereafter began her PhD at the Sint Maartenskliniek and the Radboud university medical center in 2020, where she continued to pursue her passion for healthcare and technological innovation.

Currently, Eline is working as a program manager healthcare improvement at NEO Huisartsenzorg, the regional organization for general practitioners in Nijmegen and the surrounding area. In this role, she is engaged in improving the local collaboration between general practitioners and other healthcare providers.

List of publications

Zwijgers E, van Dijsseldonk RB, Vos-van der Hulst M, Hijmans JM, Geurts ACH, Keijsers, NLW. Efficacy of walking adaptability training on walking capacity in ambulatory people with motor incomplete spinal cord injury: a multicenter pragmatic randomized controlled trial. Neurorehabil Neural Repair. 2024;38(6):413-424.

Zwijgers E, Vos-van der Hulst M, van Dijsseldonk RB, Temlali TY, Hijmans JM, van Nes IJW, Geurts ACH, Keijsers, NLW. Conventional locomotor and strength training and walking adaptability training for ambulatory people with motor incomplete spinal cord injury: does intervention sequence matter? *Submitted*

Zwijgers E, van Asseldonk EHF, Vos-van der Hulst M, Geurts ACH, Keijsers NLW. Impaired foot placement strategy during walking in people with incomplete spinal cord injury. J Neuroeng Rehabil. 2022;19:1–9.

Zwijgers E, Nienhuis B, Rijken H, van Nes IJW, Geurts ACH, Keijsers NLW. The effect of limited sensory information on exoskeleton performance in people with complete spinal cord injury. IEEE 2022 International Conference on Rehabilitation Robotics (ICORR). 2022:1–5.

Zwijgers E, Lobo-Prat J, Koomen PPSJ, van Nes IJW, Geurts ACH, Kreamer-Tonin K, Keijsers NLW. Sensory substitution in exoskeletons for people with motor complete spinal cord injury: should we implement vibrotactile feedback? *Submitted*

Portfolio

Donders Graduate School

Courses	Organizer	Year	ECTS
Introduction Day	Radboud university medical center	2020	0.25
Movement Science in Rehabilitation	Radboud University	2020	3
Project Management for PhD Candidates	Radboud University	2020	2
Presentation Skills	Radboud University	2020	1.5
BROK	NFU BROK Academie	2020	1.5
Design & Illustration	Radboud University	2020	1
Graduate School Introduction Day	Donders Graduate School	2020	0.25
Graduate School Day 1 & 2	Donders Graduate School	2020-2021	0.5
Scientific Integrity Course	Donders Graduate School	2021	0.25
Analytic Storytelling	Radboud University	2021	1
Summer School on Wearable Robotics	COST Action CA16116	2021	1.25
Statistics for PhD's by using SPSS	Radboud University	2021	2
Science Journalism and Communication	Radboud University	2022	3
Writing Scientific Articles	Radboud University	2022	3

Lectures, webinars, workshops, other		Organizer	Year	ECTS
Webinar	Mental health and wellbeing during Covid-19	RIHS	2021	0.1
Workshop	How to write a rebuttal	RIHS	2021	0.1
Webinar	Realizing the benefits of haptic technology for medical wearables	Elitac Wearables	2021	0.1

Webinar	Electronics X textiles: Selecting the optimal integration technique for your wearable	Elitac Wearables	2021	0.1
Webinar	Wearable Robotics - Educational wearable robotics - Occupational exoskeletons - Medical systems - Standardization & benchmarking	Eurobench and COST Action	2021	0.25
Lecture	Decision-making strategies	Donders	2021	0.1
Webinar	Medical Device Regulation (MDR)	VR4Rehab	2022	0.1
Lecture	Micro-experiments at the muZIEum	Donders	2022	0.1
Lecture	The mystery of walking	ICMS	2022	0.1
Lecture	Rehabilitation of spinal cord injury, now and in the future	ICMS	2022	0.1
Webinar	Electrodes for wearables	Elitac Wearables	2022	0.1
Workshop	Communication - writing for scientists and talking to the media	The Online Scientist	2022	0.25
Workshop*	Data visualization	Sint Maartenskliniek	2022	0.1
Workshop	Presenting for PhD students	Spies & Spreken	2023	0.25
Meeting	Research meeting	Radboud university medical center	2020-2022	0.5
Workshop*	Meet the PhD	Sint Maartenskliniek	2021-2023	0.4
Meeting	Research lunch and lab lunch	Sint Maartenskliniek	2020-2024	2

Meeting	Research Content Meeting (ReCoMe)	Sint Maartenskliniek	2020-2024	2
Meeting	Balance & control meeting	Sint Maartenskliniek, University of Twente	2021-2024	2
Meeting	Wearable Robotics monthly meeting	Wearable Robotics	2020-2024	2
Demonstration*	Vibrotactile feedback in exoskeletons	Verder in Beweging congres	2022	0.1

* presenter

Conferences	Role	Location	Year	ECTS
The 60th International Spinal Cord Society (ISCoS) annual scientific meeting	Poster presentation	Online	2021	1
Dutch Congress of Rehabilitation Medicine (DCRM)	Invited lecture	Online	2021	0.1
International Society of Posture & Gait Research (ISPGR) world congress	Poster presentation	Montreal, Canada	2022	1.5
RehabWeek- International Conference on Rehabilitation Robotics (ICORR)	Poster presentation and workshop speaker	Rotterdam, The Netherlands	2022	1.5
Society for Movement Analysis Laboratories in the Lower Lands (SMALLL) congress	Poster presentation	Hasselt, Belgium	2022	0.5

The Interdisciplinary Consortium for clinical Movement Sciences & technology (ICMS) annual event	Poster presentation	Nijmegen, The Netherlands	2022	0.25
The 4th International Congress on Neurorehabilitation and Neural Repair (NNR)	Oral presentation	Maastricht, The Netherlands	2023	0.5
International Society of Posture & Gait Research (ISPGR) world congress	Poster presentation	Online	2023	1.5
The 62nd International Spinal Cord Society (ISCoS) annual scientific meeting	Oral presentation and workshop speaker	Edinburgh, Scotland	2023	1
Society for Movement Analysis Laboratories in the Lower Lands (SMALLL) congress	Workshop speaker and organizing committee member	Nijmegen, The Netherlands	2023	0.5
The Interdisciplinary Consortium for clinical Movement Sciences & technology (ICMS) annual event	Poster presentation - best poster award (2023)	Nijmegen, The Netherlands	2023	0.25

Symposiums	Location	Year	ECTS
Wearable Robotics symposium	Soesterberg (NL)	2019	2
	Online	2020	
	Zeist (NL)	2021	
	Nijmegen (NL)	2022	
International Society of Posture & Gait Research (ISPGR) symposium	Online	2020	0.25
	Online	2021	
The Interdisciplinary Consortium for clinical Movement Sciences & technology (ICMS) symposium	Online	2021	0.1

NL = The Netherlands

Project supervision	Year	Duration
Master student Medicine - University of Groningen	2020	3 months
Master student Biomedical Engineering - University of Twente	2022	3 months

Research data management

Ethics and privacy

This thesis is based on the results of medical-scientific research with human participants. The studies were subject to the Medical Research Involving Human Subjects Act (WMO) and were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). The medical ethical review committee 'METC Oost-Nederland' has given approval to conduct these studies (chapter 2, 3, 4: NL69379.091.19; chapter 5: NL74476.091.20; chapter 6: NL82999.091.22). Informed consent was obtained from participants for the collection, processing, and subsequent sharing of their data after the research. The privacy of the participants was warranted by the use of pseudonymization.

Data collection and storage

Data for chapters 2 and 3 were collected through electronic Case Report Forms (eCRF) using Castor EDC (Castor, Amsterdam, the Netherlands). Subsequently, this data was transferred from Castor EDC to SPSS (SPSS Inc., Chicago, Illinois, USA). Chapter 4 data were collected through D-Flow (Motek Medical B.V., Houten, the Netherlands) and Vicon (Vicon Motion Systems Ltd., Oxford, UK), then transferred to Matlab (MathWorks, Natick, Massachusetts, USA), and subsequently to SPSS. Chapters 5 and 6 data were acquired through sensors and eCRF using Castor EDC, and subsequently transferred to Matlab. Pseudonymized data were stored and analyzed on the department server and in Castor EDC, accessible only to project members working at the Sint Maartenskliniek. These secure storage options ensure the availability, integrity, and confidentiality of the data. Paper (hard copy) data are stored in cabinets within the department.

Data sharing

The datasets suitable for reuse are published in the Radboud Data Repository (DOI; chapter 2: 10.34973/7px6-0q75; chapter 4: 10.34973/833x-qa11; chapter 5: 10.34973/jfg3-ew50). Data were made reusable by adding sufficient documentation, by using preferred and sustainable data formats and by publishing under the RUMC-RA-DUA-1.0 license. Requests for access will be checked by a data access committee formed by the department. The data not suitable for reuse will be archived for 15 years after termination of the study.

Donders Graduate School for Cognitive Neuroscience

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

Thesis Sint Maartenskliniek

Ensink, C. (2025) Sensing the path to mobility- advancing gait rehabilitation with sensor technology. Radboud University Nijmegen, Nijmegen. The Netherlands.

Boekesteijn, R. (2024) Evaluating walking in lower-extremity osteoarthritis: Beyond the lab, towards the real world. Radboud University Nijmegen, Nijmegen. The Netherlands.

Den Broeder, N. (2024) More than tapering, less than full dose- Efficient use of biologics in the treatment of rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Kuijpers, R. (2024) Adapt your step: Clinical assessment and training of walking adaptability in children with mild motor disorders. Radboud University Nijmegen, Nijmegen. The Netherlands.

Te Molder, M. (2024) The unhappy patient after TKA. A paradigm shift in assessing outcome. Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Hal, T. (2024) A rheumatologist undercover: research of psoriatic arthritis at the dermatology clinic. Radboud University Nijmegen, Nijmegen. The Netherlands.

Veenstra, F. (2024). About gout. Studying potential targets for improvement of care. Radboud University Nijmegen, Nijmegen. The Netherlands.

De Jong, L.A.F. (2023). Effects of lower limb orthotic devices in people with neurological disorders. Radboud University Nijmegen, Nijmegen. The Netherlands.

Michielsens, C. (2023). Tapering strategies of biologics in inflammatory disorders. Radboud University Nijmegen, Nijmegen. The Netherlands.

Pouls, B. (2023). Supporting patients'medication management using eHealth. Test cases in rheumatology. Radboud University Nijmegen, Nijmegen. The Netherlands.

Stöcker, J. (2023). Accessible and effective non-pharmacological care for persons with systemic sclerosis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Mulder, M. (2022). Going off-road. Exploring and mapping psoriatic arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Huiskes, V. (2022). The synergistic role of patients and healthcare providers in reducing drugrelated problems. Radboud University Nijmegen, Nijmegen. The Netherlands.

Marsman, D. (2022). Polymyalgia rheumatica. Clinical characteristics and new treatment opportunities. Radboud University Nijmegen, Nijmegen. The Netherlands.

Alingh, J. (2021). Effect of robotic gait training on the post-stroke gait pattern. Evaluation of LOPES II. Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Dijsseldonk, R. (2021). Step into the future: mobility after spinal cord injury. Radboud University Nijmegen, Nijmegen, The Netherlands.

Pelle, T. (2021). Beating osteoarthritis by e-self management in knee or hip osteoarthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Heuckelum, M (2020). Novel approaches to improve medication adherence in rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Mathijssen, E. (2020). The voice of patients with rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Bakker, S. (2019). Regional anesthesia and total knee arthroplasty. Anesthetic and pharmacological considerations. Radboud University Nijmegen, Nijmegen. The Netherlands.

Claassen, A. (2019). Strategies for patient education in rheumatic diseases. Radboud University Nijmegen, Nijmegen. The Netherlands.

Fenten, M. (2019). Optimizing locoregional anesthesia in fast track orthopaedic surgery. Radboud University Nijmegen, Nijmegen. The Netherlands.

Minten, M. (2019). On the role of inflammation and the value of low dose radiation therapy in osteoarthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Verhoef, L. (2019). Effective and efficient use of bDMARDs in rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Bekker, C. (2018). Sustainable use of medication. Medication waste and feasibility of redispensing. Utrecht University, Utrecht. The Netherlands.

Bikker, I.(2018). Organizing timely treatment in multi-disciplinary care. University of Twente, The Netherlands.

Bouman, C. (2018). Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors. Radboud University Nijmegen, The Netherlands.

Mahler, E. (2018). Contributors to the management of osteoarthritis. Utrecht University, The Netherlands.

Tweehuysen, L. (2018). Optimising biological treatment in inflammatory rheumatic diseases. Predicting, tapering and transitioning. Radboud University Nijmegen, Nijmegen, The Netherlands.

Geerdink, Y. (2017). Getting a grip on hand use in unilateral cerebral palsy. Radboud University, Nijmegen, The Netherlands.

Remijn, L. (2017). Mastication in children with cerebral palsy. Radboud University, Nijmegen, The Netherlands.

Selten, E. (2017). Beliefs underlying treatment choices in osteoarthritis. Radboud University, Nijmegen, The Netherlands.

Van Hooff, M. (2017). Towards a paradigm shift in chronic low back pain? Identification of patient profiles to guide treatment. VU University Amsterdam, Amsterdam, The Netherlands.

Lesuis, N. (2016). Quality of care in rheumatology. Translating evidence into practice. Radboud University, Nijmegen, The Netherlands.

Luites, J. (2016). Innovations in femoral tunnel positioning for anatomical ACL reconstruction. Radboud University, Nijmegen, The Netherlands.

Pakvis, D. (2016). Survival, primary stability and bone remodeling assessment of cementless sockets. An appraisal of Wolff's law in the acetabulum. Radboud University, Nijmegen, The Netherlands.

Schoenmakers, K. (2016). Prolongation of regional anesthesia. Determinants of peripheral nerve block duration. Radboud University, Nijmegen, The Netherlands.

Altmann, V. (2015). Impact of trunk impairment on activity limitation with a focus on wheelchair rugby. Leuven University, Leuven, Belgium.

Bevers, K. (2015). Pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis. Utrecht University, Utrecht, The Netherlands.

Cuperus, N. (2015). Strategies to improve non-pharmacological care in generalized osteoarthritis. Radboud University, Nijmegen, The Netherlands.

Kilkens, A. (2015). De ontwikkeling en evaluatie van het Communicatie Assessment & Interventie Systeem (CAIS) voor het aanleren van (proto-)imperatief gedrag aan kinderen met complexe ontwikkelingsproblemen. Radboud University, Nijmegen, The Netherlands.

Penning, L. (2015). The effectiveness of injections in cuffdisorders and improvement of diagnostics. Maastricht University, Maastricht, The Netherlands.

Stegeman, M. (2015). Fusion of the tarsal joints: outcome, diagnostics and management of patient expectations. Utrecht University, Utrecht, The Netherlands.

Van Herwaarden, N. (2015). Individualised biological treatment in rheumatoid arthritis. Utrecht University, Utrecht, The Netherlands.

Wiegant, K. (2015). Uitstel kunstknie door kniedistractie. Utrecht University, Utrecht, The Netherlands.

Willems, L. (2015). Non-pharmacological care for patients with systemic sclerosis. Radboud University, Nijmegen, The Netherlands.

Witteveen, A. (2015). The conservative treatment of ankle osteoarthritis. University of Amsterdam, Amsterdam, The Netherlands.

Zwikker, H. (2015). All about beliefs. Exploring and intervening on beliefs about medication to improve adherence in patients with rheumatoid arthritis. Radboud University, Nijmegen, The Netherlands.

Koenraadt, K. (2014). Shedding light on cortical control of movement. Radboud University, Nijmegen, The Netherlands.

Smink, A. (2014). Beating Osteoarthritis. Implementation of a stepped care strategy to manage hip or knee osteoarthritis in clinical practice. VU University Amsterdam, Amsterdam, The Netherlands.

Stolwijk, N. (2014). Feet 4 feet. Plantar pressure and kinematics of the healthy and painful foot. Radboud University, Nijmegen, The Netherlands.

Van Kessel, M. (2014). Nothing left? How to keep on the right track. Spatial and non-spatial attention processes in neglect after stroke. Radboud University, Nijmegen, The Netherlands.

Brinkman, M. (2013). Fixation stability and new surgical concepts of osteotomies around the knee. Utrecht University, Utrecht, The Netherlands.

Kwakkenbos, L. (2013). Psychological well-being in systemic sclerosis: Moving forward in assessment and treatment. Radboud University, Nijmegen, The Netherlands.

Severens, M. (2013). Towards clinical BCI applications: assistive technology and gait rehabilitation. Radboud University, Nijmegen, The Netherlands.

Stukstette, M. (2013). Understanding and treating hand osteoarthritis: a challenge. Utrecht University, Utrecht, The Netherlands.

Van der Maas, A. (2013). Dose reduction of TNF blockers in Rheumatoid Arthritis: clinical and pharmacological aspects. Radboud University, Nijmegen, The Netherlands.

Zedlitz, A. (2013). Brittle brain power. Post-stroke fatigue, explorations into assessment and treatment. Radboud University, Nijmegen, The Netherlands.

Beijer, L. (2012). E-learning based speech therapy (EST). Exploring the potentials of E-health for dysarthric speakers. Radboud University, Nijmegen, The Netherlands.

Hoogeboom, T. (2012). Tailoring conservative care in osteoarthritis. Maastricht University, Maastricht, The Netherlands.

Boelen, D. (2011). Order out of chaos? Assessment and treatment of executive disorders in braininjured patients. Radboud University, Nijmegen, The Netherlands.

Heesterbeek, P. (2011). Mind the gaps! Clinical and technical aspects of PCL-retaining total knee replacement with the balanced gap technique. Radboud University, Nijmegen,The Netherlands.

Hegeman, J. (2011). Fall risk and medication. New methods for the assessment of risk factors in commonly used medicines. Radboud University, Nijmegen, The Netherlands.

Smulders, E. (2011). Falls in rheumatic diseases. Risk factors and preventive strategies in osteoporosis and rheumatoid arthritis. Radboud University, Nijmegen, The Netherlands.

Snijders, G. (2011). Improving conservative treatment of knee and hip osteoarthritis. Radboud University, Nijmegen, The Netherlands.

Vriezekolk, J. (2011). Targeting distress in rheumatic diseases. Utrecht University, Utrecht, The Netherlands.

Willems, P. (2011). Decision making in surgical treatment of chronic low back pain. The performance of prognostic tests to select patients for lumbar spinal fusion. Maastricht University, Maastricht, The Netherlands.

Aarts, P. (2010). Modified constraint-induced movement therapy for children with unilateral spastic cerebral palsy: the Pirate group intervention. Radboud University, Nijmegen, The Netherlands.

Groen, B. (2010). Martial arts techniques to reduce fall severity. Radboud University, Nijmegen, The Netherlands.

Van Koulil, S. (2010). Tailored cognitive behavioral therapy in fibromyalgia. Radboud University, Nijmegen, The Netherlands.

Van den Bemt, B. (2009). Optimizing pharmacotherapy in patients with rheumatoid arthritis: an individualized approach. Radboud University, Nijmegen, The Netherlands.

Van Nes, I. (2009). Balance recovery after supratentorial stroke. Influence of hemineglect and the effects of somatosensory stimulation. Radboud University, Nijmegen, The Netherlands.

Ruiter, M. (2008). Speaking in ellipses. The effect of a compensatory style of speech on functional communication in chronic agrammatism. Radboud University, Nijmegen, The Netherlands.

Baken, B. (2007). Reflexion on reflexes. Modulation during gait. Radboud University, Nijmegen, The Netherlands.

Gaasbeek, R. (2007). High tibial osteotomy. Treatment of varus osteoarthritis of the knee. Radboud University, Nijmegen, The Netherlands.

Koëter, S. (2007). Patellar instability. Diagnosis and treatment. Radboud University, Nijmegen, The Netherlands.

Langeloo, D. (2007). Monitoring the spinal cord during corrective spinal surgery: a clinical study of TES-MEP. Radboud University, Nijmegen, The Netherlands.

De Haart, M. (2005). Recovery of standing balance in patients with a supratentorial stroke. Radboud University, Nijmegen, The Netherlands.

Den Otter, R. (2005). The control of gait after stroke: an electromyographic approach to functional recovery. Groningen University, Groningen, The Netherlands.

Spruit, M. (2005). Surgical treatment of degenerative disc conditions of the lumbar spine. Biomechanical, clinical and radiological aspects. University Utrecht, Utrecht, The Netherlands.

Weerdesteyn, V. (2005). From the mechanisms of obstacle avoidance towards the prevention of falls. Radboud University, Nijmegen, The Netherlands.

Jongerius, P. (2004). Botulinum toxin type-A to treat drooling. A study in children with cerebral palsy. Radboud University, Nijmegen, The Netherlands.

Van de Crommert, H. (2004). Sensory control of gait and its relation to locomotion after a spinal cord injury. Radboud University, Nijmegen, The Netherlands.

Van der Linde, H. (2004). Prosthetic prescription in lower limb amputation. Development of a clinical guideline in the Netherlands. Groningen University, Groningen, The Netherlands.

Hendricks, H. (2003). Motor evoked potentials in predicting motor and functional outcome after stroke. University of Nijmegen, Nijmegen, The Netherlands.

Hosman, A. J. F. (2003). Idiopathic thoracic spinal deformities and compensatory mechanisms. University of Nijmegen, Nijmegen, The Netherlands.

Donker, S. (2002). Flexibility of human walking: a study on interlimb coordination. Groningen University, Groningen, The Netherlands.

Hochstenbach, J. (1999). The cognitive, emotional, and behavioural consequences of stroke. University of Nijmegen, The Netherlands.

De Kleuver, M. (1998). Triple osteotomy of the pelvis. An anatomical, biomechanical and clinical study. University of Nijmegen, Nijmegen, The Netherlands.

Van Balen, H. (1997). A disability-oriented approach to long-term sequelae following traumatic brain injury. Neuropsychological assessment for post-acute rehabilitation. University of Nijmegen, Nijmegen, The Netherlands.

Tromp, E. (1995). Neglect in action: a neuropsychological exploration of some behavioural aspects of neglect. University of Nijmegen, Nijmegen, The Netherlands.

Van Lankveld, W. (1993). Coping with chronic stressors of rheumatoid arthritis. University of Nijmegen, Nijmegen, The Netherlands.

Geurts, A. (1992). Central adaptation of postural organization to peripheral sensorimotor impairments. University of Nijmegen, Nijmegen, The Netherlands.

De Rooij, D. (1988). Clinical and serological studies in the connective tissue diseases. University of Nijmegen, Nijmegen, The Netherlands.