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DYNAMICS OF LOWER LIMB & STANDING BALANCE RECOVERY EARLY POST-STROKE – MEASUREMENT, MECHANISMS AND TREATMENT

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GLOSSARY OF TERMS

Activity: An ICF level containing the ability to execute a functional task or action by an individual.[1] Hence, activities encompass goal-directed movement behavior. Difficulties performing activities are called disabilities.

Balance: The act of maintaining, achieving, or restoring a state of balance during any posture.[2] Following this definition, balance has two meanings - the *state* of being in balance and the *actions* that preserve this state. In this thesis, if not explicitly stated otherwise, we use the term balance to describe the control actions.

Behavioral restitution: A return toward more normal patterns of motor control with the impaired effector. Restitution reflects the process of "true (neurological) recovery".[3]

Body functions: Physiological functions of body systems.[1] Problems in body functions, such as a significant deviation or complete loss, are called impairments.

Center of pressure (COP): The point on the base of support at which the ground reaction forces can be considered to act. Displacement of the COP can be used as a biomechanical measure of stabilizing postural reactions exerted through the lower limbs.[4]

Center of mass (COM): The point in space at which the mass of the body can be considered to be located for the purpose of analyzing the forces acting on the body.[4]

(Behavioral) compensation: The ability to accomplish a goal through substitution with a new approach rather than using their normal, pre-stroke behavioral repertoire. In the motor domain, compensation strategies employ the use of intact muscles, joints, and effectors to accomplish the desired functional task.[3]

Diaschisis: A phenomenon of a temporally downsizing of activity in remote, yet functionally connected brain tissue that is widespread over the entire brain, elsewhere referred to as cerebral "shock".[5]

Force plate: An instrumented platform, on which the subject stands, that is commonly used to characterize balance by measuring changes in the center of pressure (COP) of the ground reaction forces acting on the feet.[4]

Functional task: A functional task requires the assembly of rudimentary motor execution abilities into goal-directed movements. These tasks can be accomplished either through behavioral restitution or compensation, or a combination of both. Thus, functional tasks are defined at the ICF level of activities.[6]

Hemiplegia and hemiparesis: Loss of strength in the arm, leg, and sometimes face on one side of the body. Hemiplegia refers to a complete loss of strength, whereas hemiparesis refers to an incomplete loss of strength.[1]

International Classification of Functioning (ICF): Multipurpose classification that provides a standard language and framework for categorizing health and health-related conditions.[1]

Inverted pendulum: A biomechanical model of the body in which the mass of the body is considered to be situated at the upper end of a rigid bar that pivots about a single joint at the base, i.e., the ankles.[4]

Kinetics and kinematics: Kinetics deals with action of forces and torques in producing or changing the motion of an object. On the other hand, kinematics deals with motion without reference to the forces causing that motion. This is the displacement and velocity of our bodies' segments and joints.

Lower limb: The part of the body from the hip to the toes. The lower limb (or extremity) includes the hip, knee, and ankle joints; and the bones of the thigh, shank, and foot; and the muscles and ligaments spanning over these joints.

Motor control: An area of physics exploring laws of nature defining how the nervous system interacts with other body parts and the environment to produce purposeful, coordinated actions.[7] More specifically, "good" motor control leads to the proper execution of a movement with a particular effector in a specific task context.[6]

Penumbra: The area that is adjacent to the infarct and contains partial blood flow. Some neurons will survive in this area.[8]

Phases of recovery: A framework of five epochs based on the biology of recovery: Hyper-acute: 0-24 hours post-stroke, acute: 1-7 days, early subacute: 7 days – 3 months, late subacute: 3-6 months, and the chronic phase: > 6 months post-stroke.[3]

Plasticity: The sum of molecular, physiological, and structural changes that alter motor output for a given sensory input.[9] Importantly, plasticity can be triggered by a stroke in the absence of training to mediate spontaneous neurological improvements.

Pressure plate: Originally designed for plantar-pressure distribution measures (i.e., baropodometry), a pressure plate or mat can also measure COP excursions using pressure sensors and only the vertical forces under the foot. In contrast to traditional force plates, a pressure plate has the advantage of being lightweight, usually more affordable, and easily transportable.[10]

Quiet standing: A posture defined as standing upright on both feet without any large external or internal (i.e., willed movement) perturbation. Maintaining quiet standing requires steady-state balance.

Recovery: An improvement in any domain of the ICF can be viewed as a sign of ongoing recovery.[3] This definition differs from other scientific work where the term recovery is exclusively used to describe impairment reductions or "true recovery" at the ICF level of body functions.

(Neuro)Rehabilitation: Defined following the WHO as a set of measures that assist individuals, who experience or are likely to experience disability, to achieve and maintain optimal functioning in interaction with their environments.

Quality of Movement (QoM): Operationally defined through a direct comparison of a patient's motor execution of a functional task or action with a reference population of non-disabled, age-matched control subjects. The closer the movement matches those seen in controls, the "better" the QoM.[3]

Reliability: The degree to which the measurement (regarding a specific instrument or metric) is free from measurement error.[11] In this thesis, we specifically refer to test-retest reliability, defined as the extent to which trial repetitions obtained for the same subjects and under the same conditions yield the same scores.[11]

Sensitive period: A time-limited plasticity environment defined by unique genetic, molecular, physiological, and structural events, that mediate spontaneous neurobiological recovery and falls off as a function of time and distance from the infarct.[9]

Steady-state balance: The ability to control the center of mass relative to the base of support in fairly predictable and nonchanging conditions, such as quiet standing.[12] Steady-state balance is distinguished from anticipatory or reactive balance control that aim to restore a balance state, respectively, in advance of willed movement or after unexpected perturbations.

Strength: The ability to produce maximum voluntary force or torque through muscle contractions acting around a single joint.

Stroke: Rapidly developed clinical sign of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than of vascular origin.[13]

(Muscle) Synergies: Although different definitions and constructs of muscle synergies exist in the literature,[14] in this thesis the term synergies is used to describe the clinical phenomenon of "pathological (or abnormal) intralimb synergies" meaning the loss of independent joint control leading to the emergence of stereotypical flexor and extensor movements in the hemiplegic limb(s) after stroke.[15]

Spontaneous neurobiological recovery: Rapid recovery of body functions in the first weeks to months after stroke onset due to changes (i.e., repair) in the brain.[16]

Validity: The degree to which an instrument measurement truly reflects the construct(s) it purports to measure. More specifically, criterion validity is defined as the degree to which the scores of a novel alternate instrument are an adequate reflection of a "gold standard".[11]

Wearable exoskeleton: A standalone, wearable robotic device with programable controls, that actuates movement of at least one joint either unilaterally or bilaterally for overground standing and walking practice.[17]

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CHAPTER 1

1

GENERAL INTRODUCTION

(Technical terms are underlined upon first appearance and explained in the glossary.)

Maybe you are standing right now while holding and reading this book. While making this very sentence up, I was walking along a thicket footpath on my way to our offices, not paying much attention to where I placed my feet. Hence, controlling balance to stay upright and walk happens in the background during almost all activities we perform in daily life. However, compelling biomechanical and neurophysiological evidence gathered over half a century illustrate the complexity of human balance control.[1-4] What seems effortless, belies sophisticated control mechanisms that are continuously exerted and tuned to ever-changing task and environmental demands.

Although it remains unknown to what extent specific brain regions contribute to balance control during functional tasks, it is well established that a broad neural network preserves our upright position. This includes the most advanced region of the neural hierarchy – the cerebral cortex – as evident by broad cortical activation responses to induced balance perturbations,[5,6] or even during transient moments of instability that occur naturally when quiet standing.[7] This becomes apparent in those with cortical damage such as stroke, leaving patients vulnerable to falls.[8-10] This has a major impact on performing daily activities and participation.

People living with the long-term consequences of a stroke recently ranked difficulties in maintaining balance and performing walking as the top-prioritized research area for improving their quality of life.[11] In line with this request, the overarching aim of this thesis is to advance our understanding of adaptive balance control strategies and their time courses early post-stroke. The expectation is that this knowledge will contribute to more effective neurorehabilitation strategies to enhance recovery and enable autonomous and qualitative living after hospital discharge.

Defining stroke

The World Health Organization (WHO) defines stroke as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than of vascular origin".[12] Each year, approximately 1.5 million people in Europe suffer a stroke, of whom around 75% survive.[13,14] As a result, the prevalence of people in Europe living with the long-term consequences of a stroke is estimated to be 9 million, making stroke one of the main causes of acquired disability in adults. Stroke incidence is estimated to further increase due to demographic changes[13] and increasing prevalence of metabolic[15] and environmental risk factors, such as air pollution.[14]

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It is apparent that prevention measures (i.e., identification and lowering of underlying risk factors) and acute care are crucial to reduce the number of cases and to detect and treat a stroke as soon as possible. However, at the same time, investing in neurorehabilitation is important to enhance post-stroke recovery. This is important for patients and their surroundings, and society. In 2010, the health care costs of stroke were estimated to be €42 billion in Europe.[16] However, this number does not reflect indirect costs arising, for example, from unemployment and (in)formal caregiving, which can account for up to 32% of the total costs resulting from a stroke.[17] Hence, reducing disability in cases that could not be prevented is important to lower the strain on health and societal care.

Physiology of stroke-related damage and repair

Stroke can be caused by either an intracerebral hemorrhage or ischemia.[18] A cerebral hemorrhagic stroke occurs when a blood vessel bursts within the brain, causing localized bleeding in the surrounding tissue. An ischemic stroke is caused by a blood clot that blocks blood flow in an artery supplying brain tissue.[18] Although different in their etiology, both stroke types lead to hypoperfusion, which hampers brain tissue from getting oxygen and nutrients. Depending on the severity and duration of this state, a stroke can lead to irreversible damage. The experimental work presented in this thesis includes cohorts of patients who either suffered a hemorrhage or ischemia. Where appropriate, we controlled for potential discrepancies in recovery between etiologies.

At-risk tissue surrounding the damaged core (i.e., ischemic penumbra) is dysfunctional due to hypoperfusion. To prevent these cells from dying and to reverse temporal dysfunction, reperfusion is required within hours post-stroke.[19] This enables penumbral tissue to recover and functionally suppressed remote areas due to diaschisis[20] (elsewhere referred to as “shock of the nervous system”) to reactivate. A cascade of cellular and molecular actions is set into motion aimed at neuroprotection and angiogenesis (i.e., new blood vessel formation) to enhance reperfusion-driven repair.[21] Hence, these mechanisms restore temporally dysfunctional neural networks to their original state – a process called neuronal restitution – and are thought to be mostly responsible for spontaneous neurological recovery in the initial weeks after stroke onset.[22]

A sensitive period for post-stroke rehabilitation

Beyond the regenerative processes, this cascade also enables a “neuroplastic milieu”, as gene expression and proteins that are important for neuronal growth, synaptogenesis, and axonal sprouting appear enhanced early after stroke onset.[21,23] Much like sensitive periods in the developing brain, neural networks appear particularly adaptive to functionally re-organize in the first days to weeks after acquired damage.[23-25] This may further augment neuronal restitution as well as neuronal substitution, which means the formation and strengthening of alternate pathways in intact brain tissue.[26] The latter is thought to require learning-dependent plasticity.

Due to the optimal conditions of neuroplasticity, this period is seen as an ideal time to intervene with neurorehabilitation, as supported by several animal stroke models.[25,27] For example, rodents with subtotal motor infarction fully recovered their prehension ability if reaching exercises were delivered prior to 7 days post-stroke.[28,29] The same intervention delivered at later time points was ineffective,[28,29] even if its intensity was greatly increased.[30] The claim is that motor training directs the formation of new neural connections important for recovery, which becomes impossible as soon as this time-restricted plasticity window shuts. That the same principle applies to clinical stroke care has been suggested by observation,[31,32] whereas randomized controlled trials (RCTs) that put this assumption to the test by delivering standardized rehabilitation protocols at different, biologically informed timings are lacking. This literature gap was the starting point of this thesis.

Defining post-stroke recovery

Before advancing, it is important to clarify what recovery means. Recovery is defined as “any improvement on the different levels of the International Classification of Functioning (ICF)”.[33] Hence, recovery is an ambiguous term by definition. Therefore, the use of the ICF – a framework that distinguishes stroke-related consequences according to three different interrelated levels: body functions and structures, activities, and participation – is advised to specify the aspect of recovery that is addressed in each case. The ICF level of body functions is directly related to primary neurological impairments such as loss of, or deviation in, strength, sensation and cognition. The activity domain refers to disabilities in performing basic daily life activities, such as maintaining a standing posture or walking. These skills are required for safe and efficient participation in the household and community (Figure 1).

Recovery from motor impairments at the ICF level of body functions

At the level of body functions, the initial flaccidity or loss of any motor function at the contra-lesional body side (i.e., hemiplegia) often resolves within days to weeks after stroke. In most cases, this results in a return of willed movement with remaining strength deficits (i.e., hemiparesis). In his classic 1951 paper "The restoration of movement following hemiplegia in man",[34] Thomas E. Twitchell meticulously described the transition from hemiplegia to hemiparesis and identified a sequence of recovery stages. Signe Brunnström further distinguished these stages in the sixties.[35] Basically, flaccidity is followed by willed movement with increased co-articulation in the affected limbs. Therefore, strength re-emerges in so-called flexor and extensor synergies, characterized by involuntary co-activation. Patients then gradually improve by dissociating movement from these "abnormal" muscle synergies, which eventually results in selective joint control if all recovery stages are completed.[34]

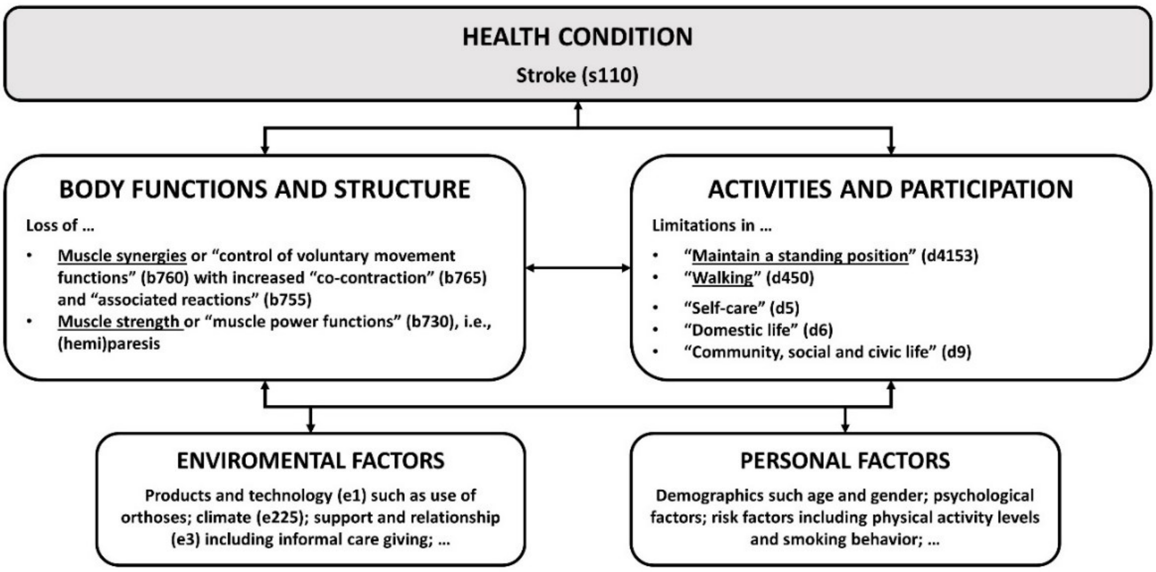

Figure 1. Overview of the impairments and activity limitations regarding the lower limb post-stroke, categorized according to the International Classification of Functioning, Disability and Health (ICF) framework. Only items that will be actively investigated in this thesis are shown. The items underlined are particularly emphasized in the following chapters. The codes provided in parentheses are ICF codes with b, body function; d, activity and participation; and e, environmental factors.

Building on Brunnström's work, Axel R. Fugl-Meyer developed a clinical tool to measure the progress through synergy-dependent recovery stages.[36] By applying the Fugl-Meyer Lower Extremity motor scores (FM-LE) serially in time, large cohort studies[37,38] demonstrated rapid improvements in muscle synergies over the first 5 to 8 weeks post-stroke. Thereafter, recovery tends to level off. Muscle strength, assessed by applying resistance to single-joint movement, follows a similar time-dependent course[38,39] and appears equally distributed over the hip, knee, and ankle joints.[40]

More recently, prospective cohort studies have found that the extent of FM-LE recovery at 3 to 6 months post-stroke is predictable and proportional to a patient's baseline severity.[41,42] At the same time, a subgroup of patients with severe impairments (~10%) failed to show any motor improvement in the flaccid lower limb.[42] These so-called non-recoverers are also less likely to show upper limb recovery[42] or improvement in other modalities such as visuospatial neglect[43] and somatosensation,[44] suggesting common biological mechanisms.

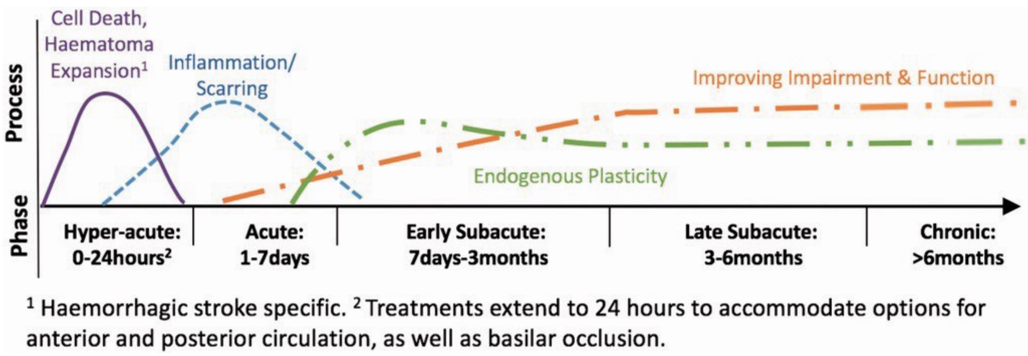

Figure 2. Definitions of critical time-points post-stroke that link to the currently known biology of recovery. Figure from Bernhardt et al., 2017.

Because the mechanisms of neuronal restitution remain poorly understood, they can be conceptualized as <u>spontaneous neurobiological recovery</u> reflected by the progress of time after stroke onset.[38] This emphasizes the importance of applying repeated measurements at fixed times post-stroke to properly report the progress of recovery. For this purpose, critical timepoints were defined,[45,46] separated by five <u>phases of recovery</u>: the hyper-acute (first 24 h post-stroke), acute (1 to 7 days), early subacute (7 days to 3 months), late subacute (3 to 6 months), and chronic phase (> 6 months) (Figure 2).

Recovery of balance and mobility at the ICF level of activities

At the ICF level of activities, walking has been the primary investigated task for describing recovery courses. Approximately 65 to 85% of stroke survivors eventually regain walking independence within 3 to 6 months post-stroke.[47-51] Furthermore, the Copenhagen Stroke Study[47] – the largest epidemiological recovery study in this field – showed in about 1,200 acute cases that walking independence returns mainly within the first 5 weeks, and up until 11 weeks post-stroke in those with more severe impairments.

Standing balance yields a similar time course, e.g., scores on the Berg Balance Scale (BBS) are maximal by 3 months post-stroke.[52] These balance improvements precede, and are conditional for, achieving walking independence.[50] This corresponds to a number of prognostic studies[53-55] showing that early reacquisition of sitting and standing balance, approximately within the first 4 weeks post-stroke, is strongly associated with patients' ability to walk and perform daily life activities at 6 months post-stroke.

While it seems reasonable that recovery in activities in the chronic stage depends entirely on learning to use compensation strategies, early skill reacquisition during the window of spontaneous neurobiological recovery is more ambiguous. Unfortunately, recovery studies have largely failed to show *how* patients improved their balance and walking by being restricted to clinical outcomes that rate a task merely by its goal (e.g., can a patient walk 10 m?). This becomes apparent in those "well-recovered" patients with near-normal BBS scores or walking speeds, as they may exhibit significant reliance on using the non-hemiplegic leg for controlling balance[56,57] or body propulsion to increase their walking speeds.[58] Clinical scales, although often psychometrically sound, have the major drawback of being confounded by <u>compensation</u>.

Behavioral restitution vs. compensation

To achieve a greater understanding of the mechanisms underlying skill reacquisition after stroke, it is necessary to use sensitive measurements that can adequately delineate <u>behavioral restitution</u> from the use of compensation strategies.[24,33,59] The former reflects on the process of returning toward more *normal* patterns of movement execution with the impaired effector, as seen in age-matched healthy controls.[33] Compensation, on the other hand, describes *new* approaches to accomplish a task through substitution, by employing the use of an alternate effector or using intact muscles and joints within the impaired effector in alternate patterns.[45]

In the above example, it becomes apparent that even patients who do show spontaneous impairments reductions to regain (some) motor control over the hemiplegic leg may utilize a substitution strategy as the less-affected side appears to “take over” the control of balance or gait. Thus, compensation strategies while performing tasks may be more or less obvious and difficult to measure in the absence of kinetic or kinematic movement quantification.

Measuring quality of movement (QoM)

The dichotomy between the extent of behavioral restitution and reliance on compensation determines a patient’s quality of movement (QoM) (Figure 3), which is defined “through a direct comparison of a patient’s motor execution of a task […] to a reference population of non-disabled age-matched control subjects”.[60] This means, the closer the movement matches those seen in controls, the better a patient’s QoM. Accordingly, the choice of performance metric to adequately assess QoM requires, in addition to sound psychometric evidence, a profound understanding of “normal” task behavior.

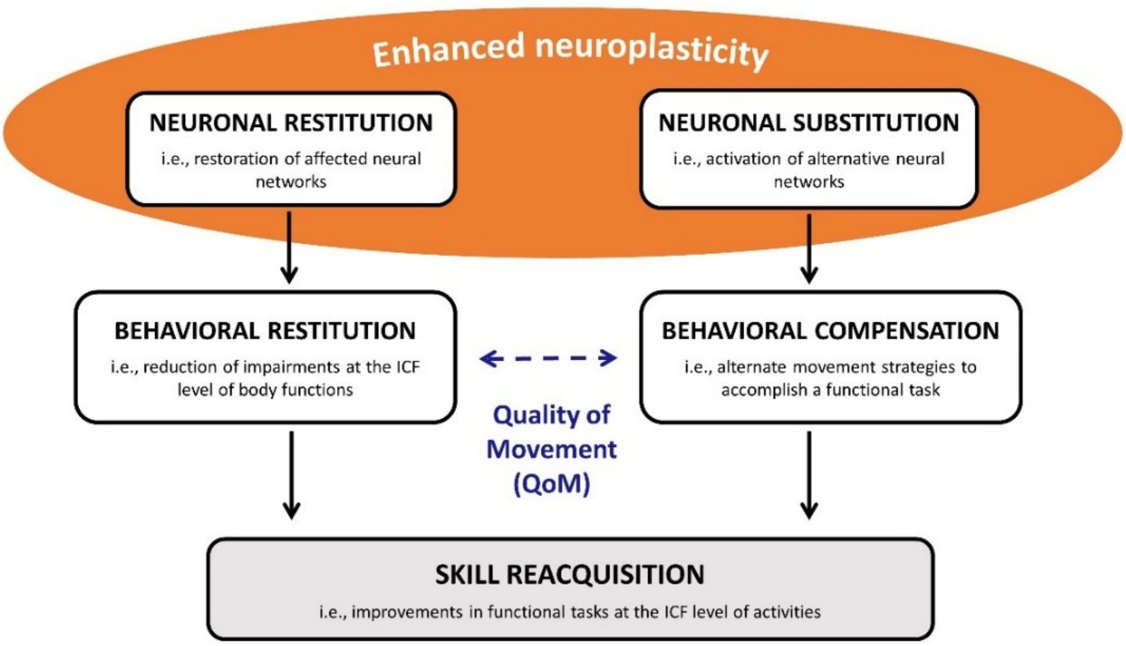

Figure 3. Conceptual model of skill reacquisition after stroke.
Figure adapted from Buma et al., 2013.

Normal vs. abnormal balance behavior during standing.

As we are bipeds, our center of mass (COM) is elevated far above ground when standing and must be balanced within a relatively small base of support, defined by our feet. As a result, even smallest deviations from the equilibrium position must be readily corrected to avoid excessive sway and eventually a fall. Thus, we never really stand still. This continuous swaying motion can be modeled as a single-joint inverted pendulum that pivots back and forth about the ankles (Figure 4).

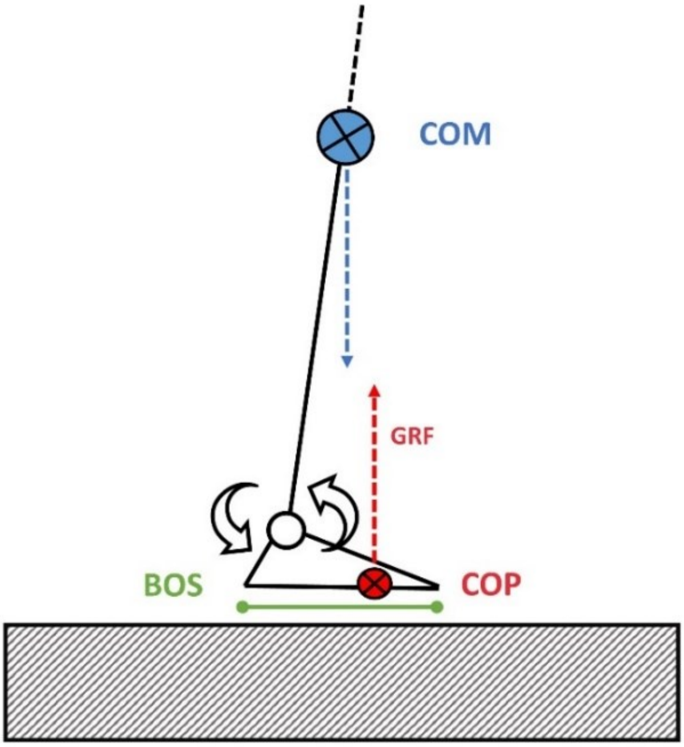

Figure 4. Simplified version of the inverted pendulum model of human balance control during quiet two-legged standing. The body sways back and forth about the ankle joint, displacing the center of mass (COM) relative to the base of support (BOS) defined by the feet. In response, the ground reaction force (GRF) vector determining the center of pressure (COP) position is shifted by ankle torques to adjust the distance-relationship between the COM and COP as a control variable. In the case illustrated here, the COP is placed in front of the COM to slow down and eventually reverse a forward swaying motion.

How do we control balance? Most physiological insights have been gained by experiments using motorized platforms that can be moved (i.e., translations) to exaggerate body sway. This includes the seminal work of Lewis M. Nashner in the seventies and eighties. By analyzing electromyography (EMG) responses to translations, Nashner and colleagues proposed that our erect posture is governed by central set of motor programs that are highly coordinated and quickly adapted to the direction of instability.[2] For example, induced forward sway is counteracted by ankle activity at onset latencies as fast as 80 to 120 ms, followed by knee and hip muscle activity in a distal-to-proximal gradient to stiffen the rest of the body.[2] The pendulum is stabilized, as it were, from the base upwards. This so-called ankle strategy acts by exerting torques that adjust the center of pressure (COP) position at the feet to steer the COM back to equilibrium (Figure 4).[3] It is only if these primary feet-in-place strategies fail that we alter our BOS through reactive stepping or grasping for support.[61]

COP oscillations recorded with force plates in healthy controls standing quietly, that are associated with continuous modulation of the calf muscle activity,[62,63] are highly synchronized.[3,64] This makes sense; both limbs act toward the same goal of preventing forward (or backward) falling due to gravity. In people with poststroke hemiplegia, however, this interlimb coordination is reduced[64,65] and characterized by asymmetric COP profiles with a larger relative contribution by the less-affected limb.[66-69] The underlying neurophysiological deficit remains unknown but may involve delayed muscle responses in the affected limb with improper coarticulation after platform translations,[70-73] when compared with the “normal” distal-to-proximal sequence described above. This coordination deficit appears to contribute to instability[74] and perturbation-induced falls,[75] and resembles the clinical phenomenon of abnormal post-stroke muscle synergies.

Taken together, equal limb contributions to regulatory COP movements appear, at least in the sagittal plane, a hallmark feature of human balance control. Therefore, QoM is assumed to be strongly reflected in metrics that reflect interlimb asymmetries. Normative symmetry ranges obtained in healthy age-matched controls can then be used as a benchmark against which a patient’s motor performance can be tested.

Aims and outline of this thesis

This thesis aims to strengthen our mechanistic understanding of early skill reacquisition post-stroke, based on the conceptual model presented in Figure 3. To this end, QoM is assayed longitudinally during quiet standing with COP-based performance metrics applied serially and at fixed times post-stroke. This task is easily standardized and has relatively low functional demands to start measurements as early as possible post-stroke and on the background of spontaneous neurobiological recovery and enhanced brain plasticity. To this end, this thesis investigates the psychometric properties of instrumented tools for measuring balance control (**chapter 2**), the time courses of QoM (**chapters 3 and 4**), and the effects of neurorehabilitation on enhancing lower limb motor recovery to improve functional tasks such as quiet standing and walking (**chapters 5 and 6**).

More specifically, in **chapter 2**, we investigate the <u>validity</u> and <u>reliability</u> of using a <u>pressure plate</u> to quantify COP-based performance metrics, by treating floor-mounted, laboratory-grade <u>force plates</u> as the "gold standard." Because the pressure plate is portable, its introduction may contribute to feasible testing protocols for conducting repeated measurements in clinical or community settings where the patient resides, instead of demanding frequent transportation to a specialized laboratory.

Chapters 3 and 4 present, respectively, the design and results of the TARGEt-1 trial. This prospective cohort study investigates fine-grained changes in quiet standing balance relative to neurological recovery of lower limb muscle synergies and strength within the first 3 months post-stroke. We hypothesize that the latter is, in line with the above-mentioned literature, mainly significant in the first 5 to 8 weeks post-stroke and makes a beneficial contribution to skill reacquisition by a (partial) return toward normal levels of interlimb symmetry in balance control. Inspired by some recent kinematic upper limb recovery studies,[76-78] we expect a time-restricted period early post-stroke during which QoM during standing "normalizes". This period may then serve as an ideal time to intervene with impairment-focused rehabilitation therapies.

Chapter 5 comprises a systematic review with meta-analyses on task training interventions targeting the reacquisition of independent walking early post-stroke. We use the ICF to categorize the effects of training on enhancing neurological recovery from lower limb impairments, and on improving walking ability at the activity level. In **chapter 6**, which presents the TARGEt-2 trial, we test specific therapeutic effects of using a <u>wearable exoskeleton</u> that enforces normal symmetric movement during practice. In this pilot study, we hypothesize that "normalization" of QoM by exoskeletal training is restricted to a time-restricted period of enhanced neuroplasticity, such that a later delivery of the same intervention is ineffective in preventing compensation with the less-affected side to achieve quiet standing and walking. To this end, we assume that the sensitive period parallels the time window of spontaneous neurobiological recovery in the first 5 weeks post-stroke.

The chapters of this thesis are based on data collected during the TARGEt project. TARGEt is an acronym for Temporal Analyses and Robustness of hemiplegic Gait and standing balance Early post-stroke and was funded by the Research Foundation Flanders (FWO, Flanders, Belgium; application no. 1S64819N), awarded to Jonas Schröder as a pre-doctoral strategic basic research fellowship. **Chapter 7** concludes with an overview of the main findings from the TARGEt project to provide recommendations for further research.

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CHAPTER 2

2

IS A PORTABLE PRESSURE PLATE AN ALTERNATIVE TO FORCE PLATES FOR MEASURING POSTURAL STABILITY AND INTERLIMB COORDINATION OF STANDING BALANCE CONTROL? A VALIDITY AND RELIABILITY STUDY.

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ABSTRACT

Background: Center-of-pressure (COP) synchronization and symmetry can inform adaptations in balance control following one-sided sensorimotor impairments (e.g., stroke). As established force plates are impossible to transport, we aimed to validate a portable pressure plate for obtaining reliable COP synchronization and symmetry measures, next to conventional postural stability measures.

Methods: Twenty healthy adults participated. In a single session, three 40-s eyes-open and eyes-closed quiet stance trials were performed per plate-type, randomly ordered. Individual-limb COPs were measured to calculate between-limb synchronization (BLS) and dynamic control asymmetry (DCA). Net COP (i.e., limbs combined) area, amplitude, and velocity were used to describe anteroposterior (AP) and mediolateral (ML) postural stability. Criterion validity was evaluated using Spearman correlations (r) and Bland-Altman plots. Test-retest reliability was tested using intraclass correlation coefficients (ICC).

Results: Strong correlations ($r > 0.75$) and acceptable reliability ($ICC > 0.80$) were found regarding individual-limb COP velocity and DCA, net COP ML amplitude, and AP and ML COP velocities. Bland-Altman plots yielded possible proportional bias; the pressure plate systematically underestimated COP scores by force plates and a larger error associated with a larger measurement.

Significance: Despite correlations between instruments and sufficient reliability for measuring postural stability and DCA with a pressure plate, this technical note strongly suggests, due to a systematic deviation, using the same plate-type to accurately assess change within subjects.

2

Background

Pathologies causing one-sided sensorimotor impairments (e.g., stroke) compromise balance control and increase the risk of falls.[1] However, recovery studies in this field remain scarce and often fail to distinguish behavioral restitution from compensations by relying on clinical scales, such as the Berg Balance Scale (BBS),[2] that have considerable ceiling effects[3] and do not show qualitative changes on the rated tasks.[4,5] Likewise, most posturographic studies measuring, for example, the center-of-pressure (COP) area, velocity, or amplitude as a more precise postural stability measure are confounded by using only one force plate. This is insufficient to separate the limbs and inform adaptations in standing balance as reflected by, for example, the between-limb synchronization (BLS)[6,7] and dynamic control asymmetry (DCA).[8,9] These metrics inform, respectively, how well both limbs work together to control balance and how much each limb contributes.

Measuring BLS and DCA requires posturographic systems with two floor-mounted force plates by established brands, which are currently considered the “gold standard”.[10,11] However, these force plates are expensive and impossible to transport, which makes clinical studies difficult to conduct over the first 3 to 6 months post-stroke – the period of significant balance recovery[2] - while patients are being discharged from stroke services to their own homes or care facilities in the region. Acknowledging this limitation, pressure plates (or mats) have recently been proposed as a portable and more-affordable clinical tool to measure postural stability.[12-14] Although not yet investigated, these instruments can record individual-limb COP movements using a single plate due to a larger number of embedded sensors. This advantage may further mitigate the need for extensive infrastructure to measure BLS and DCA, thus improving clinical feasibility of conducting serial measurements.

As a “first step” toward its criterion validation, the current study involving healthy adults compared a portable pressure plate with gold standard force plates for measuring COP synchronization (i.e., BLS) and symmetry (i.e., DCA) while standing, next to conventional descriptors of postural stability. Acknowledging that repeatable measures are conditional for showing agreement between assessment methods,[15] we investigated the test-retest reliability of each plate type before comparing them. Our research questions were as follows:

1. Are three immediate test-retest repetitions using a pressure plate or gold standard force plates sufficient to achieve reliable measures of postural stability, BLS, and DCA in healthy adults standing quietly?
2. Are averaged pressure plate measures of postural stability, BLS, and DCA in agreement with those obtained using gold standard force plates in healthy adults standing quietly?

2

We expected to confirm the literature by showing a high test-retest reliability (i.e., intraclass correlation coefficients (ICC) ≥ 0.80) of AMTI (Advanced Mechanical Technology Inc., MA, USA) force plates for measuring postural stability,[10,11] and hypothesized to find similar results with respect to BLS and DCA. Furthermore, we expected that a pressure plate's reliability for measuring postural stability, BLS, and DCA would be comparable to force plates. Regarding our second question, we expected to find high positive correlations in these outcomes between instruments (i.e., a correlation coefficient ≥ 0.75), in line with three prior validation experiments using similar pressure-sensitive devices.[12-14] Because correlations alone are insufficient to detect systematic biases, we additionally aimed to explore the level of agreement with a Bland-Altman analysis.[15,16] Measurement bias with lower COP values by a pressure plate was priorly suggested,[12,14] warranting further investigation.

Methods

Design

Ten female and ten male adults with a perfect BBS score volunteered to participate. No back or lower limb injury, use of medication, or neurological condition were reported. All volunteers provided written informed consent according to the policy of the local ethics committee (Antwerp University Hospital, BE; protocol no. 19/18/233; date 24/06/2019).

In a single session, a 0.5 m Footscan (RS Scan, Materialize, BE) pressure plate (578 x 418 x 12 mm, sampling frequency 500 Hz) and two AMTI Type OR 6-7 force plates (500 x 400 mm, sampling frequency 1,000 Hz) were used to quantify quiet standing balance during separate, randomly ordered measurements to avoid interference of the differently sized, rigid plates. As such, per instrument six 40-s trials were performed, alternatively with the eyes open or closed. The feet position was standardized (8.4 cm heel-to-heel distance, 9° toe-out angle), and subjects were instructed to stand as still as possible while keeping the eyes fixated at a 3-m distant target placed in front of them or with the eyes closed. This protocol aligns with typical clinical posturographic testing.[8,9]

To assess test-retest reliability per instrument, variation in three immediate test repetitions in the same subject and under the same condition (i.e., eyes-open or eyes-closed) was analyzed using ICCs.[17] Regarding criterion validity, defined following COSMIN[18] as the extent to which outcomes reflect results by the gold standard, averaged outcomes per condition and subject were compared between instruments.

Data processing

For each eligible trial, we calculated the net (i.e., both limbs combined) and individual-limb COP with anteroposterior (AP) and mediolateral (ML) coordinates from the last 30 s to avoid starting effects. The reference axes were rotated by 9° to coincide with the foot axis. We followed these steps, as described per instrument:

1. Force plates: Raw tri-axial force data from four load sensors - one in each corner - were collected with Nexus (Vicon Motion Systems Ltd, UK). Then, a custom-made MATLAB (version R2018a) algorithm was used to compute the COP for each side using these equations:

$$COPy(t) = \frac{-(My(t) + Fx(t) * Oz)}{Fz(t)} + Ox$$

$$COPx(t) = \frac{-(Mx(t) + Fy(t) * Oz)}{Fz(t)} + Oy$$

   Here, *x*, *y* and *z* are the AP, ML and vertical directions, respectively; *F* are the forces; *M* are the moments; and *O* is the offset from the geometric plate center.

   Subsequently, the net COP was calculated as a weighted average using this equation:

$$COP_{net} = \frac{COP_{most\ affected} * Fz_{most\ affected} + COP_{less\ affected} * Fz_{less\ affected}}{Fz_{most\ affected} + Fz_{less\ affected}}$$

2. Pressure plate: Many embedded sensors (2.6 sensors/cm2) record the plantar distribution of vertical forces, or *Fz*. COP was then computed using the system’s own software (Footscan 9, RS Scan, Materialize, BE) as the point of application of the summed forces

using all sensors bearing weight at the entire plate (i.e., net COP), or at either geometrical side to extract individual-limb COPs.

Finally, the COP signals from both instruments were identically low-pass filtered (2^{nd} order Butterworth, 10 Hz) in MATLAB, and the same scripts were used to calculate outcomes metrics.

Outcome metrics

Peak-to-peak sway amplitude in mm ($nCOP_{amp\text{-}ap}$, $nCOP_{amp\text{-}ml}$) and root mean square velocity in mm/s ($nCOP_{vel\text{-}ap}$, $nCOP_{vel\text{-}ml}$) were determined in the AP and ML directions as traditional descriptors of postural stability.[19] In addition, the net COP area ($nCOP_{area}$) was calculated in mm^2 as an ellipse that covered 85% of the entire signal using principal component analyses.[20]

Amplitudes ($iCOP_{amp\text{-}ap}$, $iCOP_{amp\text{-}ml}$) and velocities ($iCOP_{vel\text{-}ap}$, $iCOP_{vel\text{-}ml}$) were also determined for each individual limb, next to BLS as a cross-correlation coefficient between COP movements at a zero time-lag[6,7] and DCA as a symmetry index[8] following this equation:

$$DCA = \frac{2 * (\ iCOP_{Vel-AP}\ loaded - \ iCOP_{Vel-AP}\ unloaded\ )}{iCOP_{Vel-AP}\ loaded + \ iCOP_{Vel-AP}\ unloaded} * 100\%$$

The loaded and unloaded sides were determined by dividing the mean vertical force under each limb. We focused on the AP direction, and BLS and DCA were not calculated with ML COPs because frontal plane sway is mainly controlled by a loading-unloading mechanism that is not reflected by COP changes.[6]

Statistical analyses

Regarding question 1, we computed the ICCs using a two-way mixed-effects model ($ICC_{3,3}$) as a measure of agreement between the three test-retest measurements.[17] A multiple-measurement type was chosen because the actual application is based on averaging trials.[10,11] Acceptable reliability was defined as an $ICC_{3,3} > 0.80$. Specifically, $ICC_{3,3} \geq 0.90$ was interpreted as excellent and 0.80–0.90 as good reliability.[21]

For question 2, averaged COP scores were plotted per subject to observe general trends between instruments. Spearman's rank correlation coefficients (r) were calculated for each outcome and $r \geq 0.75$ were interpreted as strong, 0.50–0.74 as moderate, and < 0.50 as low or no relationship.[21] Mean differences were statistically analyzed using Wilcoxon singed rank tests because the averaged outcomes per instrument were not normally distributed. In conjunction, Bland-Altman plots (i.e., subject-specific mean scores by difference scores) were created, including the mean difference line with its standard error and the limits of agreement (LOA).[15] Narrower LOA encompassing zero reflect better agreement, whereas the distribution of difference scores was visually analyzed for bias. According to Ludbrook,[16] a significant difference by a constant amount is interpreted as fixed bias and a slope pattern as proportional bias. The significance level of all analyses was set two-tailed at 0.05.

A sample of 20 subjects was defined *a priori*, by offering 80% power to detect a correlation coefficient of a least r = 0.60 between both devices at a significance level of 0.05.

Results

One subject had a corrupted dataset, and 19 subjects (10 female) with a mean (± SD) age of 35.4 ± 15.9 years were included in the analyzes. Their body weight and length were 77.3 ± 13.7 kg and 171.2 ± 7.0 cm, respectively.

Table 1 shows the reliability outcomes with $ICC_{3,3}$ point-estimates and their confidence intervals. Regarding the force plates, $ICC_{3,3} \geq 0.80$ were found for both visual conditions regarding $nCOP_{area}$, $nCOP_{amp\text{-}ml}$, $nCOP_{vel\text{-}ap}$, $nCOP_{vel\text{-}ml}$, $iCOP_{vel\text{-}ap}$, and DCA. A pressure plate yielded $ICC_{3,3} \geq 0.80$ regarding the $nCOP_{vel\text{-}ml}$, $iCOP_{vel\text{-}ap}$, and DCA under both visual conditions. In addition, the pressure plate reached sufficient reliability for measuring $nCOP_{amp\text{-}ml}$ and $nCOP_{vel\text{-}ap}$ under EC conditions. In general, ICCs < 0.80 were found for measuring amplitudes (i.e., $nCOP_{amp\text{-}ap}$, $iCOP_{amp\text{-}ap}$) and BLS, irrespective of the instrument.

Figure 1 illustrates that a relatively higher COP score by the pressure plate corresponds to a higher force plate score, and *vice versa*. In line with this observation, Table 2 shows strong correlation coefficients of r ≥ 0.75 for both visual conditions regarding $nCOP_{vel\text{-}ml}$, $iCOP_{vel\text{-}ap}$, and DCA. In addition, $nCOP_{area}$, $nCOP_{amp\text{-}ml}$, $nCOP_{vel\text{-}ap}$, and $iCOP_{amp\text{-}ap}$ were strongly correlated between instruments with r ≥ 0.75 with respect to the EC measurements.

A second observation from Figure 1 is that the pressure plate COP scores are consistently lower than those of the force plates. In the same vein, mean differences between instruments were highly significant with respect to each COP metric investigated (*P* < .001, Table 2). Bland-Altman plots further show that most difference scores were positioned within the LOA with broad ranges that were situated below zero, except for $nCOP_{area}$ (Figure 2). In addition, an inclined distribution slope is shown for nCOParea, nCOPamp-ml, nCOPvel-ap, nCOPvel-ml, iCOPvel-ap, and iCOPvel-ml, such that an increasingly larger difference was observed relative to the mean score, indicating proportional bias.

Mean differences in BLS and DCA were non-significant (*P* > .05, Table 2) and Bland-Altman plots show difference scores that are evenly distributed within LOA, ranging above and below zero.

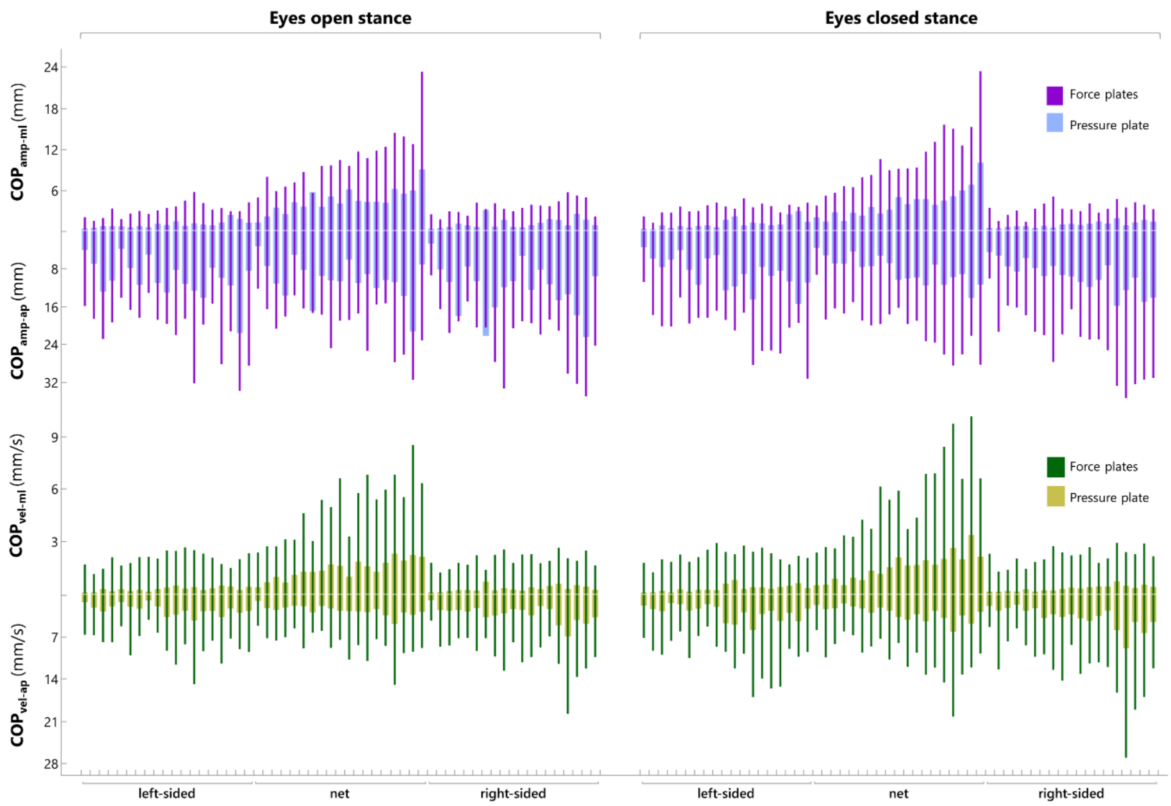

Figure 1. Mean COP scores per subject measured using either a pressure plate or force plates. Peak-to-peak amplitude and root mean square velocity of the COP at the limbs separately and combined (i.e., net) are plotted per subject (N=19) to visually compare the types of plates. Thicker bars reflect pressure plate scores, and thinner bars reflect force plates as the “gold standard”.

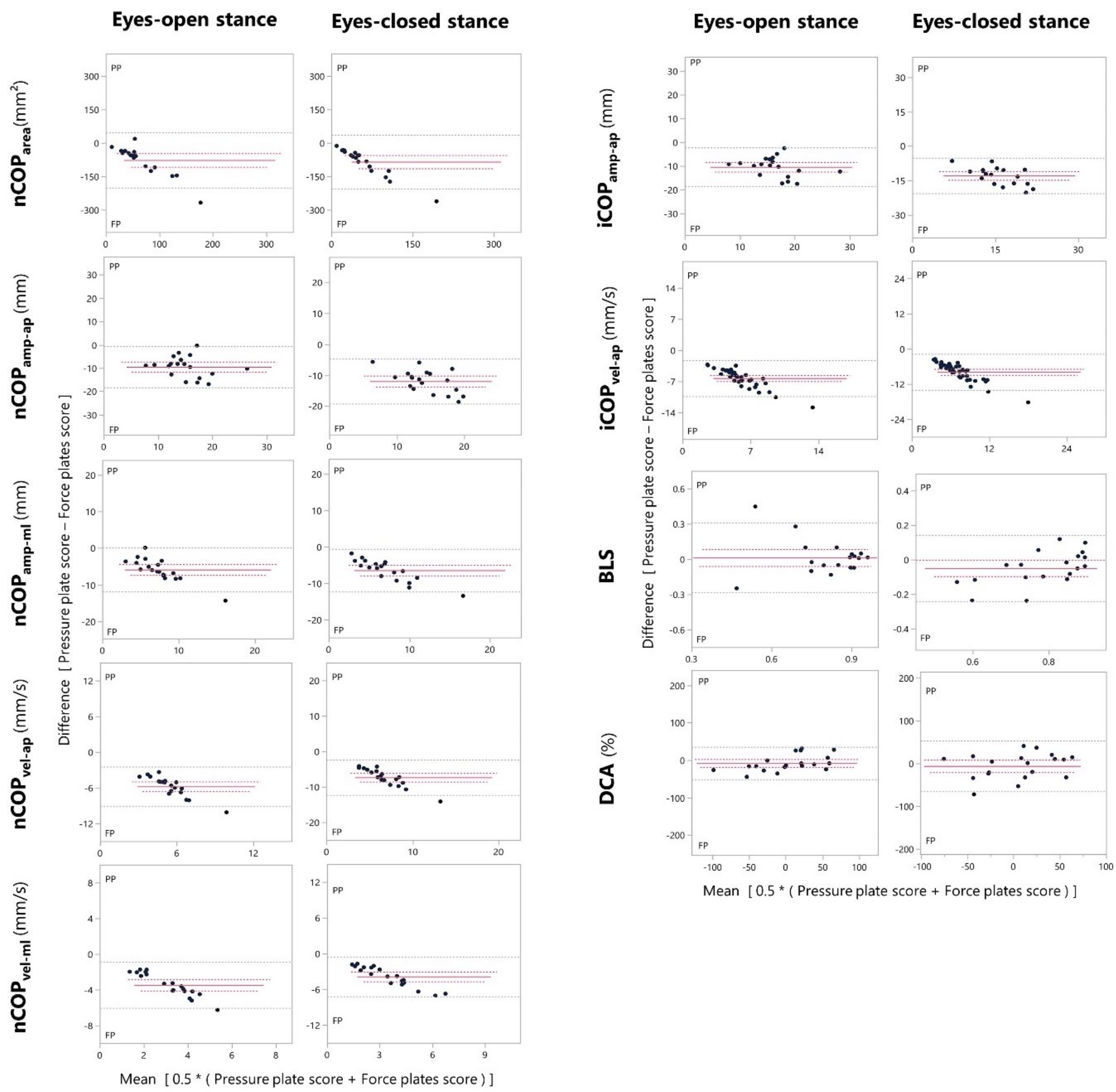

Figure 2. Bland-Altman plots with subject-specific differences and mean scores between a pressure plate and two force plates as the gold standard. The Y-axis shows the subject-specific difference scores between the two measurement devices, and the X-axis represents the mean scores per subject. Solid red lines represent the mean difference, dotted red lines represent the standard error of the mean, and gray dotted lines represent the upper and lower ends of the limit of agreement. On the left, the net COP metrics reflecting postural stability are displayed. On the right, individual-limb COP and interlimb coordination metrics are displayed. PP, pressure plate; FP, force plates.

	Eyes-open stance		Eyes-closed stance	
	$ICC_{3,3}$ [Force plates]	$ICC_{3,3}$ [Pressure plate]	$ICC_{3,3}$ [Force plates]	$ICC_{3,3}$ [Pressure plate]
Net COP measures of postural stability (n=19)				
$nCOP_{area}$ (mm^2)	**0.84 (0.66; 0.94)*** [a]	0.04 (-1.24; 0.63)	**0.81 (0.59; 0.93)***	0.70 (0.37; 0.88)
$nCOP_{amp\text{-}ap}$ (mm)	0.53 (-0.43; 0.81)	0.47 (-0.14; 0.78)	0.70 (0.35; 0.88)	0.62 (0.18; 0.84)
$nCOP_{amp\text{-}ml}$ (mm)[c]	**0.92 (0.84; 0.97)**** [a]	0.69 (0.30; 0.88)	**0.89 (0.76; 0.95)***	**0.83 (0.64; 0.93)***
$nCOP_{vel\text{-}ap}$ (mm/s)[c]	**0.89 (0.75; 0.95)***	0.72 (0.39; 0.89)	**0.91 (0.81; 0.97)****	**0.86 (0.70; 0.94)***
$nCOP_{vel\text{-}ml}$ (mm/s)[b,c]	**0.95 (0.90; 0.98)****	**0.84 (0.65; 0.94)***	**0.94 (0.87; 0.98)****	**0.85 (0.67; 0.94)***
Individual-limb COP – dominant limb (n=19)				
$iCOP_{amp\text{-}ap}$ (mm)	0.73 (0.41; 0.89)	0.59 (0.11; 0.83)	**0.85 (0.67; 0.94)*** [a]	0.57 (0.07; 0.82)
$iCOP_{vel\text{-}ap}$ (mm/s)[b,c]	**0.95 (0.89; 0.98)****	**0.80 (0.55; 0.92)***	**0.95 (0.89; 0.98)****	**0.89 (0.77; 0.96)***
Individual-limb COP – non-dominant limb (n=19)				
$iCOP_{amp\text{-}ap}$ (mm)	0.41 (-0.32; 0.77)	0.48 (-0.11; 0.79)	0.44 (-0.22; 0.77)	0.62 (0.18; 0.84)
$iCOP_{vel\text{-}ap}$ (mm/s)[b,c]	**0.80 (0.56; 0.92)***	**0.81 (0.59; 0.93)***	**0.84 (0.65; 0.93)***	**0.84 (0.66; 0.93)***
Interlimb coordination measures (n=19)				
BLS	0.75 (0.43; 0.90) [a]	0.47 (-0.14; 0.78)	0.39 (-0.36; 0.75)	0.23 (-0.49; 0.66)
DCA (%)[b,c]	**0.90 (0.78; 0.96)***	**0.91 (0.81; 0.96)****	**0.92 (0.83; 0.97)***	**0.93 (0.85; 0.97)***

Table 1. Test-retest reliability of a pressure plate and laboratory-grade force plates for measuring postural stability and interlimb coordination in quiet standing balance control. $ICC_{3,3}$ point-estimates with 95% confidence intervals are shown, reflecting variation between three immediate 30-s trial repetitions within a single measurement session. Results are shown per instrument and visual condition. $ICC_{3,3}$ estimates highlighted in **bold** reflect a statistical significance finding with *, reflecting good reliability ($ICC_{3,3}$ 0.90-0.80), and **, reflecting excellent reliability ($ICC_{3,3}$ >0.90).

[a], discrepancy between instruments of ICC3,3 > 0.20 favoring the marked value.

[b], ICC3,3 ≥ 0.80 reflecting good reliability across instruments for the eyes open condition.

[c], ICC3,3 ≥ 0.90 reflecting excellent reliability across instruments for the eyes closed condition.

	Eyes-open stance								Eyes-closed stance							
	Pressure plate (SD)		Force plates (SD)		Mean difference (SE)		*P*	r	Pressure plate (SD)		Force plates (SD)		Mean difference (SE)		*P*	r
Net COP measures of postural stability (n=19)																
$nCOP_{area}$ (mm^2)	27.55	(16.55)	104.63	(71.01)	**-77.08**	**(14.48)**	**<.001**	0.60*	17.47	(15.04)	102.07	(74.11)	**-84.60**	**(14.13)**	**<.001**	0.80**
$nCOP_{amp\text{-}ap}$ (mm)	10.44	(4.17)	19.91	(5.19)	**-9.47**	**(1.04)**	**<.001**	0.43	8.39	(2.82)	20.37	(4.86)	**-11.99**	**(0.85)**	**<.001**	0.61*
$nCOP_{amp\text{-}ml}$ (mm)	4.47	(1.73)	10.31	(4.20)	**-5.84**	**(0.70)**	**<.001**	0.67*	3.99	(2.07)	10.33	(4.69)	**-6.35**	**(0.69)**	**<.001**	0.82**
$nCOP_{vel\text{-}ap}$ (mm/s)	2.61	(0.79)	8.40	(2.28)	**-5.79**	**(0.39)**	**<.001**	0.68*	3.12	(1.19)	10.47	(3.48)	**-7.35**	**(0.58)**	**<.001**	0.80**
$nCOP_{vel\text{-}ml}$ (mm/s)	1.41	(0.55)	4.88	(1.77)	**-3.47**	**(0.30)**	**<.001**	0.89**	1.53	(0.76)	5.40	(2.35)	**-3.87**	**(0.39)**	**<.001**	0.87**
Individual-limb COP measures (n=38)																
$iCOP_{amp\text{-}ap}$ (mm)	11.24	(4.81)	21.72	(6.22)	**-10.48**	**(0.79)**	**<.001**	0.65*	9.26	(3.28)	22.07	(6.07)	**-12.81**	**(0.77)**	**<.001**	0.57*
$iCOP_{vel\text{-}ap}$ (mm/s)	2.88	(1.19)	9.18	(3.00)	**-6.30**	**(0.34)**	**<.001**	0.75**	3.40	(1.58)	11.29	(4.36)	**-7.89**	**(0.51)**	**<.001**	0.78**
Interlimb coordination measures (n=19)																
BLS	0.82	(0.14)	0.81	(0.17)	0.01	(0.03)	0.77	0.65*	0.76	(0.14)	0.81	(0.09)	-0.05	(0.02)	0.06	0.61*
DCA (%)	-0.70	(50.98)	7.39	(39.80)	-8.09	(5.06)	0.16	0.86**	0.50	(46.26)	7.34	(38.62)	-6.84	(6.95)	0.52	0.76**

Table 2. Criterion validity of a pressure plate for measuring postural stability and interlimb coordination in quiet standing control using two laboratory-grade force plates as the gold standard. The mean values and their standard deviations (SDs) are shown per instrument. Mean differences are presented between devices with a standard error (SE). P values are the probability statistics that the mean values are the same (null hypothesis) assessed with Wilcoxon signed rank tests. Results highlighted in **bold** are statistically significant (P < .05). Lastly, r estimates show the strength of the Spearman correlation coefficients between instruments with *, reflecting a statistically significant correlation of moderate strength (r=0.5-0.74); and **, reflecting a significant strong (r ≥0.75) correlation.

Discussion

In the current study, a head-to-head comparison was performed between a pressure plate and two gold standard force plates for measuring COP while quiet standing. We advanced prior validation experiments[12-14] by addressing the capability of a single pressure plate to capture individual-limb COP movements to address postural stability, as reflected by the total amount of COP sway, and interlimb coordination in terms of BLS and DCA. We found acceptable test-retest reliability for measuring velocity-based COP metrics with the pressure plate, including DCA, with strong correlations relative to force plates. COP amplitudes and BLS were found less reliable. Despite strong correlations between instruments, we identified a systematic deviation. The pressure plate systematically underestimated force plate outcomes of COP with proportional bias. Seemingly, both instruments acted in a similar, but not identical way. These findings are discussed with implications for clinical use.

Similar to prior validation studies,[12-14] we found strong correlations between a pressure plate and established force plates for measuring postural stability. In our analyzes, this association was strongest for velocity-based measures of COP (Table 2), and we have shown for the first time a similar correlation strength regarding DCA, i.e., a symmetry index of individual-limb COP velocities.

COP velocities are known to be particularly consistent, requiring two to three trials to reach reliable outcomes.[10,11] This reliability is thought to result from a sensitivity to high-frequency changes in the COP signal that are more consistent and reflect stabilizing responses to body sway.[19] In agreement, we found AMTI force plates to yield good-to-excellent reliability for measuring $nCOP_{vel-ml}$, $nCOP_{vel-ap}$, $iCOP_{vel-ap}$, and DCA, whereas displacement-based measures including COP amplitudes and BLS were less reliable, despite averaging three 30-s trials (Table 1). A low reliability of force plates for measuring BLS agrees with a previous study in stroke patients.[22] In comparison, the pressure plate exhibited a similar reliability in the same measures during the eyes-closed condition, whereas eyes-open measurements often yielded ICCs < 0.8, or insufficient reliability (Table 2). This suggest that a pressure plate's measurement precision is slightly lower relative to force plates, but improves when sway is provoked by closing the eyes, which causes larger and more regular COP movements.[23]

Notwithstanding strong correlations and acceptable test-retest reliability, we identified a systematic deviation. COP scores by the pressure plate were significantly smaller than those by force plates (Table 2), and this deviation increased proportionally to the magnitude of the measure (Figure 2). Proportional bias was earlier suggested,[12,14] pointing toward an underlying cause inherent to the use of different soft- and hardware. Although speculative, this may include the sensor type because, relative to force plates, horizontal forces are not recorded by a pressure plate. Furthermore, averaging forces over many embedded sensors could result in a smoothing effect, causing a lower COP velocity and amplitude. Alternatively, the different sampling frequencies (pressure plate 500 Hz vs force plates 1,000 Hz) may have caused bias, acknowledging that COP measures are sensitive to sampling frequencies,[24] although both instruments exceed the recommended 100 Hz.[11]

Interestingly, Bland-Altman plots do suggest agreement between instruments for measuring DCA (Figure 2). Apparently, the systematic deviation is controlled by using two instrument-dependent COP measures to calculate the symmetry index. This underpins our finding of systematic rather than random deviation when measuring COP with a pressure plate relative to force plates. However, whether both plate types agree in cases of asymmetric balance, such as in stroke subjects with hemiplegia,[7,8] requires further investigation.

Implications

First, strong correlations between instruments indicate that the pressure plate can serve as an alternative; however, because of systematic bias, it cannot replace force plates. Therefore, it is strongly recommended using the same instrumentation when longitudinally monitoring performance changes *within* subjects. Second, the pressure plate yielded similar reliability to gold standard force plates when visual input was suppressed. This suggests utility of a pressure plate when balance is challenged by task modulation, or in clinical populations with greater spontaneous sway. Third, velocity-based measures are particularly reliable and therefore advised for describing balance performance, irrespective of the choice of plate-type. Finally, general similarities between instruments suggest that existing recommendations for standardizing force plate measurements are applicable to pressure plates. This includes that at least 90 s of COP data should be collected per session.[10,11] In line with prior reliability studies,[10,11,19] averaging three 30-s trials was sufficient to achieve reliable outcomes in our study. This is important for clinical use because pathological populations are often unable to adhere to longer assessments. Our own protocol, as part of a recently completed stroke recovery study,[25] is attached in supplement.

Limitations

We included a rather small sample of mostly younger adults. Replication in larger samples, including the elderly, who show a decline in balance with ageing,[26] is warranted to confirm our findings and provide normative values in higher-age categories. Moreover, generalization of our findings to people with asymmetric balance remains unknown. Second, we did not record COP data simultaneously by “stacking” plates to avoid interference. However, simultaneous recordings are recommended for future studies to allow more-accurate comparisons by eliminating within-subject variability. Third, our analyses should be viewed within the specific context of outcome metrics, devices, and balance conditions. Finally, we tested intrasession test-retest reliability. Assessing test-retest reliability *between* sessions is warranted as this is another important aspect for developing standardized testing protocols for clinical use.

Conclusion

The current results suggest that the pressure plate is a reliable assessment tool, yielding strong correlations with gold standard force plates for measuring postural stability and individual limb contributions to balance control, as reflected by DCA. However, there are some concerns with its criterion validity as we found a systematic deviation causing lower COP scores compared with outcomes by force plates. This strongly suggests using of the same instrumentation to accurately assess performance changes *within* subjects. If this limitation is considered when designing data collection protocols, a pressure plate holds promise as a clinical tool to make serial measurements as part of longitudinal studies in populations with impaired balance and an increased fall risk feasible. Therefore, validation experiments investigating measurement properties of pressure plates for assessing balance, next to portable force plates that are emerging,[27] in pathological populations are encouraged.

DECLARATION OF AUTHORSHIP CONTRIBUTIONS: JS collected, analyzed, and interpreted the data, and was a major contributor in writing the manuscript. AH contributed substantially to the data processing and writing the manuscript. WS, LY and GK contributed by revising the manuscript. ST contributed to the conception of this study and revised the manuscript. All authors have read and approved the final manuscript.

DECLARATION OF COMPETING INTERESTS: The authors declare that they have no competing interests. The manufacturers of the investigated devices (AMTI, MA, US & Materialize, BE) or other parties involved in their commercial distribution were not involved in the design or conduction of this study, nor did we consult them with the current findings before writing and submission of this manuscript.

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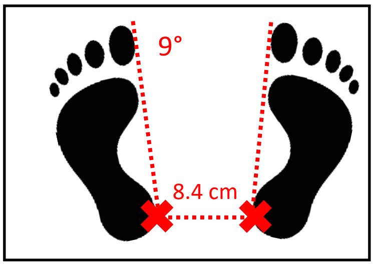
Appendix

Standardized testing protocol: Center-of-pressure (COP) recordings during quiet stance

Material

- Non-distracting environment
- Solid chair
- Measuring devices that can record COP data at the limbs separately with a minimum sampling frequency of 100 Hz; such as:
    - Two floor-mounted force plates (in well-equipped movement analysis laboratory) positioned side-by-side and as close as possible without touching.
        - Weight-bearing asymmetry in quiet stance can be estimated from a single force plate,[1] whereas two plates are required to examine individual-limb balance contributions.
    - A portable pressure plate with the system's own hard- and software.
        - A single plate is sufficient for measuring individual-limb COP changes due to a larger quantity of embedded load sensors.
- Template for foot placement made out of high-elastic thin foam sheets
    - The distance between the medial edges of the heel should be marked, together with a line starting in this position for orienting the medial edges of the feet to achieve a standardized toe-out angle (see picture below).



Task definition

- Two-legged stance on the bare feet.

[1] Genthon N, Gissot A-S, Froger J, Rougier P, Pérennou D. Posturography in patients with stroke: estimating the percentage of body weight on each foot from a single force platform. *Stroke*. 2008;39:489–491.

- Feet are in a standardized position (9 degrees toe-out-angle, 8.4 cm heel-to-heel distance, medial feet edges equidistant to the gap between two force plates, or the center of the pressure plate), ensured by using a template.
    - If the patient is unstable and needs to move his/her feet, the trial is immediately terminated.
- The arms are hanging (relaxed if possible) in an extension position alongside the trunk.
    - If the arm position cannot be achieved without causing pain or discomfort, a subject specific arm position is chosen.
    - If the assessor observes any arm movement that is unrelated to keeping balance, such as scratching the nose, the trial is immediately terminated and/or later excluded. Swaying of the arms to maintain balance in the static position is allowed.
- For eyes open stance, the subject fixates his/her eyes on a visual target (e.g., cross out of tape) mounted on the opposite wall.
    - The distance between the subject and the visual target depends on the room size and may differ between settings. It is therefore advised to measure and report the distance.
- Standing without aids or orthoses attached to the lower limbs.
- Manual support by the assessor is not allowed.
    - Even fine touch support must be avoided as sensory input through contact cues can significantly reduce sway.[2]

Procedures

<u>Before testing:</u>

- Take of shoes and any orthosis attached to the lower limbs.
- Measure and note a subject's body weight and length with light clothing.
- Attach the foot placement template on the measuring plate(s).
- Calibrate measurement instruments immediately before the assessment during a zero-load condition.

[2] Jeka JJ. Light touch contact as a balance aid. *Physical Therapy*. 1997;77(5):576-87.

- Place the chair near the measuring plates. The chair must not touch the measuring plate(s)!
    - The chair allows to position the feet conveniently while the patient is seated.
    - The chair maintains behind the patient to provide safety in case of instability.

<u>During testing:</u>

- Assist the subject in standing up, while maintaining that standardized foot position.
- Instruct the patients to “stand as still as possible”.
    - Instructions given to the subjects matter! Sway results obtained when subjects were asked to “stand as still as possible” showed higher consistency[3] as compared to “stand quietly”, and is therefore preferred.
- Each quiet stance trial lasts 40 seconds.
    - One assessor maintains close to the subject and provides immediate assistance in case of a potential fall.
- Repeat trials in an alternative sequence with the eyes open and closed, until at least 2 and ideal 3 eligible trials are obtained for each visual condition.
    - Averaging outcomes of several successive trials improves reliability of COP data.[4]

<u>After testing:</u>

- Trial meta-data are recorded, including the subject’s number, trial numbers, duration, and any other notes.

Data processing

- The raw data is converted to forces and moments.[5]
- The first 10 seconds of data are cropped to avoid influence of starting effects.

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[3] Zok M, Mazza` C, Cappozzo A. Should the instructions issued to the subject in traditional static posturography be standardised? Med Eng Phys 2008;30:913–6.
[4] Lafond D, Corriveau H, Hebert R, Prince F. Intrasession reliability of center of pressure measures of postural steadiness in healthy elderly people. Arch Phys Med Rehabil 2004;85:896–901.
[5] Data processing may be performed, in part, using the measuring systems own software, or costum-written algorithms, for example applied in MATLAB. Our own MATLAB codes can be made available upon reasonable request.

- Based on the resultant 30 seconds of data, the COP trajectories with anteroposterior (AP) and mediolateral (ML) coordinates are calculated separately for each foot. The net COP is computed as a weighted average of the left and right COPs.
- The COP coordinates are passed through a digital, low-pass, second-order Butterworth style filter at a 10 Hz frequency.
    - 10 Hz cut-off frequency is advised to get rid of high-frequent noise while keeping all relevant balance data.[6]
- Outcome metrics are calculated and average over (2 to) 3 successive trials.
    - The choice of metric should cover the constructs of postural (in-)stability and postural (a-)symmetry.
        - A broad range of (conventional) COP metrics reflecting postural (in-)stability are available, whereas minimal, maximal or peak-to-peak metrics such as COP sway amplitude should be avoided as they are subjects to great variance and low reliability[7].
    - Metrics reflecting postural (a-)symmetry are less-well studied. Previously the following metrics have been proposed:
        - Cross-correlations between individual-limb COP changes, e.g., the Between-Limb Synchronization[8]
        - Symmetry indexes of conventional COP metrics, e.g., the Dynamic Control Asymmetry

[6] Schmid M, Conforto S, Camomilla V, Cappozzo A, D'Alessio T. The sensitivity of posturographic parameters to acquisition settings. Med Eng Phys 2002;24:623–31.
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2

CHAPTER 3

3

TIME COURSE AND MECHANISMS UNDERLYING STANDING BALANCE RECOVERY EARLY AFTER STROKE - DESIGN OF A PROSPECTIVE COHORT STUDY WITH REPEATED MEASUREMENTS.

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ABSTRACT

Introduction: Although most stroke survivors show some spontaneous neurological recovery from motor impairments of the most-affected leg, the contribution of this leg to standing balance control remains often poor. Consequently, it is unclear how spontaneous processes of neurological recovery contributes to early improvements in standing balance.

Objective: We aim to investigate (1) the time course of recovery of quiet stance balance control in the first 12 weeks post-stroke and (2) how clinically observed improvements of lower limb motor impairments longitudinally relate to this limb's relative contribution to balance control.

Methods and analysis: In this prospective longitudinal study, a cohort of 60 adults will be recruited within the first 3 weeks after a first-ever hemispheric stroke and mild-to-severe motor impairments. Individual recovery trajectories will be investigated by means of repeated measurements scheduled at 3, 5, 8, and 12 weeks post-stroke. The Fugl-Meyer Motor Assessment and Motricity Index of the lower limb serve as clinical measures of motor impairments at the hemiplegic side. As soon as subjects are able to stand independently, bilateral posturography during quietly standing will be measured. First, the obtained center-of-pressure (COP) trajectories at each foot will be used for synchronization and contribution measures that establish (a-)symmetries between lower limbs. Second, the COP underneath both feet combined will be used to estimate overall stability. Random coefficient analyses will be used to model time-dependent changes in these measures and, subsequently, a hybrid model will be used to investigate longitudinal associations with improved motor impairments.

Discussion: The current study aims to investigate how stroke survivors 're-learn' to maintain standing balance as an integral part of daily life activities. The knowledge gained through this study may contribute to recommending treatment strategies for early stroke rehabilitation targeting behavioral restitution of the most-affected leg or learning to compensate with the less-affected leg.

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CONTRIBUTION TO THE FIELD

Many stroke survivors show residual standing balance deficits which may contribute to chronic disability and falls. However, the scientific evidence about the time course and mechanisms underlying standing balance recovery is disproportionally low as compared to the resultant medical and societal burden. Particularly, *how* stroke survivors 're-learn' to maintain quiet stance in the early recovery phase when motor functions of the most-affected leg improve remains unknown. Therefore, there is a need for explorative longitudinal research that incorporates time-series analyses with sensitive and specific measures of task performance as early as possible after stroke onset. In the current manuscript, we describe the design of such an observational study that investigates prospectively the time course of recovery of quiet stance balance control in a cohort of 60 patients after a first-ever hemispheric stroke. Simultaneously, we clinically observe the time course of recovery of motor impairments of the most-affected leg to investigate longitudinal associations with this leg's contribution to balance control. Eventually, this knowledge may further direct how we should manage and treat standing balance deficits in rehabilitation facilities to enable stroke survivors a fast and safe re-integration back into society.

Introduction

Background

Stroke is a major cause for acquired serious disability in adults worldwide.[1] It is well known that stroke affects standing balance, for example posturographic studies revealed that stroke survivors show increased body sway reflected by center-of-pressure (COP) movements.[2-5] Recovering the ability to maintain standing balance is seen as a prerequisite for regaining walking independence,[6] and residual deficits are associated with limited community ambulation[7,8] and falls.[9-11] Accordingly, falls remain a major problem with approximately 50 to 70% of community-dwelling stroke survivors experiencing a fall recently after being discharged home from rehabilitation facilities.[9,10,12] As such, deficient standing balance control may contribute to chronic disability and fall-related injury resulting in greater economic costs due to the need of care[13] and poor quality of life.[14]

Improving stroke rehabilitation services requires a profound understanding about the behavioral changes underlying impaired as well as improved balance control execution, together with the time windows in which they develop. This may enable clinicians to define appropriate treatment targets and rehabilitation goals early onwards. From this perspective, particularly explorative longitudinal research with repeated measurements early in time is warranted to distinguish between behavioral restitution and compensation when control of standing balance is restored.[15,16] As stroke recovery is a complex process, that likely involves both spontaneous and learning-dependent mechanisms,[17,18] this research should be based on a commonly shared framework for classifying and using uniform terminology.

The WHO's international classification of function, disability and health (ICF) model may serve as such framework by categorizing the consequences of stroke in terms of body functions, activities and participation.[17,19] Following the ICF, we will discuss available literature and, subsequently, the design of an ongoing observational study into the time course and mechanisms underlying standing balance recovery. For this purpose, we distinguish between recovery of motor impairments of the most-affected lower limb (i.e., ICF level of body functions) and an improved ability to maintain standing balance as an integral part of daily life activities (i.e., ICF level of activities).

Time course of lower limb recovery

Unfortunately, only few longitudinal studies have been designed to investigate prospectively the time course of recovery of lower limb function[20-23] and activities[24-26] early after stroke. These studies suggest that recovery from motor impairments, such as synergy-dependency[20,22,23] and weakness,[21,23] mainly occurs in the first 5 weeks and levels off between 8 to 12 weeks post-stroke.[20-22] However, most survivors experience residual impairments in dissociating voluntary foot and leg movements from intralimb synergies[27,28] and muscle strength[23] which is associated with a decreased contribution of this leg to standing balance control.[29-32] These early time-dependent changes remain poorly understood, but can be conceptualized as spontaneous neurological recovery as reflected by the passage of time.[23]

Similar regularities in recovery patterns of activities involving the lower limbs have been shown. Likewise, most improvements in walking[6,24-26] and other daily life activities[21,23] were seen in the first weeks, and regaining standing balance is found imperative to such recovery.[6] One might suggest that spontaneous neurological recovery is associated with, if not determinant for these rapid improvements. This would mean that the ability to complete tasks is restored with the same movement repertoire, or quality, the patient had before the stroke (i.e., behavioral restitution).[18,19,33] However, previous longitudinal research is largely limited to outcomes showing the mere accomplishment on tasks. As these measures are unable to discriminate *how* the task is performed,[19,34,35] little has been learned so far about the time course of recovery regarding qualitative aspects of movement when standing balance is restored.

Mechanisms underlying recovery of standing balance control

As recently suggested,[28] a number of severely affected subjects fail to show neurological recovery,[28] leaving them entirely dependent on learning to use alternative ways to maintain their standing balance (i.e., behavioral compensation). However, even 'well-recovered' patients with near normal clinical scores may show a disproportional reliance on the less-affected leg to balance control.[31,36] This is illustrated by more recent posturographic studies showing that bilateral COP displacements at the feet separately, as a reflection of the anticipatory modulation of ankle muscle activity aiming to minimize body sway,[37,38] are poorly synchronized[32,39] and unequal[29-31,40,41] as compared to healthy controls. It seems that neurological recovery, even if occurring, is rarely complete and an even larger portion of survivors may depend on using compensation strategies to deal with residual impairments.

In favor of this notion, few longitudinal studies did show that standing balance improves in many patients *without* any concomitant improvements in anticipatory control of most-affected leg muscles in response to rapid arm movements,[34,42] or *without* restitution of symmetric exertion of corrective COP movements during unperturbed quiet stance.[2,30,40] However, these studies did unfortunately not start in the first weeks and assessed subjects at only few, arbitrary time-points, leaving longitudinal associations with neurological recovery entirely underexplored.

As it remains unknown *how* stroke survivors 're-learn' to maintain standing balance in the early recovery phase when motor functions at the hemiplegic side improve, there is a need for early-started longitudinal research incorporating sensitive measures of task performance next to clinical scales. These studies may eventually progress our understanding of *how* spontaneous neurological recovery contributes to the re-acquisition of bipedal balance skills early after stroke onset.

Objectives

In the current manuscript, we describe an observational cohort study that aims to prospectively investigate the time course of recovery of quiet stance balance control in the first 12 weeks after a first-ever hemispheric stroke. The relatively low functional demands of this condition (as compared to perturbed stance or walking) enable us to describe the process of balance skill re-acquisition even in more-severely impaired subjects and in the time window of spontaneous neurological recovery. Simultaneously, we will clinically observe the time course of recovery from lower limb motor impairments to investigate longitudinal associations with this leg's contribution to balance control.

The pre-defined research questions and hypotheses are the following:

1. What is the time course of recovery in the first 12 weeks post-stroke in terms of balance control (a-)symmetries and overall stability during quiet stance? (*i.e.,* project A)

First, we hypothesize that improvements in balance control symmetries towards values seen in healthy controls, as assessed through bilateral posturography (i.e., between-limb synchronization and contribution measures of corrective COP movements), are restricted to the first 5 weeks post-stroke. Second, we hypothesize that an improved ability to maintain a stable standing position following traditional posturographic measures of body sway (i.e., stance stability) may develop beyond the time window and up until 12 weeks post-stroke. As such, these later changes are hypothesized to reflect compensatory body stabilization exerted through the less-affected leg.

2. How are improvements in muscle synergies and ankle strength of the most-affected leg longitudinally associated with this leg's contribution to quiet stance balance control in the first 12 weeks post-stroke? (*i.e.,* project B)

First, we hypothesize that clinical improvements in muscle synergies (i.e., Fugl-Meyer Motor Assessment) and strength (i.e., Motricity Index) at the hemiplegic side are mainly seen within the first 5 weeks post-stroke, in accordance with previous longitudinal studies investigating time-dependent change.[20,23] Second, we hypothesize to find within this time window longitudinal associations between recovery on these scales, particularly independent activation and strength around the ankle joint (*i.e.*, ankle item of the Motricity Index), and improved between-limb symmetry in balance control. This means that clinically observed improvements in motor impairments relate over the first weeks to an improved ability of this leg to contribute to corrective COP movements while standing quietly.

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Methods

The protocols of prospective repeated-measurement studies from which participants will be recruited for this longitudinal investigation are registered online (ClinicalTrials.gov Identifier: NCT03728036; NCT03727919). These studies are designed and executed in adherence to the STROBE statements and were approved by the local Ethics Committee of the Antwerp University Hospital (Edegem, Belgium) in accordance with the declaration of Helsinki (main ethics committee protocol number: 18/25/305; Belgium trial registration number: B300201837010). The responsible ethics committees of all other involved clinical sites were asked for advice and additional approval before the study started.

Participants

In total, this study will include a cohort of 60 patients after a first-ever hemispheric stroke of ischemic or hemorrhagic cause within, at most, 3 years of recruitment. This cohort will be recruited from the stroke units at the University Hospital Antwerp (Edegem, Antwerp, Belgium), the GZA Hospital campus St Augustinus (Wilrijk, Antwerp, Belgium) and the General Hospital Geel

(Antwerp, Belgium). All cooperating hospitals are located in the larger Antwerp region in Flanders, Belgium.

Stroke survivors will be screened and asked to participate as soon as possible and within the first 3 weeks after stroke onset. Only survivors who are, or will be admitted to one of the involved rehabilitation facilities (RevArte, Edegem, Antwerp, Belgium or the rehabilitation hospital Geel, Geel, Antwerp, Belgium) for inpatient treatment (eventually followed by outpatient treatment) are considered for inclusion, as the repeated measurements will be performed there. In addition, ten middle-aged (i.e., 45 to 65 years) healthy adults (gender equally distributed) with no known musculoskeletal or neurological injury or illness that may affect balance control will be recruited to serve as controls for the interpretation of posturographic measures.

Before entry, an information brochure about the study's aim, content, and potential risks, together with information about the investigators is provided to each prospective subject (and if adequate to her/his family). If the subject feels sufficiently informed and agrees to participate, an informed consent is signed, and eligibility is determined according to the following criteria:

Inclusion Criteria

- A first-ever, CT- or MRI-confirmed, supra-tentorial stroke in the anterior or middle cerebral arteria territory of ischemic or hemorrhagic cause;
- Impaired motor functions of the lower limb, defined as a score of > 0 on the NIHSS item 6 (i.e., at least "drift of the leg within 5 s without a fall") within 3 days after stroke onset (or self-reported if data is missing), and a MI-LE score of ≤ 91 (i.e., at least "movement against resistance but weaker" in one item) at the moment of inclusion;
- Age between 18 and 90 years;
- Sufficient motivation to participate.

Exclusion criteria

- Dependent in daily life activities before stroke onset, defined as a pre-morbid Functional Ambulation Category score of < 4 and a modified Rankin Scale score of > 1;
- Having a preexisting orthopedic or neurological condition that affects motor functions of the lower limbs and/or standing balance control;
- Severe cognitive or communication deficits that may hinder informed consent and execution of the study;

- Not Dutch, German or English speaking prior to the stroke incident.

Design

The current recovery study is a non-interventional observational study meaning that no systematic interventions are applied next to usual care. For the duration of inpatient rehabilitation, this consists of 30- to 60-min sessions of physical and occupational therapy each workday following local guidelines.

After eligible subjects are included within the first 3 weeks post-stroke, serial measurements will be scheduled at 3, 5, 8, and 12 weeks post-stroke. Clinical evaluations are performed by the same assessor for each participant to decrease the effect of inter-rater variability when measuring change within subjects. In total, two physical therapists are available for clinical testing who underwent a training period to standardize assessment procedures prior to the study start.

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As soon as subjects are able to stand independently barefoot over at least 30 s, bilateral posturography will be performed during a standardized quiet stance task. For this purpose, either two separate force-plates (Type OR 6-7, AMTI, MA, USA; measurement frequency 1 kHz) arranged in a side-by-side configuration as part of a stationary movement analysis laboratory (*M²OCEAN*, University Hospital Antwerp, Edegem, Belgium) or a portable pressure-plate system (0.5m footscan 3D, RS Scan, Belgium; measurement frequency 500 Hz) will be used. This provides the advantage of executing this study in multiple (clinical) settings to facilitate recruitment and continuous data acquisition. Importantly, repeated within-subject measurements are always performed with the same equipment and these measurements are performed by a trained physiotherapist who is educated in using the measuring instruments.

Data collection and processing

During the uptake procedure, the participant's demographics including sex and age together with information about the stroke lesion in terms of type (i.e., infarct or bleeding) and side (i.e., left or right hemisphere affected) is collected. Length of stay in the rehabilitation hospital and discharge destination will be recorded throughout the study.

Before each balance assessment, the subject's body weight and length are measured. Next, the subject's bare feet will be positioned in parallel with an 8.4 cm heel-to-heel distance and in a 9° toe-out angle on the measuring plate.[40] Manual support will be provided during standing up until the subject feels comfortable to stand independently. Now, the subject is instructed to maintain this position for 40 s with the arms alongside the trunk and the eyes open. They are asked to look straight ahead at a visual target at an approximately 2-m distance. Subjects are encouraged to adopt a spontaneous, stable posture rather than standing as symmetric as possible. Three trials will be performed and if the subject got distracted, lost balance or moved the arms or head in a way that is not related to balance, the trial is excluded.

From each eligible trial, the first 10 s will be removed to prevent the influence of starting effects. Previously it was shown that 30 s quiet stance registrations yield excellent test-retest reliability.[43] Limb-specific COP trajectories will be calculated based on raw force components and low-pass filtered using a zero-lag, second-order Butterworth filter with a 10 Hz cutoff frequency. For the calculation of synchronization and contribution measures, these trajectories will be split into an anteroposterior (AP) and mediolateral (ML) signal based on the orientation of the feet by rotating the reference system. The COP underneath both feet combined will be used to estimate overall stance stability. For this purpose, we focus on velocity parameters as these are shown to have greatest reliability[44,45] which has been confirmed for bilateral posturography in stroke survivors.[46] These studies also show that usually two to three trials are sufficient to reach reliable outcomes[45,46] which is of relevance for this project since instability is pronounced early after stroke allowing to acquire only few standing attempts. All data processing (and parameter calculation, as documented below) will be done by using custom-made Matlab scripts (The MathWorks Inc., MA, USA).

Outcomes

Post-stroke recovery is a complex matter and the inconsistent use of terminology in the literature creates opportunities for confusion. Therefore, we first define the chosen outcome variables following the ICF framework (see Figure 1) and differentiate between dependent and independent variables for subsequent analyses.

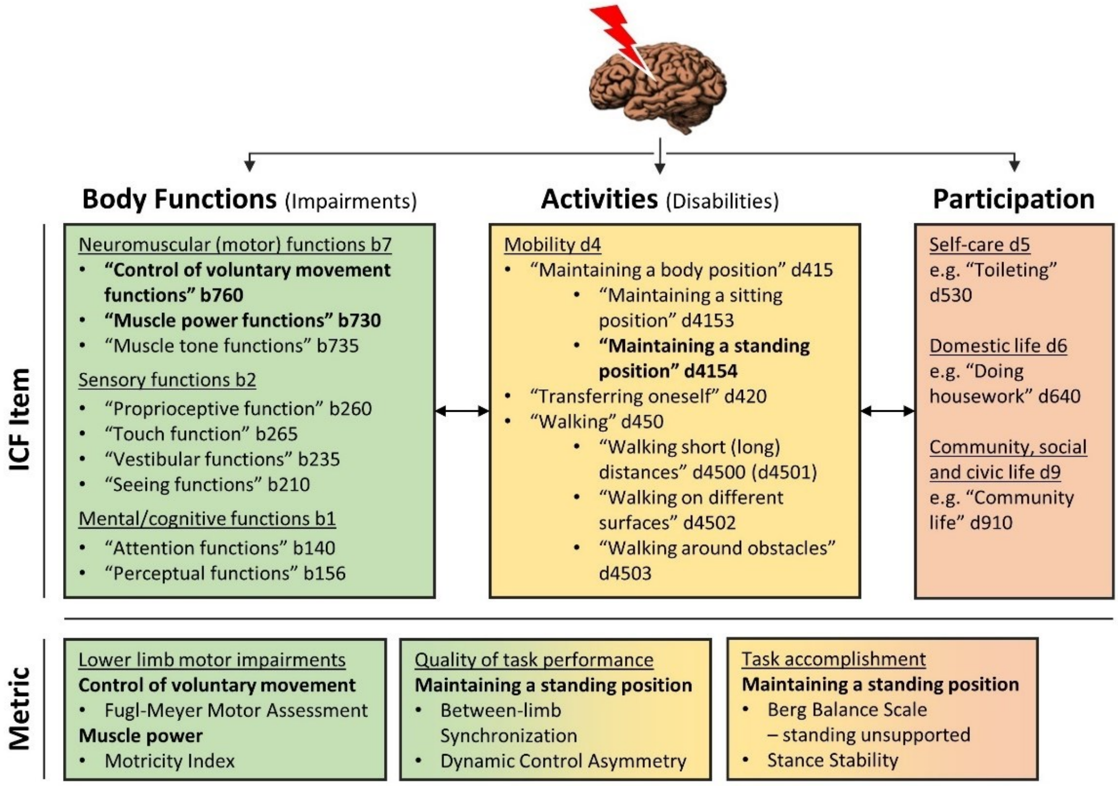

Figure 1. ICF model. The upper panel provides an overview of ICF items that are required for (i.e., level of body functions, colored green) and dependent on (i.e., level of activities, colored yellow, and participation, colored red) standing balance control. The items that are directly assessed in the current study are highlight in bolt. In the lower panel metrics corresponding to these items of interest are provided. The color-coding indicates that metrics of quality of task performance and task accomplishment are both primarily situated on the level of activities, whereas the first indicates how movement execution functions (i.e., level of body functions) are assembled to execute a balance task. Contrary, task accomplishment means if a subject is successful in maintaining standing balance, irrespective of the underlying control strategy, as a determinant of independence in daily life activities and participation (i.e., level of participation).

Independent variables of outcome

The main independent variables for modelling longitudinal associations with balance control measures (i.e., project B) are time-dependent, or dynamic, and situated on the ICF level of body functions. On this level, recovery means the restitution of rudimental functions of movement execution,[19,35] such as synergy-dependency and strength which we define as follows.

Dynamic variables

Although different definitions and constructs of muscle synergies exists in the literature,[47] we refer to synergies as the clinical phenomenon of "pathological intralimb synergies" meaning the loss of independent joint control leading to the emergence of stereotypical flexor and extensor movements (i.e., ICF item b760 "Control of voluntary movement functions").[48] As such, muscle synergies are defined as an "increased co-activation between muscles in the paretic limb that can be elicited voluntarily".[48] Second, muscle strength is defined as the ability to produce a "maximum voluntary force or torque" through a muscle or muscle group contraction around a single joint (i.e., ICF item b730 " Muscle power functions").[49] The following standardized clinical scales will be used to address these functions.

- **Fugl Meyer motor assessment – lower extremity (FM-LE)**: Muscle synergies will be assessed by means of scores on the FM-LE, ranging from 0 (i.e., unable to move the limb or evoke tendon reflexes) to 34 points (i.e., able to selectively flex the knee and ankle joint in standing and normal reflexes). This scale has been reported to have excellent inter-rater (Pearson's r = 0.96;[50] ICC = 0.91, 95% CI [0.97; 1.0][51]) and intra-rater reliability (ICC = 0.99, 95% CI [0.91; 1.0][51]) when assessed in stroke survivors. Moreover, we use the standardization method of See et al.[52] to improve scoring consistency.
- **Motricity Index – lower extremity (MI-LE)**: Muscle strength in hip flexion, knee extension and ankle dorsiflexion direction will be assessed with the MI-LE. Active range of motion and force against manual resistance will be compared between both sides and evaluated with scores varying between 0 (i.e., no voluntary muscle contraction) and 33 points (i.e., full movement against gravity and equal strength) for each item. This scale has shown excellent intra-rater (ICC = 0.93, 95% CI [0.84; 0.97][53]) and inter-rater reliability (Spearman's r = 0.87[54]) in stroke survivors.

Fixed variables

Fixed, or time-dependent variables that are hypothesized to be potential confounders will be used as additional covariates. This includes the subjects' age and gender at inclusion, as well as their Body Mass Index (BMI). Body weight is serially assessed at each occasion and if significant fluctuations are seen over time, the BMI may be added as a dynamic variable. In addition, the stroke type and side will be added. Lastly, the used equipment for serial subject-specific measurements will be evaluated as a potential confounder.

Domain/measure	Measurement occasions (time post-stroke) < 3 weeks (inclusion)	3 weeks	5 weeks	8 weeks	12 weeks
Uptake procedure					
Informed Consent	X				
Independent variables: Potential covariates/confounders					
Demographics: Sex (m/f/x), Age (years)	X				
Lesion characteristics: Type (infarct/bleeding), Side (left/right hemisphere)	X				
Anthropometrics: Body Height (mm), Body Weight (kg)*,	X	X*	X*	X*	X*
Other: Equipment (force-plates/pressure-plate)	X				
Independent variables: Body functions level - Motor impairments of the lower limb					
Fugl Meyer assessment – lower extremity		X	X	X	X
Motricity Index – lower extremity		X	X	X	X
Dependent variables: Activity level - Quality of task performance					
Between-limb synchronization		X	X	X	X
Dynamic control asymmetry		X	X	X	X
Dependent variables: Activity level - Task accomplishment					
Berg Balance Scale – standing unsupported item		X	X	X	X
Stance stability		X	X	X	X

Table 1: Measurements per assessment occasion. A scheme of the obtained metrics and items per assessment occasion is presented. Note, body weight (as marked with *) is the only potential additional covariate that is considered time-dependent and is therefore assessed at each follow-up occasion.

Dependent variables of outcome

Dependent variables of outcome will be investigated in this study on the time course of recovery (i.e., project A) and longitudinal associations (i.e., project B). These outcomes are situated on the ICF level of activities where recovery comprises a general improvement in the ability to execute purposeful movements in a task context.[19,35] In the current study, the task of maintaining a quiet standing posture (i.e., ICF item d4154) will be evaluated which is defined as "the ability to control the body's center-of-mass relative to the base of support in fairly predictable and non-changing conditions".[55] For this purpose, we use and distinguish metrics addressing the quality of performance from those showing the mere accomplishment on this task.

Quality of task performance

Quality of task performance is “defined through a direct comparison of a patient’s motor execution of a task […] to able-bodied control subjects”.[35] This means that the closer the movement matches those seen in controls, the better the quality. With regard to standing balance, quality of performance is best reflected by measures that establish the (a)symmetry between the most- and less-affected sides considering that healthy balance control is characterized by equal output generated through the legs in the form of corrective COP movements.[39,56,57] For this purpose, synchronization and contribution measures will be calculated that show how well both limbs act together[32,39,56] and are equally involved[31,57] in maintaining standing balance. As COP in the ML direction is less meaningful for bipedal balance control,[56] we focus on the sagittal plane.

- **Between-limb synchronization:** Between-limb synchronization is a measure of the temporal structure and similarity between bilateral COP.[39,56] For this purpose, the mean position is subtracted from left and right AP COP trajectories and, next, a cross-correlation at zero-phase leg on a frame-by-frame basis is calculated. This measure therefore shows how well COP displacements are alike, or synchronized.
- **Dynamic control asymmetry (DCA)**: DCA is a symmetry index of the root mean square (RMS) of the AP COP velocities for each leg separately.[31,57] A score of zero indicates equal contribution of both legs to balance control and positive or negative values indicating a relatively larger involvement of the less- or more-affected leg, respectively.

Task accomplishment

Metrics on task accomplishment are designed to show if a patient re-acquired the ability to complete the task irrespective of the underlying control strategy. With regard to standing balance, this is exemplified by, first, the level of independence following clinical scales and, second, by traditional posturographic measures of body sway that show how well a subject can stabilize their center-of-mass within the base of support. Therefore, these outcome variables will be used to address the process of regaining and optimizing the ability to maintain standing balance, respectively, regardless of underlying asymmetries.

- **Berg Balance Scale – standing item (BBS-s)**: The BBS-s assesses the ability to maintain a quiet standing posture without using the arms or support by another person. A score is assigned based on the level of independence needed to complete this task, where a score of 0 indicates no standing ability and a score varying between 1 and 4 indicate independent stance over 30 s to 2 min. The BBS has been reported to have excellent internal consistency as reported by a systematic review.[58]
- **Stance stability**: To investigate overall stability when subjects attempt to stand quietly, we will calculate the root mean square (RMS) velocity of the net COP (i.e., combining two feet together without correction for feet orientation) in AP and ML direction. As the position of the net COP and the vertical representation of the body's center-of-mass correlate,[59] these metrics reflect the ability to maintain a standing position with minimal sway.

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Data analysis

Descriptive analysis

Subjects' demographics at baseline together with lesion characteristics will be descriptively analyzed. The length of stay in the inpatient rehabilitation facility and discharge destination will be reported. In addition, adherence to the study protocol will be illustrated by reporting the number of subjects leaving the study prematurely and reasons for dropping out entirely or missing assessments. We will use the BBS-s to show how soon subjects recovered standing balance and were able to participate in posturographic assessments.

Statistical analysis

Project A

In project A, we aim to investigate time-dependent changes in metrics of quiet stance balance control. To estimate how each parameter is changing as a function of time post-stroke, we use a random coefficient analysis (or mixed model analysis) with "TIME" of measurements as the main fixed effect (JMP Pro, version 15). Additionally, time will be entered as an independent covariate in form of an subject-specific slope (*i.e.,* the interaction term "SUBJECTxTIME") to adjust for dependency of repeated observations. However, the greatest advantage of this method is its flexibility in dealing with missing values. The latter may result from subjects being unable to stand at first occasions, being unavailable due to hospital discharge or transfers, or by no longer corresponding to eligibility criteria for example due to a recurrent stroke or other sudden medical condition (potentially) affecting outcome variables. Moreover, the value on the addressed metric at 3 weeks post-stroke will be added to account for inter-subject variability.

In addition, fixed covariates that are hypothesized to be potential confounders will be entered in the model. This includes “SEX”, “AGE” and “BMI” considering their influence on standing balance control (i.e., females and elderly tend to show greater body swa [60] and obesity is associated with instability[61]). Second, stroke “SIDE” and “TYPE” will be added, as right-sided lesions typically result in greater balance deficits[62] and subjects with hemorrhagic strokes may display delayed recovery.[63] Lastly, “EQUIPMENT” is added as a potential confounder considering technical variations in measuring instruments.

Statistical analysis of the difference in each measure of quiet stance balance control between subjects and healthy controls will be performed using the Mann-Whitney U test for each measuring system separately.

Project B

After describing the recovery time course, we aim to investigate longitudinal associations between motor impairments in terms of leg muscle synergies (i.e., FM-LE) and ankle strength (i.e., ankle item of the MI-LE) serving as independent variables, and the DCA which is the dependent variable. First, we analyze the pattern of neurological recovery following these clinical scales by using similar methods as outlined above. Second, we will apply a recently discussed hybrid model[64] to investigate longitudinal associations over the first 12 weeks post-stroke. This method has the advantage of disentangling the *between*- and *within*-subject effects of this relation.

For all statistical tests, the likelihood ratio test will be used to examine the need to enter random effects into the model and the Wald test will be used to obtain *P* values for regression coefficients in the final model. A 2-tailed significance level of 0.05 will be used for all analyses.

Sample size justification

To the best of our knowledge, this is the first study to prospectively investigate changes in the variables over time early after stroke. This certainly limits the effectiveness of a sample size determination based on a power analysis. Therefore, we determine and justify our sample size of N=60 based on recruitment (2.2 participants/month) and drop-out (15%) rates as seen during the first year of recruitment. Considering that we will include not more than 3 to 4 (main) covariates in our random coefficient and hybrid models, we meet the *rule of thumb* saying that 10 subjects per variable are sufficient to perform bivariate and multivariate regression analyses.

Trial status

Participant recruitment began in January 2019 in the University Hospital Antwerp and the RevArte rehabilitation hospital, in the GZA Sint-Augustinus hospital in April 2019 with a temporal suspension of recruitment in all involved sites between March and September 2020 due to COVID-19 measures. In response, an additional partnership with the General Hospital Geel in January 2021 was set-up. By now (October 2021), 52 stroke survivors were recruited indicating feasibility of reaching the desired sample size within the proposed recruitment period.

Discussion

In this manuscript, we describe the design of an ongoing observational study with repeated measurements in time. This study aims to prospectively investigate individual recovery trajectories in a cohort of 60 mild-to-severely impaired subjects early after a first-ever, ischemic or hemorrhagic, hemispheric stroke. Bilateral posturography will be used to measure balance control asymmetries and overall stability during a quiet stance task to investigate the time course of recovery following these posturographic measures within subjects (project A) and, subsequently, longitudinal associations with recovery of lower limb motor impairments (project B). The knowledge gained through this study may contribute to our understanding of how progress of time as a reflection of spontaneous recovery contribute to regaining standing balance control through the most-affected leg, as well as dependency on compensatory stabilization exerted through the less-affected leg.

Time course of lower limb recovery

Recent upper limb recovery studies[65,66] attest to the effectiveness of incorporating sensitive and specific task performance measures into longitudinal research. Based on repeated kinematic measures of a reaching task, it was shown that recovery of movement quality with the hemiplegic arm plateaus in most patients over the first 5 weeks post-stroke.[65,66] This suggests that further task improvements are most likely explained on the basis of compensatory mechanisms, such as increased trunk movements to assist arm and hand transport.[19] If assuming that neurological recovery regarding the upper and lower limb develops in parallel, as suggested by previous clinical research,[20,22,23] a similar distinct time window of behavioral restitution of standing balance control through the most-affected leg might be expected.

Previous posturographic studies already showed that the DCA shows little tendency to diminish over inpatient rehabilitation,[40] resulting in a poor contribution of the most-affected leg to balance control.[29,31,32,41] Acknowledging that recovery of standing balance may extend far beyond the first weeks - improvements are seen in response to specific training even in the chronic stage[67] - it seems that learning to compensate with the intact leg drives the reacquisition of functional balance skills after stroke. In favor of this notion, few longitudinal studies report consistent improvements over the first months in timed muscle activation with the less-affected leg to effectively correct balance after perturbations.[34,42,68] Simultaneous changes at the hemiplegic side are often absent. However, how progress of time contributes to the relative involvement of the most-affected limb to balance control and, consequently, when such compensation needs to emerge has hardly been investigated early after stroke. This makes project A of the current study unique.

Mechanisms underlying recovery of standing balance control

When standing, even smallest movements of the body must be corrected to avoid excessive sway and eventually a fall. As such, fine motor control is demanded for effective balance control. However, balance-related leg muscle activation is often disturbed after stroke. Abnormal intralimb coordination patterns[68,69] and delayed muscle onset[34,42,68] characterize reactive balance control through the hemiplegic leg, and interlimb muscle activity about the ankle joints is poorly synchronized[11,32,39] and unequal exerted[2,29-31,40] during unperturbed stance. What determines poor muscle control as seen during balancing tasks is unknown but may involve synergy-dependency.[30,31]

Already in 1951, Twitchell showed based on meticulous clinical observations that regaining control over the hemiplegic limb goes through synergy-dependent stages.[48] This is later confirmed by longitudinal studies[20,22,23] showing progressively increasing scores on the FM-LE over the first 5 weeks post-stroke. One might suspect a relationship between such clinical gains and an improved ability to execute functional movements with this leg, but this has been investigated cross-sectionally only with regard to standing balance.[30-32] Although a relation was suggested, it is considered weak.[31,32] It was recently even shown that patients with near normal scores on the FM-LE may still show considerable control asymmetries.[31] Although speculative, one may suggest that subtle fine motor control impairments go undetected by these scales, while it remains entirely unknown how this relation develops early after stroke. Since this knowledge has implications for rehabilitation practice, project B can be regarded as being innovative and of clinical relevance.

Clinical and scientific significance

It is important for rehabilitation clinicians to distinguish improved standing balance resulting from behavioral restitution of the most-affected limb and compensatory stabilization through the less-affected limb. Historical treatment concepts strive to restore normal movement patterns,[70] and even recent therapies such as feedback-based balance training involve teaching patients to stand as symmetric as possible.[71] This might be questioned acknowledging that many stroke survivors seem unable to restore symmetric balance control.[31,40] These patients may even benefit from some asymmetric loading to make corrective COP movements at the less-affected side more effective.[57] From this perspective, the knowledge gained through this study may further direct how stroke survivors should be trained early onwards. This may eventually result in faster reaching of independence in daily life activities to enable patients to engage as early as possible in more intensive, semi-supervised therapies[72] and supported discharge.[73]

However, implications may go far beyond clinical rehabilitation practice alone. An improved understanding of recovery that distinguishes behavioral restitution from compensation will contribute to the design of rehabilitation devices as well as development of sensitive measurements of quality of movement. The latter will improve future trial design regarding the choice of outcome measures.[16] Specifically, addressing effectiveness of novel behavioral and pharmacological treatments based on such measures is warranted.[35] Moreover, interpretation of neuroimaging may greatly benefit from this knowledge. Current literature argues the importance of knowledge about the associations between behavioral improvements and changes in brain activity and connectivity,[35] yet the neural correlates of behavioral restitution remain so far unknown.

Study limitations

The study described in the current report also has some limitations. Although the number of participants that will be included in the current study is greater as compared to previous prospective balance recovery studies[30,34,40,42,68] (ranging between N=13[68] to N=37[40]), the desired sample size is limited. Second, since we use one specific balance condition it is not possible to determine whether results can be generalized to other balance tasks. Recent literature suggests that increasing challenges may reduce the degree of asymmetry in bipedal balance control[74] and balancing in everyday life environments requires rather reactive control skills.[11] The results may therefore not fully capture the upper boundary of neurological recovery at the hemiplegic side and translation to dynamic balance conditions remains unknown. However, incorporating more-challenging paradigms may lead to a greater amount of missing values since many subacute patients with hemiparesis are not able to safely withstand perturbations when standing[34,42] or perform dynamic tasks such as walking[75] until several weeks after stroke. Third, repeated measurements were performed with either force-plates or a mobile pressure-plate system. This enables us to perform measures in various settings and recruit more broadly. However, while both systems can extract bilateral COP profiles, technical variations differ. To control for this, focus lies on within-subjects time series analyses and, additionally, we will add “EQUIPMENT” as a covariate to our regression models. Fourth, measurements are restricted to the first 12 weeks. Yet, it might be of interest to further continue measurements acknowledging that few studies revealed that about 15% of survivors improve[76] and 25% will deteriorate beyond the first 6 months.[77] Lastly, the study did not monitor the type and amount of therapy provided to each participant and we are unable to correct for these factors. The lack of using uniform guidelines for stroke rehabilitation in Flanders, Belgium could lead to differences in how subjects are treated in cooperating facilities. Moreover, mildly affected subjects may be discharged earlier and receive less intensive outpatient therapy afterwards. However, evidence that current rehabilitation interventions impact neurological recovery is still lacking,[17,78] particularly if provided as part of standard care which is low-dosed.[79,80] Since usual care has not been systematically modified, differences in rehabilitation treatment are expected to have a limited impact on outcomes of the current study.

CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHORS CONTRIBUTION: *JS, ST* and *WS* participated in the planning and initial conception of this study. *GK* and *LY* participated in further conceptual work and designing the study. *JS* is responsible for the study process and day-to-day study management under guidance of *WS*. *JS* wrote the initial manuscript. All authors were involved in drafting the manuscript and have approved the final version for publication.

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3

CHAPTER 4

4

RECOVERY OF QUIET STANDING BALANCE AND LOWER LIMB MOTOR IMPAIRMENT EARLY POST-STROKE – HOW ARE THEY RELATED?

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ABSTRACT

Background: Recovery of quiet standing balance early post-stroke has been poorly investigated using repeated measurements.

Objective: To investigate (1) the time course of steady-state balance in terms of postural stability and interlimb symmetry, and (2) longitudinal associations with lower limb motor recovery in the first 3 months post-stroke.

Methods: Forty-eight hemiparetic subjects (age: 58.9±16.1 years) were evaluated at weeks 3, 5, 8 and 12 post-stroke. Motor impairments concerned the Fugl-Meyer assessment (FM-LE) and Motricity Index total score (MI-LE) or ankle item separately (MI-ankle). Postural stability during quiet two-legged stance was calculated as the net center-of-pressure area (COP_{Area}) and direction-dependent velocities (COP_{Vel-ML}, COP_{Vel-AP}). Dynamic control asymmetry (DCA) and weight-bearing asymmetry (WBA) estimated interlimb symmetries in balance control and loading. Linear mixed models determined (1) time-dependent change and (2) the *between*- and *within*-subject associations between motor impairments and postural stability or interlimb symmetry.

Results: Time-dependent improvements were significant for FM-LE, MI-LE, MI-ankle, COP_{Area}, COP_{Vel-ML} and $COP_{Vel-AP,}$ and tended to plateau by week 8. DCA and WBA did not exhibit change. *Between*-subject analyses yielded significant regression coefficients for FM-LE, MI-LE and MI-ankle scores with COP_{Area}, COP_{Vel-ML} and COP_{Vel-AP} up until week 8, and with WBA until week 12. *Within*-subject regression coefficients of motor recovery with change in COP_{Area}, COP_{Vel-ML}, COP_{Vel-AP}, DCA or WBA were generally non-significant.

Conclusions: Postural stability improved significantly in the first 8 weeks post-stroke, independent of lower limb motor recovery at the most-affected side *within* subjects. Our findings suggest that subjects preferred to compensate with their less-affected side, making interlimb asymmetries in balance control and weight-bearing invariant for change early post-stroke.

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Introduction

Regaining steady-state balance during quiet standing is mainly achieved within the first 3 months post-stroke[1,2] and is a prerequisite for accomplishing independent gait and most activities of daily life.[2-4] Despite its clinical importance, a limited number of observational studies have investigated how lower limb motor recovery associates longitudinally with steady-state balance improvements within this time window.

A few longitudinal studies[5-9] have suggested that lower limb motor recovery follows a proportional and predictable time course in the first 3 to 6 months post-stroke. This includes clinical improvements in synergistic-independent motor control,[5,7-9] as measured with the Fugl-Meyer lower extremity motor score (FM-LE), and strength,[6,7] as measured for example with the Motricity Index (MI-LE). These findings corroborate observations of the upper limb,[5,7,10] as significant improvements occur in most patients up until week 5[5,6] to 8[7] post-stroke, and a small proportion (10-15%) fail to show any motor recovery.[8]

At the same time, steady-state balance control remains deficient after independent stance is regained, with stroke patients exhibiting greater postural sway of the net center-of-pressure (COP) than healthy controls and loading more body weight on the less-affected leg.[11-13] More recent posturographic studies[14-16] examined the individual-limb COP trajectories to show that this weight-bearing asymmetry (WBA) is further characterized by an asymmetric exertion of stabilizing ankle torques. This so-called dynamic control asymmetry (DCA) reflects the most-affected leg's contribution to balance control in the sagittal plane, relative to the less-affected side.[14,16] It has been suggested that the DCA is associated with impairment severity,[17] although Roelofs et al[16] have recently shown that even patients with (almost) complete FM-LE recovery may still exhibit significant balance control asymmetries favoring the less-affected leg. How this relationship develops *within* subjects over the first weeks after stroke is currently unclear.

To investigate the quality of movement regarding steady-state balance post-stroke, the literature[15,17] recommends complementing conventional instability measures, such as the net COP sway area (COP_{Area})[12,13,17] and velocities in frontal ($COP_{Vel\text{-}ML}$) and sagittal planes ($COP_{Vel\text{-}AP}$),[14,16] with metrics that reflect asymmetries, such as DCA and WBA. These metrics may yield different, yet complementary information about how an improved postural stability is achieved in patients with hemiparesis, by distinguishing “normalization” of interlimb symmetry from persistent compensatory stabilization through the less-affected leg, in reference to a control population of healthy adults.

So far, very few attempts have been made to implement such metrics in stroke recovery studies[11,18,19] and an earlier study by De Haart and colleagues[14,17] investigated recovery using repeated measurements at arbitrary time-points, often beyond the period in which the recovery of muscle synergies and strength plateaus. According to this knowledge gap, the overall aim of the present observational study was to prospectively investigate the time course of quiet standing balance in terms of posture stabilization and recovery from interlimb asymmetries early after stroke onset. Subsequently, we aimed to relate these fine-grained task performance changes to motor recovery at the level of the entire lower limb (i.e., FM-LE and MI-LE) and ankle separately (by using the dorsiflexion item of the Motricity Index [MI-ankle]), considering that steady-state balance is mainly controlled through ankle torques.[20] The following research questions were addressed:

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1. What is the time course of muscle synergies (i.e., FM-LE) and strength (i.e., MI-LE and MI-ankle) in the most-affected leg within the first 3 months post-stroke?
2. What is the time course of postural stability (i.e., COP_{Area}, $COP_{Vel\text{-}ML}$ and $COP_{Vel\text{-}AP}$) and interlimb symmetry (i.e., DCA and WBA) during quiet stance within the first 3 months post-stroke?
3. How is the severity of motor impairments (i.e., FM-LE, MI-LE and MI-ankle) associated with postural instability (i.e., COP_{Area}, $COP_{Vel\text{-}ML}$ and $COP_{Vel\text{-}AP}$) and interlimb asymmetry (i.e., DCA and WBA) during quiet stance *between* subjects within the first 3 months post-stroke?
4. How are improvements in motor impairments (i.e., FM-LE, MI-LE and MI-ankle) associated with change in postural instability (i.e., COP_{Area}, $COP_{Vel\text{-}ML}$ and $COP_{Vel\text{-}AP}$) and interlimb asymmetry (i.e., DCA and WBA) during quiet stance *within* subjects over the first 3 months post-stroke?

In line with recovery models of the paretic upper limb,[10] we hypothesized for the first question that significant time-dependent change in FM-LE, MI-LE and MI-ankle would occur within the first 8 weeks post-stroke. For the second question, we hypothesized that steady-state balance would parallel motor recovery and follow the same pattern as previously described for upper limb motor performance.[21,22] Recovery of steady-state balance is here defined as posture stabilization reflected by decreases in COP_{Area}, COP_{Vel-ML} and COP_{Vel-AP}. Concomitant reductions in asymmetries in DCA and WBA in the direction of norm values in age-matched healthy controls are seen as an indicator of an improved quality of movement. For the third question, we assumed that patients with lower FM-LE, MI-LE and MI-ankle scores would exhibit greater postural instability (i.e., COP_{Area}, COP_{Vel-ML} and COP_{Vel-AP}) and asymmetries in DCA and WBA, with an increased involvement of the less-affected leg. Lastly, we hypothesized concerning the fourth question that the *within*-subject associations between recovery of impairments and steady-state balance would be time-dependent. That is, rising FM-LE, MI-LE and MI-ankle scores would associate with reductions in postural instability (i.e., COP_{Area}, COP_{Vel-ML} and COP_{Vel-AP}) and asymmetries in DCA and WBA mainly within the first 8 weeks post-stroke.

Methods

The present longitudinal study is part of the larger TARGEt research project. TARGEt is an acronym for Temporal Analyses and Robustness of hemiplegic Gait and standing balance Early post-stroke, and was funded by the Research Foundation Flanders (FWO, BE; application no. 1S64819N). This project was approved by the Medical Ethics Committee of the University Hospital Antwerp (No. 18/25/305; Belgian trial registration no. B300201837010) and additional approval was obtained from the ethics committees of other hospitals involved. All procedures were conducted in accordance with the Declaration of Helsinki. The design of the study protocol has been reported elsewhere[23] and the protocol is also registered online (ClinicalTrials.gov identifier: NCT03728036). The manuscript was written in conformity with the STROBE statement.[24]

Participants

Patients admitted to one of the three cooperating hospitals and two rehabilitation facilities (Antwerp region, Belgium) after an acute ischemic or hemorrhagic stroke were screened for participation between December 2018 and December 2021. Screening and recruitment were performed by the study coordinator (JS) together with the medical doctors and physiotherapists employed at the stroke units and rehabilitation facilities. All participants met the following inclusion criteria: (1) having experienced a first-ever hemispheric stroke confirmed by CT and/or MRI scan; (2) having been included within the first 3 weeks after stroke; (3) having reduced leg strength, defined as > 0 points on item 6a/b of the NIHSS (i.e., at least “drift within 5 s”) within 72 h post-stroke and an MI-LE score < 91 (i.e., at least “movement against resistance but weaker” for one item) at inclusion; (4) age between 18 and 90 years; (5) premorbid independence in daily life activities (i.e., modified Rankin Scale score of 0-1); (6) no severe orthopedic condition of the lower limbs and trunk or another neurological illness present before stroke; (7) no severe cognitive or communicative deficit that may interfere with understanding instructions and study procedures; and (8) providing written informed consent. These criteria were chosen to recruit a cohort of initially hemiplegic patients with some residual motor impairment who require inpatient rehabilitation care.

Additionally, we recruited age- and sex-matched adult subjects without reported history of neurological and/or orthopedic conditions to obtain healthy reference values of interlimb symmetry while standing.

Procedures

In line with recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR),[25,26] serial measurements were scheduled for each participant at weeks 3, 5, 8, and 12 post-stroke. At each time-point, clinical scales were complemented by posturographic measurements of steady-state balance. Two trained assessors (EE, JS) were available to administer clinical scales during face-to-face sessions, while the same observer conducted all serial measurements of individual participants. Posturography was performed by a single assessor (JS) who was trained in operating the measuring instruments. The same measurements were performed once in healthy controls for comparison.

Clinical measurements

During intake, subjects’ sex, age, stroke type (i.e., ischemic or hemorrhagic) and most-affected body side (i.e., left or right) were recorded. Serial follow-up measurements included, first, the “standing unsupported” item of the Berg Balance Scale (BBS-s) to determine if subjects were eligible for posturography. Second, impairments in synergistic-depended motor control and strength were evaluated at the most-affected side using the FM-LE[5] and MI-LE,[27] respectively. Synergy was defined as a pathological pattern of muscle co-activation occurring with voluntary movement, referring to the clinical phenomenon of “abnormal muscle synergies”.[28,29] The FM-LE (0-34) is valid and highly reliabile,[30] and we used a standardization method developed by See and colleagues.[31] The MI-LE (0-99) was administered by asking subjects to produce a maximum voluntary hip flexion, knee extension and ankle dorsiflexion against resistance. The MI-LE is valid and reliable.[27] We treated the MI-ankle as a separate outcome variable.

Posturographic measurements

The current study investigated steady-state balance defined as "the ability to control the body's center-of-mass (COM) relative to the base of support in fairly predictable conditions and non-changing environments".[32] Accordingly, subjects were instructed to stand quietly on both legs for 40 s with their arms alongside their trunk and their eyes fixated on a non-moving visual target. The bare feet were positioned side-by-side in a standardized way (8.4 cm heel-to-heel distance and 9° toe-out angle) and subjects were asked to stand still without further instructions regarding weight-bearing. Measurements started as soon as patients could stand (i.e., BBS-s > 0) and, if tolerated, three trials were performed with seated resting breaks in between. The first 10 s were removed from each trial.

We used either two laboratory-grade force plates (Type OR6-7, AMTI, MA, USA) or a portable plantar pressure plate (0.5m Footscan pressure plate 3D, RS Scan, Materialize, BE) to record ground reaction forces in- or outside the lab environment. The collected raw force data was converted to the net and individual-limb COP trajectories (appendix B, force data acquisition and COP calculations) which were low-pass filtered with a 10 Hz second-order Butterworth filter. Comparability of the two instruments for measuring COP was assessed in advance in healthy controls during vision-deprived stance, yielding high consistency according to Pearson correlation coefficients, yet significant mean differences (appendix A, comparability analyses). To account for these systematic differences, serial *within*-subject measures were always performed with the same type of plate, while *between*-subject variations explained by the choice of measurement instrument were corrected by entering INSTRUMENT as an additional covariate in the final analyses (appendix A, correction method).

To align the individual-limb COP with the anatomical ankle position, the coordinate system was rotated. As subjects may experience difficulties with maintaining the standardized position, the actual feet orientation was determined trial-by-trial with motion capturing (Vicon Motion Systems Ltd, UK) during force plate measurements, or by the plantar pressure distribution (Footscan, RS Scan, Materialize, BE). The AP axis was defined by a line drawn between the head of the second metatarsal bone and the heel, and the ML axis perpendicular to it.

Performance measures of steady-state balance

To quantify postural stability, we first calculated the COP_{Area} by fitting an ellipse in mm^2 that encloses about 85% of the entire signal, using principal component analysis.[33] This metric served as a general stability index by estimating the total amount of postural sway. Second, the root mean square of the AP- and ML-COP velocities ($COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$; in mm/s) served as estimates of the global balance control efficacy in specific sway directions.[14,16]

Quality of movement was operationally defined by comparing stroke subjects' task performance directly with that of healthy controls.[34] That means, the better they were able to achieve postural stability with equal contributions by both limbs, the higher their movement quality.[23] To estimate how the stabilizing mechanism of ankle torques in each leg contributed to balance control, we calculated the DCA in percentage as a symmetry index of the individual-limb $COP_{Vel\text{-}AP}$.[14,16] It is restricted to the sagittal plane, since ankle torques are less relevant to frontal plane balance.[20] A score of 0% estimates symmetry. Positive and negative values reflect greater contribution of the less and most-affected leg, respectively. WBA was calculated by dividing the average F_Z below the most-affected leg by the total F_Z (i.e., body weight), to establish a subject's preferred stance. A value of 50% was distracted from WBA, such that 0% means symmetry comparable to DCA. Posturographic outcomes were averaged over three (or at least two) successive trials per session to maximize reliability.[35]

Statistical analyses

To investigate time courses (questions 1 and 2), we first plotted individual time-series of the outcome variables FM-LE, MI-LE, MI-ankle, COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$, DCA, and WBA to observe trends in recovery. Next, for each outcome variable, a multivariable linear mixed model was applied, treating the main fixed effect, that of TIME [week 3, week 5, week 8, week 12], as a categorical predictor variable reflecting progress of time after stroke onset. AGE in years, SEX [female, male], AFFECTED SIDE [left, right], and INSTRUMENT [force plates, pressure plate] were included as covariates. A random intercept per subject was added to account for dependency between repeated measurements. Post-hoc analyses involved Tukey's HSD multiple comparison method, yielding regression coefficients (β) for time-dependent change over the entire period (i.e., weeks 3-12) and across each epoch (i.e., weeks 3–5, weeks 5–8, weeks 8–12). DCA and WBA values were statistically compared between stroke and healthy subjects at each time-point using

4

the non-parametric Steel's test for multiple pair-wise comparisons, with the healthy values treated as control. The significance level was set at 0.05.

Question 3 was addressed using linear mixed models, with COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$, DCA, or WBA as the dependent variable, and either FM-LE, MI-LE, or MI-ankle as the independent variable. TIME, AGE, SEX, AFFECTED SIDE and INSTRUMENT were added as covariates with a subject-specific intercept. Sub-analyses included four separate models at weeks 3, 5, 8 and 12. For question 4, the *within*-subject associations were calculated using the same model architecture but using change scores (i.e., Δ) with sub-analyses across the three different epochs. For questions 3 and 4, the final regression coefficient (β) predicts change in COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$, DCA, or WBA for a one-unit increase in either FM-LE, MI-LE, or MI-ankle. Multiple testing was accounted for by using Bonferroni-corrected probability values (i.e., $P < .05/n$).

All models were fitted using JMP Pro (version 16). Histograms and Q-Q plots of residuals were inspected to check model assumptions.

Results

Figure 1 shows a flow chart of the recruitment of subjects and serial measurements. Approximately 250 first-ever stroke survivors were screened during the recruitment period, of which 66 were enrolled for this cohort study. Forty-eight of these subjects participated in at least 2 posturographic measurements and were subsequently included in the analyses. Table 1 shows their main baseline characteristics at 3 weeks post-stroke. As shown, the included subjects had a mean (SD) age of 58.9 (16.1) years, 19 were female, 36 had suffered an ischemic stroke and 25 had left-sided impairments. Ten healthy control subjects were additionally included with a similar mean age of 46.9 (14.1) years and sex ratio (40% female).

As summarized in Figure 1, four measurements were missed at week 3. Out of the 44 subjects that could be tested, 37 were able to stand independently and participated in the posturographic measurement. At week 5, two measurements were missing, and three subjects had too poor balance to perform the posturographic task. At week 8 and 12, five and 12 measurements were missed, respectively. The main reason was unavailability after hospital discharge. As a result, 24 participants could be tested at all four occasions. Fifteen and nine subjects participated in three and two serial measurements, respectively. The mean time after stroke onset (SD, range) and the number of participants whose data was available at each time-point were as follows: 24.88 (1.79, 22-28) days and N=37 for week 3; 38.61 (2.10, 35-42) days and N=43 for week 5; 59.17 (2.16, 55-63) days and N=43 for week 8; 88.18 (3.66, 84-103) days and N=36 for week 12.

Demographics and stroke information (N=48)	
Study subjects	48
Age, years*	58.9 ± 16.1
Sex, female/male	19/29
Body weight, kg*	74.3 ± 13.2
Affected body side, left/right	25/23
Stroke type, ischemic/hemorrhagic	36/12
Instrument, force plates/pressure plate	19/29
Time post-stroke, days*	24.9 ± 1.8
Clinical characteristics (N=44)	
FM-LE score (0-34)*	21.9 ± 7.4
MI-LE score (0-99)*	61.2 ± 23.7
MI-ankle score (0-33)*	18.6 ± 8.8
BBS-s score (0-4)*	2.8 ± 1.5
Posturographic characteristics (N=37)	
COP_{Area} (mm^2)*	302.7 ± 359.8
$COP_{Vel\text{-}ML}$ (mm/s)*	10.0 ± 9.5
$COP_{Vel\text{-}AP}$ (mm/s)*	11.7 ± 9.3
DCA (%)*	44.1 ± 65.8
WBA (%)*	6.6 ± 9.9

Table 1: Subject characteristics at baseline (i.e., 3 weeks post-stroke)

Abbreviations: FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; BBS-s, standing unsupported item of the Berg Balance Scale; COP, center-of-pressure; COPArea, area of the net COP; COPVel-ML, rms velocity of the net COP in the frontal plane; COPVel-AP, rms velocity of the total COP in the sagittal plane; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry.

Values are means ± SD if marked (*), otherwise counts are shown. Demographics and stroke information was collected from all included subjects (N=48) at enrollment. Clinical characteristics were obtained in 44 subjects that could be tested at week 3, of which 37 could stand independently to perform the standardized balance task. Their posturographic baseline characteristics are also shown (N=37).

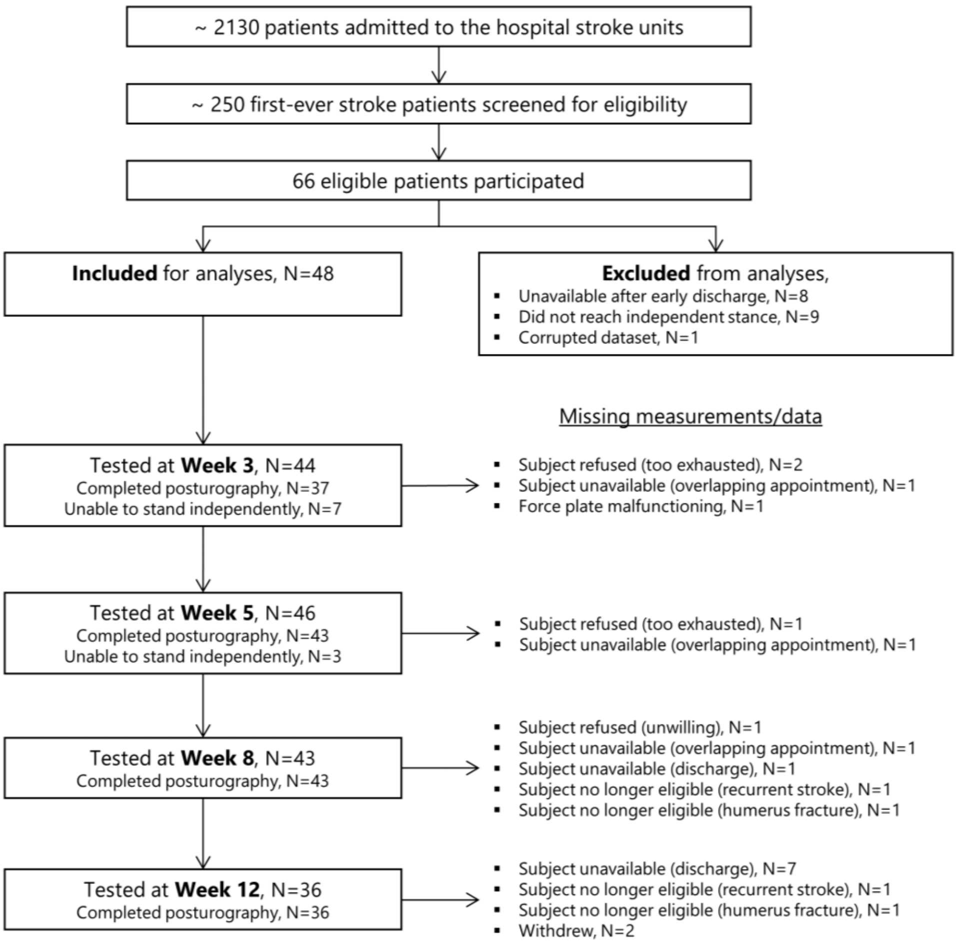
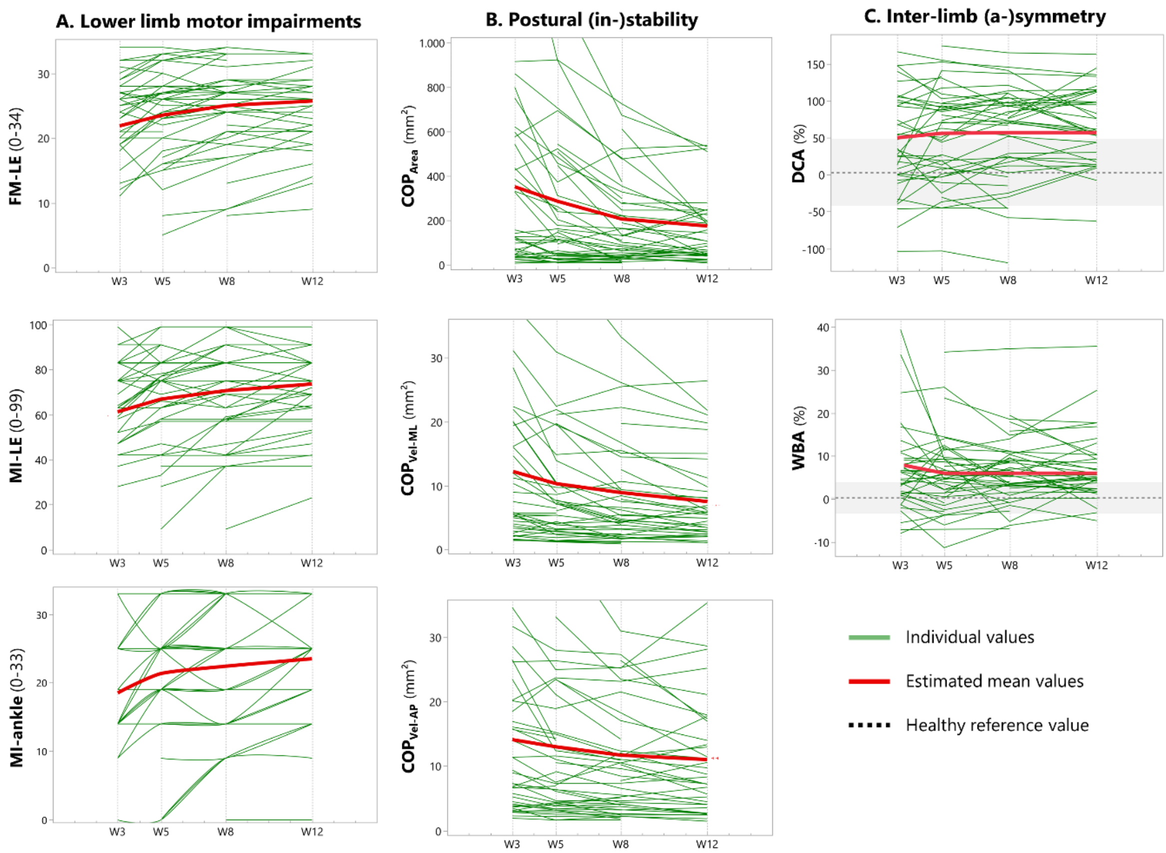


Figure 1. Flowchart of screening, inclusion, and follow-up.

Effects of time on recovery of lower limb muscle synergies and strength

Figure 2A depicts individual and mean time-dependent change in FM-LE, MI-LE, and MI-ankle. TIME was a significant factor ($P < .001$) affecting recovery of FM-LE (β = 3.84, 95%CI [2.58; 5.11], $P < .001$), MI-LE (β = 12.37, 95%CI [7.77; 16.97], $P < .001$) and MI-ankle (β = 4.99, 95%CI [2.92; 7.05], $P < .001$) from week 3 to 12. As further shown in Table 2, significant time-dependent change was found between weeks 3 and 5 for FM-LE (β = 1.66, 95%CI [0.50; 2.82], $P = .002$), MI-LE (β = 5.63, 95%CI [1.43; 9.84], $P = .004$) and MI-ankle (β = 2.83, 95%CI [0.92; 4.71], $P < .001$). A significant increase was also seen for FM-LE between weeks 5 and 8 (β = 1.49, 95%CI [0.36; 2.61], *P* =.004), whereas a non-significant change was found in MI-LE and MI-ankle scores (*P* > .05, Table 2). TIME was not a significant factor from week 8 onwards.



Figures 2A-C: Time-courses of muscle synergies and strength, and metrics reflecting steady-state balance during quiet stance between weeks 3 and 12 post-stroke.

Abbreviations: FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; MI-ankle, Motricity Index ankle item; COP, center-of-pressure; COPArea, area of the net COP; COPVel-ML, rms velocity of the net COP in the frontal plane; COPVel-AP, rms velocity of the net COP in the sagittal plane; DCA, Dynamic Control Asymmetry; WBA, Weight Bearing Asymmetry.

Recovery of lower limb muscle synergies and strength is reflected by changes in FM-LE and MI-LE (A). Quality of standing balance recovery includes, firstly, the postural stability metrics COPArea, COPVel-ML and COPVel-AP, (B) and, secondly, postural symmetry reflected by DCA and WBA (C). Thin green lines show individual time courses; thick red lines show the estimated mean values. The dashed grey line and band show mean DCA and WBA values ± SD of healthy controls as a reference.

		Week 3 - 12	Week 3 - 5	Week 5 - 8	Week 8 - 12
ΔFM-LE	β (SE)	**3.85 (0.46)**	**1.66 (0.44)**	**1.49 (0.43)**	0.70 (0.45)
(0-34)	95% CI	**2.58; 5.12**	**0.50; 2.82**	**0.36; 2.61**	-0.47; 1.86
	P-value	**<.001**	**.002**	**.004**	.408
	% of total change	**100%**	**43.2%**	**38.8%**	18.2%
ΔMI-LE	β (SE)	**12.38 (1.76)**	**5.65 (1.61)**	3.77 (1.57)	2.97 (1.63)
(0-99)	95% CI	**7.78; 16.99**	**1.44; 9.85**	-0.32; 7.86	-1.27; 7.22
	P-value	**<.001**	**.004**	.083	.266
	% of total change	**100%**	**45.5%**	30.5%	24.0%
ΔMI-ankle	β (SE)	**4.99 (0.79)**	**2.83 (0.72)**	1.07 (0.70)	1.09 (0.73)
(0-33)	95% CI	**2.92; 7.05**	**0.92; 4.71**	-0.77; 2.9	-0.81; 3.00
	P-value	**<.001**	**<.001**	.428	.445
	% of total change	**100%**	**56.7%**	21.4%	21.9%
ΔCOP_{Area}*	β (SE)	**-175.0 (33.7)**	-64.6 (31.1)	**-79.8 (30.1)**	-30.6 (31.3)
(mm^2)	95% CI	**-263.0; -87.0**	-145.6; 16.4	**-158.4; -1.2**	-112.3; 51.2
	P-value	**<.001**	.166	**.045**	.763
	% of total change	**100%**	36.9%	**45.4%**	17.7%
$\Delta COP_{Vel\text{-}ML}$*	β (SE)	**-4.71 (0.77)**	**-1.90 (0.71)**	-1.47 (0.71)	-1.34 (0.71)
(mm/s)	95% CI	**-6.73; -2.69**	**-3.75; -0.06**	-3.26; 0.33	-3.20; 0.52
	P-value	**<.001**	**.041**	.149	.244
	% of total change	**100%**	**40.4%**	31.1%	28.5%
$\Delta COP_{Vel\text{-}AP}$*	β (SE)	**-3.14 (0.75)**	-1.12 (0.69)	-1.31 (0.67)	-0.71 (0.69)
(mm/s)	95% CI	**-5.09; -1.18**	-2.91; 0.68	-3.05; 0.43	-2.52; 1.10
	P-value	**<.001**	.370	.210	.730
	% of total change	**100%**	35.4%	42%	22.9%
ΔDCA*	β (SE)	7.07 (6.23)	5.98 (5.70)	1.57 (5.54)	-0.48 (5.76)
(%)	95% CI	-9.18; 23.33	-8.90; 20.86	-12.88; 16.03	-15.50; 14.54
	P-value	.623	.721	.992	.999
	% of total change	n/a	n/a	n/a	n/a
ΔWBA*	β (SE)	-2.51 (1.13)	-1.98 (1.03)	-0.22 (1.00)	-0.31 (1.04)
(%)	95% CI	-5.45; 0.43	-4.67; 0.72	-2.84; 2.39	-3.03; 2.41
	P-value	.122	.227	.996	.991
	% of total change	n/a	n/a	n/a	n/a

Table 2: Effects of time on recovery of muscle synergies and strength, and metrics reflecting steady-state balance during quiet stance within the first 12 weeks post-stroke.

Abbreviations: Δ, change scores; FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; MI-ankle, Motricity Index ankle item; COP, center-of-pressure; COP_{Area}, area of the net COP; $COP_{Vel\text{-}ML}$, rms velocity of the net COP in the frontal plane; $COP_{Vel\text{-}AP}$, rms velocity of the net COP in the sagittal plane; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry; n/a, not applicable as the effect of TIME was not significant.

Values shown are estimated regression coefficients (β), standard error (SE), 95% confidence interval (95% CI), probability estimates (*P*-value) and the percentage of total observed change (% of total change). β-values show time-dependent change corrected for covariates AGE, SEX and SIDE in metrics reflecting lower limb muscle synergies (FM-LE), strength (MI-LE), postural stability (COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$) and interlimb symmetry (DCA, WBA). If marked with *, values include an additional correction for INSTRUMENT. A statistically significant (i.e., P <.05) coefficient is highlighted in bold.

Effects of time on recovery of steady-state balance during quiet stance

Figures 2B-C show individual and mean time-dependent change in postural stability and symmetry metrics, respectively. As shown in Table 2, TIME was a significant factor for improvements from week 3 to 12 in COP_{Area} (β = -175.0, 95%CI [-263.0; -87.0], *P* < .001), $COP_{Vel\text{-}ML}$ (β = -4.71, 95%CI [-6.73; -2.69], *P* <.001), and $COP_{Vel\text{-}AP}$ (β = -3.14, 95%CI [-5.09; -1.18], *P* < .001), after correction for INSTRUMENT as the only significant covariate for change in COP_{Area} (β = 134.3, 95%CI [77.4; 191.3], *P* < .001), $COP_{Vel\text{-}ML}$ (β = 4.86, 95%CI [2.90; 6.83], *P* < .001) and $COP_{Vel\text{-}AP}$ (β = 6.28, 95%CI [4.40; 8.16],*P* < .001). Further sub-analyses yielded significant reductions in COP_{Area} between weeks 5 and 8 (β = -79.8, 95%CI [-158.4; -1.2], *P* = .045) and in $COP_{Vel\text{-}ML}$ between weeks 3 and 5 (β = -1.90, 95%CI [-3.75; -0.06], *P* = .041). No significant time-dependent change was found for DCA and WBA. Comparison with mean symmetry values in healthy subjects (DCA: 16.3%, SD=31.8; WBA: -1.1%, SD=3.5) showed significant differences in WBA at week 3 (difference = 7.7%, standard error [SE] = 3.0, *P* = .001), week 5 (difference = 7.2%, SE = 2.9, *P* = .005), week 8 (difference = 7.5%, SE = 2.9, *P* = .009) and week 12 (difference = 8.3%, SE = 3.0, *P* = .008). Differences in DCA were statistically significant at week 8 (difference = 42.5%, SE = 20.8, *P* = .029) and week 12 (difference = 51.2%, SE = 21.2, *P* = .012). Figures 3A-B depict sway profiles at each time-point in a single subject.

Between-subject associations of lower limb impairment severity with steady-state balance

Table 3 shows the *between*-subjects analyses applied cross-sectionally at weeks 3, 5, 8, and 12 for either FM-LE, MI-LE, or MI-ankle with COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$, DCA, or WBA. Scatterplots of these associations with their linear regression lines are provided in supplement (Supplementary figure 3, appendix C). The main effects of FM-LE, MI-LE, or MI-ankle were significant for COP_{Area}, $COP_{Vel\text{-}ML}$, and $COP_{Vel\text{-}AP}$, as well as for WBA (*P* < .001, Table 3). Additional significant covariates were INSTRUMENT (*P* < .001) for the associations with COP_{Area}, $COP_{Vel\text{-}ML}$, and $COP_{Vel\text{-}AP}$ as the dependent variables; TIME (*P* < .05) for COP_{Area} and $COP_{Vel\text{-}ML}$; and AFFECTED SIDE (*P* < .05) for COP_{Area} (Table 3). *Between*-subject analyses with DCA yielded non-significant results.

Sub-analyses concerning FM-LE, MI-LE, and MI-ankle scores yielded significant regression coefficients up until week 8 for COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$, and WBA (*P* < .01, Table 3). At week 12, FM-LE remained a significant predictor of $COP_{Vel\text{-}ML}$ (β = -0.49, 95%CI [-0.77; -0.22], *P* < .001) and WBA (β = -0.64, 95%CI [-1.09; -0.21], *P* = .005). Additionally, a single significant coefficient was identified for MI-LE scores at week 12 concerning WBA (β = -0.20, 95%CI [-0.34; -0.06], *P* = .008).

Within-subject associations of lower limb motor recovery with change in steady-state balance

Regression coefficients between ΔFM-LE, ΔMI-LE, or ΔMI-ankle on the one hand, and ΔCOP_{Area}, $\Delta COP_{Vel\text{-}ML}$, $\Delta COP_{Vel\text{-}AP}$, ΔDCA, or ΔWBA on the other were estimated for weeks 3–5, weeks 5–8 and weeks 8–12, using 36, 38 and 35 individual change scores, respectively. Scatterplots with their linear regression lines are provided in supplement (Supplementary figure 4, appendix C). As shown in Table 4, the main effects of ΔFM-LE, ΔMI-LE, and ΔMI-ankle were not significant for any dependent variable. Sub-analyses across the three epochs yielded a single significant regression coefficient for ΔMI-LE with $\Delta COP_{Vel\text{-}ML}$ between weeks 8 and 12 (β = -0.12, 95%CI [-0.21; -0.04], *P* = .007).

		FM-LE (0-34)					MI-LE (0-99)					MI-ankle (0-33)				
		Main	W3	W5	W8	W12	Main	W3	W5	W8	W12	Main	W3	W5	W8	W12
COP_{Area} (mm^2)	β	**-16.13[ab]**	**-23.30[a]**	**-4.99[a]**	**-14.52[a]**	-7.32[a]	**-4.99[abc]**	**-9.00[a]**	**-5.93[a]**	**-5.04[a]**	-1.74[a]	**-11.0[ab]**	**-20.98[a]**	**-16.59[a]**	**-12.78[ac]**	-3.05[a]
	(SE)	**(3.25)**	**(8.15)**	**(0.97)**	**(2.88)**	(3.29)	**(0.97)**	**(2.26)**	**(1.59)**	**(0.85)**	(1.08)	**(2.46)**	**(6.68)**	**(3.80)**	**(2.14)**	(2.78)
	95%	**-22.60; -**	**-39.91;**	**-6.92;**	**-20.36;**	-14.03;	**-6.92;**	**-13.62;**	**-9.17;**	**-6.76;**	-3.95;	**-15.93;**	**-34.57;**	**-24.30;**	**-17.11;**	-8.72;
	CI	**9.66**	**-6.69**	**-3.06**	**-8.69**	-0.61	**-3.06**	**-4.38**	**-2.71**	**-3.33**	0.47	**-6.14**	**-7.35**	**-8.90**	**-8.45**	2.63
	P	**<.001**	**.008**	**<.001**	**<.001**	.034	**<.001**	**<.001**	**<.001**	**<.001**	.119	**<.001**	**.004**	**<.001**	**<.001**	.282
COP_{Vel-ML} (mm/s)	β	**-0.60[a]**	**-0.97[a]**	**-0.14[a]**	**-0.55[a]**	**-0.49[a]**	**-0.14[ab]**	**-0.27[a]**	**-0.19[a]**	**-0.18[a]**	-0.10[a]	**-0.24[ab]**	**-0.69[ac]**	**-0.48[a]**	**-0.45[a]**	-0.17[a]
	(SE)	**(0.09)**	**(0.14)**	**(0.03)**	**(0.13)**	**(0.13)**	**(0.03)**	**(0.05)**	**(0.05)**	**(0.04)**	(0.05)	**(0.07)**	**(0.14)**	**(0.12)**	**(0.10)**	(0.12)
	95%	**-0.78;**	**-1.25;**	**-0.20;**	**-0.79;**	**-0.77;**	**-0.20;**	**-0.37;**	**-0.29;**	**-0.26;**	-0.20;	**-0.38;**	**-0.98;**	**-0.74;**	**-0.65;**	-0.43;
	CI	**-0.42**	**-0.68**	**-0.08**	**-0.26**	**-0.22**	**-0.08**	**-0.18**	**-0.09**	**-0.10**	-0.01	**-0.09**	**-0.41**	**-0.22**	**-0.24**	0.08
	P	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	.047	**.001**	**<.001**	**<.001**	**<.001**	.170
COP_{Vel-AP} (mm/s)	β	**-0.51[a]**	**-0.69[a]**	**-0.12[a]**	**-0.49[a]**	-0.40[a]	**-0.12[a]**	**-0.18[a]**	**-0.18[a]**	**-0.16[a]**	-0.06[a]	**-0.29[a]**	**-0.52[a]**	**-0.50[a]**	**-0.41[a]**	-0.13[a]
	(SE)	**(0.09)**	**(0.13)**	**(0.03)**	**(0.12)**	(0.18)	**(0.03)**	**(0.04)**	**(0.05)**	**(0.04)**	(0.06)	**(0.07)**	**(0.11)**	**(0.12)**	**(0.10)**	(0.16)
	95%	**-0.69;**	**-0.94;**	**-0.18;**	**-0.74;**	-0.77;	**-0.18;**	**-0.27;**	**-0.28;**	**-0.23;**	-0.19;	**-0.43;**	**-0.75;**	**-0.74;**	**-0.60;**	-0.44;
	CI	**-0.33**	**-0.43**	**-0.07**	**-0.24**	-0.03	**-0.07**	**-0.09**	**-0.08**	**-0.08**	0.06	**-0.16**	**-0.29**	**-0.25**	**-0.21**	0.19
	P	**<.001**	**<.001**	**<.001**	**<.001**	.035	**<.001**	**<.001**	**<.001**	**<.001**	.301	**<.001**	**<.001**	**<.001**	**<.001**	.422
DCA (%)	β	-0.06	-3.27[d]	-0.31	-2.28	-2.30	-0.31	-1.08[d]	-0.65	-1.00	-0.76	-1.01	-3.05[d]	-1.30	**-2.88**	-2.68
	(SE)	(0.89)	(1.73)	(0.26)	(1.40)	(1.43)	(0.26)	(0.52)	(0.45)	(0.43)	(0.45)	(0.62)	(1.43)	(1.41)	**(1.06)**	(1.09)
	95%	-1.83;	-6.79;	-0.83;	-5.11;	-5.22;	-0.83;	-2.14;	-1.56;	-1.86;	-1.68;	-2.23;	-5.96;	-3.61;	**-5.02;**	-4.89;
	CI	1.72	0.26	0.20	0.54	0.63	0.20	-0.01	0.27	-0.13	0.16	0.21	-0.13	1.02	**-0.74**	-0.46
	P	.949	.068	.234	.110	.119	.234	.048	.161	.025	.103	.105	.041	.264	**.009**	.020
WBA (%)	β	**-0.75**	**-1.19**	**-0.23**	**-0.62**	**-0.64**	**-0.23**	**-0.36**	**-0.26**	**-0.17**	**-0.20**	**-0.37**	**-0.90**	**-0.63**	-0.34	-0.32
	(SE)	**(0.12)**	**(0.20)**	**(0.04)**	**(0.15)**	**(0.22)**	**(0.04)**	**(0.06)**	**(0.05)**	**(0.05)**	**(0.07)**	**(0.10)**	**(0.19)**	**(0.13)**	(0.14)	(0.19)
	95%	**-0.98;**	**-1.60;**	**-0.30;**	**-0.93;**	**-1.09;**	**-0.30;**	**-0.49;**	**-0.37;**	**-0.27;**	**-0.34;**	**-0.56;**	**-1.28;**	**-0.90;**	-0.61;	-0.70;
	CI	**-0.51**	**-0.78**	**0.15**	**-0.31**	**-0.21**	**-0.15**	**-0.24**	**-0.16**	**-0.06**	**-0.06**	**-0.17**	**-0.51**	**-0.36**	-0.06	-0.07
	P	**<.001**	**<.001**	**<.001**	**<.001**	**.005**	**<.001**	**<.001**	**<.001**	**.002**	**.008**	**<.001**	**<.001**	**<.001**	.018	.103

Table 3: *Between*-subject associations of lower limb motor impairment severity with steady-state balance during quiet stance at week 3, 5, 8 and 12 post-stroke.

Abbreviations: FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; MI-ankle, Motricity Index ankle item; COP, center-of-pressure; COP_{Area}, area of the net COP; COP_{Vel-ML}, rms velocity of the net COP in the frontal plane; COP_{Vel-AP}, rms velocity of the net COP in the sagittal plane; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry; W, week post-stroke.

Values shown are estimated regression coefficients (β), standard error (SE), 95% confidence interval (95% CI), and probability estimates (*P*). β-values predict change in postural stability (COP_{Area}, COP_{Vel-ML}, COP_{Vel-AP}) and symmetry (DCA, WBA) from a one-point difference on the FM-LE, MI-LE or MI-ankle. Models were corrected for significant covariates with [a], INSTRUMENT; [b], TIME; [c], SIDE; and [d], SEX. A Bonferroni correction was applied for declaring significance (i.e., *P* <.05/5) as indicated in **bold**.

		ΔFM-LE (0-34)				ΔMI-LE (0-99)				ΔMI-ankle (0-33)			
		Main	W3-5	W5-8	W8-12	Main	W3-5	W5-8	W8-12	Main	W3-5	W5-8	W8-12
ΔCOP_{Area} (mm²)	β (SE)	-1.85 (5.59)	-12.52(11.62)	4.34 (12.38)	-9.73 (8.27)	-0.33 (1.28)	-7.83 (3.47)	3.01 (2.62)	-4.47 (1.80)	-2.24 (2.10)	-8.54 (3.49)	-3.71 (6.57)	-5.58 (4.34)
	95%CI	-12.97; 9.26	-36.29; 11.24	-20.67; 29.34	-26.65; 7.18	-2.88; 2.22	-14.92; -0.73	-2.33; 8.36	-8.14; -0.78	-6.44; 1.95	-15.69; -1.38	-17.10; 9.68	-14.47; 3.30
	P	.741	.290	.726	.249	.799	.032	.259	.019	.289	.021	.577	.209
$\Delta COP_{Vel\text{-}ML}$ (mm/s)	β (SE)	-0.23 (0.13)	-0.55 (0.23)	-0.16 (0.25)	-0.04 (0.21)	<0.01 (0.03)	-0.09[a] (0.08)	0.08 (0.05)	**-0.12 (0.04)**	-0.04 (0.05)	-0.11 (0.08)	0.12 (0.13)	-0.24 (0.10)
	95%CI	-0.49; 0.03	-1.02; -0.07	-0.68; 0.35	-0.46; 0.39	-0.06; 0.06	-0.25; 0.07	-0.03; 0.18	**-0.21; -0.04**	-0.14; 0.05	-0.27; 0.05	-0.16; 0.39	-0.45; -0.04
	P	.084	.026	.517	.864	.927	.281	.164	**.007**	.364	.165	.389	.020
$\Delta COP_{Vel\text{-}AP}$ (mm/s)	β (SE)	-0.11 (0.16)	-0.37 (0.22)	0.12 (0.28)	-0.15 (0.33)	-0.01(0.04)	-0.02 (0.07)	0.04 (0.06)	-0.15 (0.07)	-0.04 (0.06)	-0.05 (0.07)	-0.10 (0.15)	-0.34 (0.16)
	95%CI	-0.42; 0.21	-0.82; 0.09	-0.45; 0.69	-0.82; 0.52	-0.08; 0.06	-0.17; 0.13	-0.09; 0.16	-0.29; -0.01	-0.16; 0.07	-0.19; 0.09	-0.41; 0.21	-0.67; -0.01
	P	.500	.109	.678	.659	.786	.780	.563	.049	.429	.487	.509	.047
ΔDCA (%)	β (SE)	2.38 (1.37)	3.52 (2.32)	2.98 (2.04)	-1.30 (2.63)	-0.01 (0.34)	0.05 (0.77)	0.06 (0.46)	-0.57 (0.61)	0.05(0.51)	0.45 (0.66)	-0.30 (1.13)	-2.17 (1.33)
	95%CI	-0.34; 5.09	-1.24; 8.27	-1.17; 7.14	-6.68; 4.08	-0.70; 0.67	-1.52; 1.62	-0.87; 1.00	-1.81; 0.68	-0.95; 1.06	-0.89; 1.79	-2.60; 2.00	-4.90; 0.55
	P	.085	.141	.154	.626	.967	.946	.890	.359	.917	.498	.792	.114
ΔWBA (%)	β (SE)	0.39[a] (0.24)	0.55 (0.51)	0.46 (0.42)	-0.72 (0.40)	0.14[a] (0.06)	-0.04 (0.17)	0.20 (0.09)	0.09 (0.10)	0.14[a] (0.07)	0.04 (0.14)	0.19 (0.23)	0.07 (0.22)
	95%CI	-0.08; 0.86	-0.50; 1.59	-0.39; 1.31	-1.55; 0.10	0.02; 0.26	-0.38; 0.29	-0.02; 0.37	-0.11; 0.29	-0.01; 0.29	-0.25; 0.33	-0.27; 0.65	-0.38; 0.53
	P	.102	.292	.279	.082	.026	.794	.030	.345	.061	.775	.415	.741

Table 4: *Within*-subject associations of lower limb motor recovery and change in steady-state balance during quiet stance within the first 12 weeks post-stroke.

Abbreviations: Δ, change scores; FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; MI-ankle, Motricity Index ankle item; COP, center-of-pressure; COP_{Area}, area of the net COP; $COP_{Vel\text{-}ML}$, rms velocity of the net COP in the frontal plane; $COP_{Vel\text{-}AP}$, rms velocity of the net COP in the sagittal plane; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry; W, week post-stroke.

Values shown are estimated regression coefficients (β), standard error (SE), 95% confidence interval (95% CI), and probability estimates (*P*). β-values predict ΔCOP_{Area}, $\Delta COP_{Vel\text{-}ML}$, $\Delta COP_{Vel\text{-}AP}$, ΔWBA and ΔDCA from a one-point increase on the FM-LE, MI-LE, or MI-ankle. Models were corrected for significant covariates with [a], INSTRUMENT. A Bonferroni correction was applied for declaring significance (i.e., *P* <.05/4) as indicated in **bold**.

Discussion

The present prospective cohort study involving 48 subjects investigated the time course of steady-state balance during quiet stance in relation to lower limb motor recovery within the first 3 months post-stroke. Controlling a high-positioned COM above a small base of support while standing is an easily standardized, yet skilled motor task requiring continuous postural corrections by the lower limbs. Unlike other prospective recovery studies in this field,[11,14,17-19] we were interested in how clinically assessed impairments in muscle synergies (i.e., FM-LE) and strength (i.e., MI-LE and MI-ankle) of the most-affected leg are associated with postural stability (i.e., COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$) and asymmetric limb contributions to balance (i.e., DCA, WBA) during quiet two-legged stance. We therefore performed serial measurements in the same subjects and at fixed times post-stroke.[25,26] Our main findings are summarized:

- A restricted time window of recovery concerning motor impairments and postural stability that occurs within the first 8 weeks post-stroke. (Table 2)
- Stroke subjects differ significantly from healthy controls with respect to interlimb asymmetry in terms of DCA and WBA.
- Lack of recovery in DCA and WBA in the first 3 months post-stroke, despite significant motor improvements in the most-affected leg. (Table 2)
- Significant *between*-subject associations between motor impairment severity and postural instability (i.e., COP_{Area}, $COP_{Vel\text{-}ML}$, $COP_{Vel\text{-}AP}$) as well as a preferred asymmetric stance (i.e., WBA) within the first 3 months post-stroke. (Table 3)
- Lack of significant *between*-subject associations of motor impairment severity with DCA. (Table 3)
- An overall lack of significant *within*-subject associations between improved intralimb muscle synergies and strength and change in postural stability and interlimb symmetry. (Table 4)

In agreement with our first hypothesis, the contribution of the progress of time as a reflection of spontaneous neurobiological recovery[7] was most pronounced for FM-LE, MI-LE, and MI-ankle between weeks 3 and 5 post-stroke. Approximately half of the total observed change occurred within this relatively short epoch (FM-LE: 43.2%, MI-LE: 45.5%, MI-ankle: 56.7%; Table 2). Recovery rapidly leveled off thereafter, which agrees with previous studies.[5-7] In the literature, this restricted time window has also been described for the paretic upper limb[5,10] as well as for other neurological impairments including visuospatial inattention[36] and aphasia,[37] suggesting spontaneous neurological restitution within the first 5 to 8 weeks post-stroke.

Confirming our second hypothesis, the present study shows that progress of time is also an independent factor contributing to improved postural stability. Significant reductions in $COP_{Vel\text{-}ML}$ and COP_{Area} were most prominent within the first 8 weeks post-stroke, responsible for about 75% of the total observed change (Table 2). Although $COP_{Vel\text{-}AP}$ was not statistically significant within a specific epoch, it displayed a similar pattern of change in the first 12 weeks post-stroke (Figure 2B). As such, steady-state balance became increasingly efficient, as reflected by a general COP sway reduction, in approximately the same time window as that seen for lower limb motor recovery.

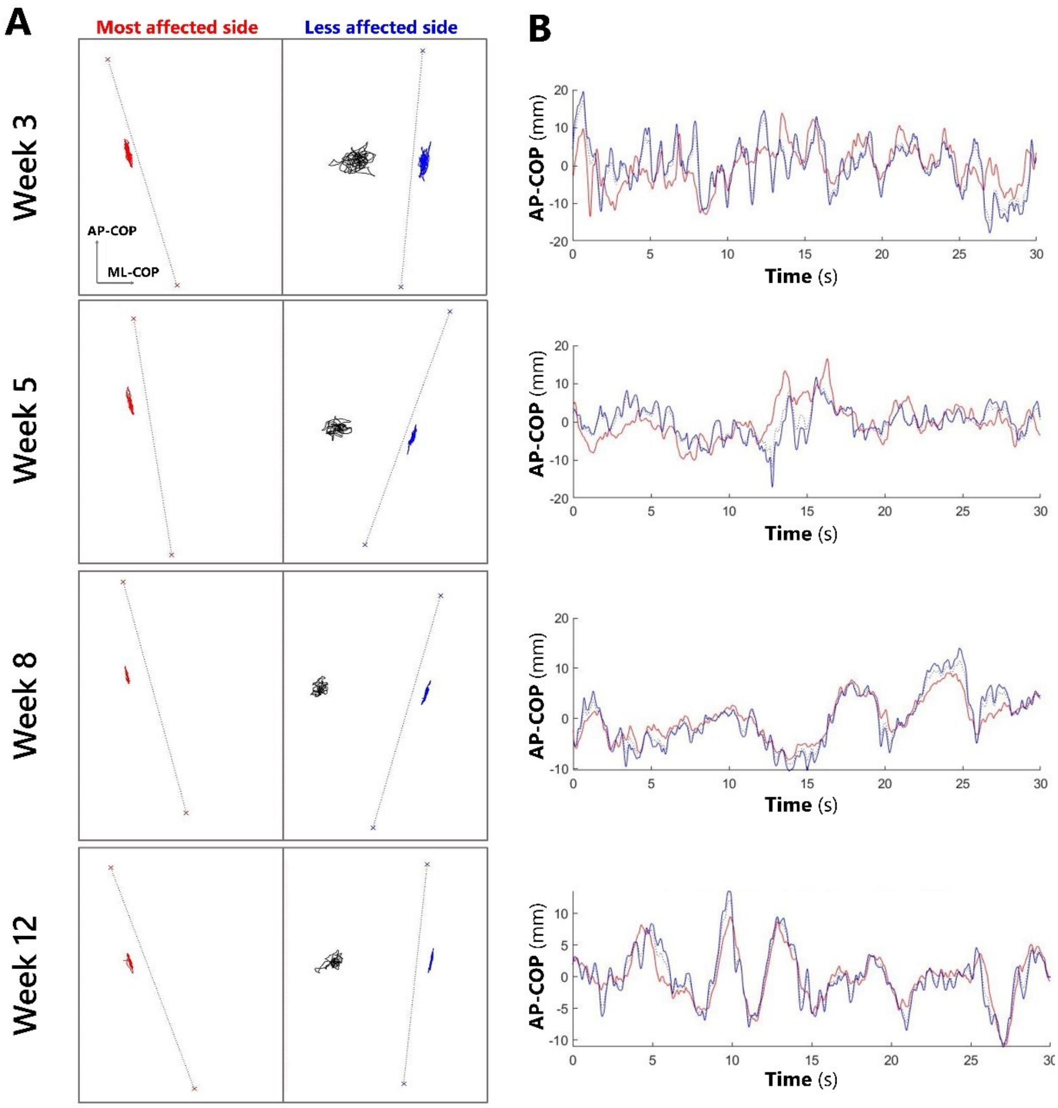
A shared period of significant recovery has also been found in kinematic studies investigating the quality of upper limb motor performance relative to the Fugl-Meyer arm motor score.[21,22] In contrast, the present study showed that DCA and WBA were, on average, invariant for change over time (Figure 2C). The persistent asymmetry of approximately 45-60% greater contribution of the less-affected limb in terms of DCA approaches values reported in chronic stroke.[16] Moreover, an unchanged asymmetric weight-bearing (about 40% of body-weight placed on the most-affected leg), despite significant COP sway reductions over time, agrees with other longitudinal studies starting their measurements within the first 3 months post-stroke.[14,18,19,38] Obviously, subjects preferred to keep and control their balance predominantly with their less-affected side to achieve posture stabilization while standing. Figures 3A-B illustrate such persistent asymmetries in a typically behaving subject.

In agreement with our third hypothesis, relatively strong *between*-subject associations were found, such that a preferred asymmetric stance appears strongly dependent on the lower limb impairment severity. It was previously shown in healthy subjects that a gradually loaded leg is increasingly involved in balance control.[15,39,40] Thus, persistent loading of the less-affected leg may indicate an attempt to actually increase the contribution of this leg's stabilizing ankle torques while standing in those with greater impairments. Our subsequent finding of a significant time-dependent association of impairment severity with postural instability up until week 8 post-stroke (Table 3), then point towards an optimization of this compensatory strategy after independent stance is regained. Interestingly, impairment severity was not significantly associated with the

DCA when comparing *between* subjects. This dissociation was already shown in the chronic phase post-stroke[16] and may involve significant reliance on compensatory stabilization with the less-affected leg even in mildly affected subjects (Supplementary figure 3, appendix C).

As shown in Table 4, a dissociation between impairment scales and DCA was also found *within* subjects over time. A mismatch between motor improvements of the paretic leg on the one hand, and persistent interlimb asymmetries on the other is a novel finding as earlier longitudinal studies[14,18,19,38] lacked measurements of change within the window of spontaneous neurobiological recovery. This finding may further explain our subsequent finding that FM-LE, MI-LE, and MI-ankle recovery neither explained *within*-subject postural stability improvements (fourth hypothesis), despite a shared recovery time window at the group level. Seemingly, recovery of the most-affected leg did not significantly contribute to an improved steady-state balance from 3 weeks post-stroke onwards, complementing our finding of persistent asymmetries favoring the less-affected side. Our results corroborate findings from electromyography (EMG) studies led by Jayne Garland,[19,38,41] showing that balance reactions with the most-affected leg in anticipation of rapid arm movements hardly normalize in the first 3 months post-stroke,[19,38,41] even after a mild stroke.[19] Instead, significant anticipatory change was consistently observed on the less-affected side.[19,38,41] The same studies[19,38] found an asymmetric control during quiet standing, similar to the present findings, suggesting that this compensatory strategy generalizes across anticipatory and steady-state balance tasks.

It should be noted, however, that the present recovery study does not give an answer to *why* patients preferred compensatory strategies despite significant motor improvements at the most-affected side. Obviously, steady-state balance is a multifactorial skill. Besides motor impairments, postural deficits in stroke patients have also been linked to impaired integration of afferent somatosensory and vestibular information,[42,43] a resultant visual dependency[17,44] and misperception of verticality,[45,46] as well as reduced balance confidence to prevent falls.[47] To disentangle the relative importance of sensory impairments, cognition, and mood, we should have measured these factors as well in a longitudinal way. Alternatively, one may assume that observed *intra*-limb improvements in terms of FM-LE and MI-LE were too small and incomplete for introducing restitution of *inter*-limb symmetry. Instead, relying on their less-affected side may have been perceived as more efficient by patients. Similar to our findings, Roelofs and colleagues showed that even those with (near) complete FM-LE recovery may show a significant dynamic control asymmetry, suggesting that DCA is a more responsive marker of remaining fine motor deficits than traditional scales.



Figures 3A-B: Center-of-pressure (COP) sway profiles of an individual subject standing quietly, recorded at week 3, 5, 8 and 12 post-stroke.

The figures on the left (A) show the two-dimensional individual-limb COP sway for the two sides separately (less-affected side: blue/right; most-affected side: red/left) and the net COP for both sides combined (black/mid). Note the decreasing net COP sway area (week 3: 318 mm²; week 5: 166 mm²; week 8: 127 mm²; week 12: 139 mm²), indicating gradual posture stabilization despite a persistent weight-bearing asymmetry reflected by the net COP deviation towards the less-affected side. The figures on the right (B) show the corresponding time series of the anteroposterior COP displacement (AP-COP) in mm. Note the larger and faster movement on the less-affected side (blue line) relative to the most-affected side (red line). Accordingly, asymmetries in DCA were found (week 3: 27.3%; week 5: 32.5%; week 8: 47.8%; week 12: 44.7%) indicating a persistently greater balance contribution of the less-affected leg.

In summary, our findings suggest that stroke subjects recover their quiet standing balance mainly in the first 8 weeks post-stroke by optimizing, rather than “normalizing” compensatory strategies involving the less-affected limb. The independency of steady-state balance improvements and motor recovery of the most-affected limb further suggests that only instrumented performance measures reflecting interlimb asymmetry, such as DCA, are suitable to address the quality of movement in order to improve our understanding of balance recovery mechanisms post-stroke.

Limitations

Several limitations of the present study should be considered. First, our sample size is limited and larger epidemiological studies incorporating serial instrumented performance measures are needed to generalize our findings. Second, since we started our assessments at 3 weeks post-stroke, we may have missed some early changes in motor performance. Despite this, the study was successful in collecting data serially *within* subjects by applying a postural task with relatively low functional demands. A third limitation is that our results are restricted to quiet two-legged standing, which obviously allows compensation strategies. This may have prevented us from measuring the extend of “true” neurological recovery in the most-affected leg for controlling balance. Third, as emphasized, our analyses are restricted to motor impairments in terms of FM-LE and MI-LE. Consequently, we did not investigate recovery in other potentially relevant impairments, such as muscle tone,[48] sensation[42] or visuospatial perception.[49] Additionally, the FM-LE and MI-LE assess distal motor control through movement range and strength in ankle dorsiflexion, whereas quiet standing balance is mainly controlled by plantarflexors that resists forwards toppling due to gravity.[50] This “narrow” emphasis of clinical scales on foot elevation alone, may have prevented us from finding significant associations. Fourth, we used two measuring instruments to allow data acquisition in various settings. Since we used the same instrument *within* subjects and added the covariate INSTRUMENT systematically to our final analyses, we believe that the use of two different platform types did not affect our conclusions. Nevertheless, more research is needed for the development and validation of portable instruments to enable even larger longitudinal studies with longer follow-ups beyond hospitalization. Lastly, we did not monitor treatment content and are unable to decide whether our findings were influenced by, for example, therapy dose or focus.

Future directions

An unaddressed key question arising from the current study is: "*Why* do clinical improvements in muscle synergies and strength of the most-affected leg hardly generalize to an improved quality of steady-state balance?" Addressing this question requires future studies with serial measurements of sensory and cognitive perception deficits as well as patients' mood (e.g., by using standardized questionnaires of balance confidence[51]). In addition, future studies with serial EMG measurements are needed to show if the actual changes in intralimb coordination of the paretic leg make a beneficial contribution to posture stabilization or, alternatively, should be seen as "noise" that needs to be suppressed while standing. Unravelling a potential mismatch between the preferred postural strategy and subjects' capacity to normalize their quality of movement by an increased balance contribution from the most-affected leg is important to address another unsolved question: "Are therapies aiming to restore symmetry, such as the Bobath approach[52] or visual feedback training,[53] counterproductive if we aim at posture stabilization and avoiding falls?" Building an evidence base for effective rehabilitation strategies is important, as falls remain a major health care problem at all stages of the disease.[54]

To drive the field forward, it is important to reach agreement on a shared language and the metrics applied to assess qualitative aspects of movement. The SRRR balance and mobility task force – a group of experts in the field of poststroke recovery research – currently gathers intending to build consensus on how future trials should address recovery. This will include standardized recommendations on taxonomy, timing, and choice of assessments as well as the metrics used to measure the quality of quiet standing balance and mobility performance within the first 6 months post-stroke.

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4

APPENDIX A

Prior to the analyses described in the manuscript, we investigated the comparability of the mobile pressure plate and laboratory-grade force plates for measuring center-of-pressure (COP) sway. A correction method based on these findings is discussed below.

Comparability analysis

Methods: Nineteen healthy adults (10 female), with a mean (SD) age of 35.4 (15.9) years, participated. Each subject performed a standardized 30-second two-legged stance task with closed eyes. They stood in random order on two laboratory-grade force plates (Type OR6-7 Biomechanics Force Platform, AMTI, MA, US) or a mobile pressure plate (0.5m Footscan, RS Scan/Materialize, BE), which were the same instruments used for the current clinical study. Descriptors of postural stability and asymmetry were computed and averaged over three trials.

Primarily, Pearson correlation coefficients (r) were used to investigate consistency between the instruments. Agreement between the types of plates was further investigated using intra-class coefficient (ICC) and mean differences, which were tested for significance using t-tests.

Results: Supplementary table 1 shows the results of the comparability analyses. For each investigated outcome variable, Pearson's r-values exceeded 0.75. Very high ICC values were found for WBA and DCA, yet low values were found for all three stability metrics COP_{Area}, $COP_{Vel\text{-}ML}$ and $COP_{Vel\text{-}AP}$. For the latter, significant mean differences were found, as outcomes obtained with the pressure plate tended to be lower.

Strong consistency is shown for all metrics. Systematic differences between devices for measuring postural stability in terms of COP are most likely explained by technical variation. Final statistical analyses including data from both type of plates require a correction method to control for this systematic difference.

Correction method

We observed a systematic difference between force plate and pressure plate for measuring postural stability in terms of COP_{Area}, $COP_{Vel\text{-}ML}$ and $COP_{Vel\text{-}AP}$. Therefore, serial measurements in a specific participant were always performed with the same plate type. Hence, *within*-subject variation in these COP-based outcome variables are not biased by this factor. However, when pooling longitudinal data *between* subjects who were assessed either with force plates or the pressure plate, statistical models must “correct for” systematic deviations in the dependent variable that are explained by the choice of measurement instrument. For this purpose, we have added INSTRUMENT as a covariate. Final regression coefficients for modelling time-dependent change (research question 2) and longitudinal associations (research question 3 & 4) are therefore corrected for a systematic difference between instruments.

	COP_{Area} (mm²)	$COP_{Vel\text{-}ML}$ (mm/s)	$COP_{Vel\text{-}AP}$ (mm/s)	WBA	DCA
Value [Pressure plate]	18.28	1.59	3.20	0.01	0.00
Value [Force plates]	106.83	5.57	10.73	0.00	0.07
Mean difference	**-88.56**	**-3.98**	**-7.53**	0.01	-0.07
Std error	**14.34**	**0.40**	**0.59**	0.00	0.07
Upper 95% CI	**-58.31**	**-3.15**	**-6.29**	0.01	0.08
Lower 95% CI	**-118.80**	**-4.82**	**-8.76**	0.00	-0.21
P-value	**<.0001**	**<.0001**	**<.0001**	0.242	0.338
Pearson’s r	0.856	0.881	0.843	0.863	0.760
ICC	0.081	0.189	0.125	0.989	0.980

Supplementary table 1: Comparability of a mobile pressure plate and two laboratory-grade force plates for measuring COP sway.

Abbreviations: FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; COP, center-of-pressure; COP_{Area}, area of the total COP; $COP_{Vel\text{-}ML}$, rms velocity of the total COP in the frontal plane; $COP_{Vel\text{-}AP}$, rms velocity of the total COP in the sagittal plane; DCA, Dynamic Control Asymmetry; WBA, Weight-Bearing Asymmetry.

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APPENDIX B

Here we briefly elaborate on the method by which the center-of-pressure (COP) trajectories were recorded and calculated from the two types of measuring plates used in the current study.

Laboratory-grade force plates

Force data acquisition: A force plate uses four load sensors - one in each corner - to record multi-dimensional (*x*,*y* and *z* being the anteroposterior (AP), mediolateral (ML) and vertical directions) forces (*F*)* and moments (*M*) at a sampling frequency of 1,000 Hz. We used two plates mounted in the floor of the movement analysis laboratory (M²OCEAN, University of Antwerp, BE) in order to record the raw force data at the feet separately. Data was collected with Nexus (version 2.8, Vicon Motion Systems Ltd, UK).

COP calculations: COP trajectories with AP and ML coordinates were calculated for each time point *t*, first, for the two sides independently. We used a custom-made MATLAB algorithms (version R2018a, The MathWorks Inc., MA, US) based on the following equation where *O* is the offset from the geometric plate center:

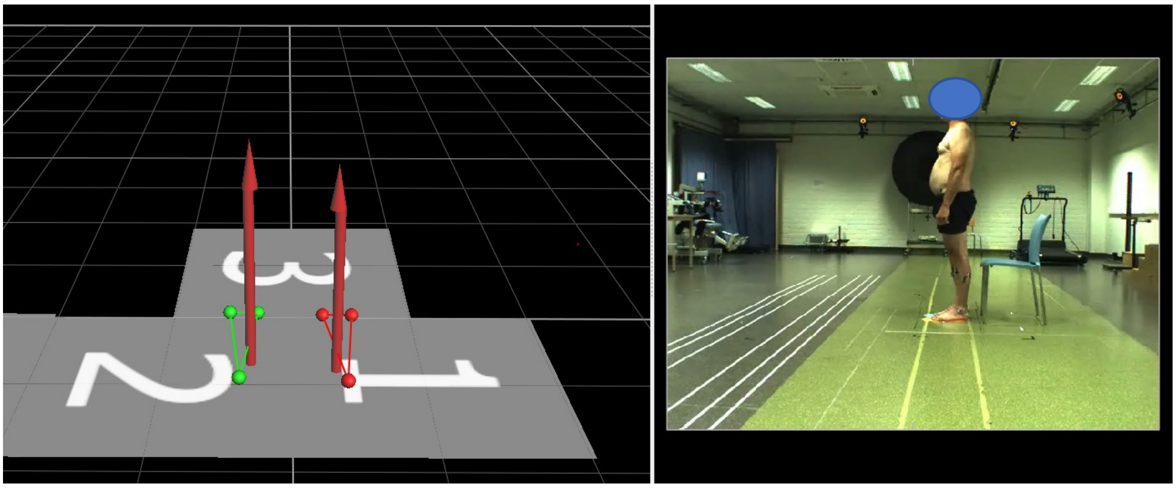
$$COPy(t) = \frac{-(My(t) + Fx(t) * Oz)}{Fz(t)} + Ox$$

$$COPx(t) = \frac{-(Mx(t) + Fy(t) * Oz)}{Fz(t)} + Oy$$

Subsequently, the net COP under the two limbs combined is calculated as a weighted average (using Fz) from the left- and right-sided COPs. We used the following equation:

$$COP_{net} = \frac{COP_{most\ affected} * Fz_{most\ affected} + COP_{less\ affected} * Fz_{less\ affected}}{Fz_{most\ affected} + Fz_{less\ affected}}$$

COP axes rotation: To align the AP and ML axes of the side-specific COPs with the foot orientation, we tracked reflective markers attached to the foot using infrared cameras (Vicon Motion Systems Ltd, UK). On a trial-by-trial basis, the AP axis was then rotated to align with a line drawn between the heel and head of the 2nd metatarsal bone. The ML axis is situated perpendicular to this line.



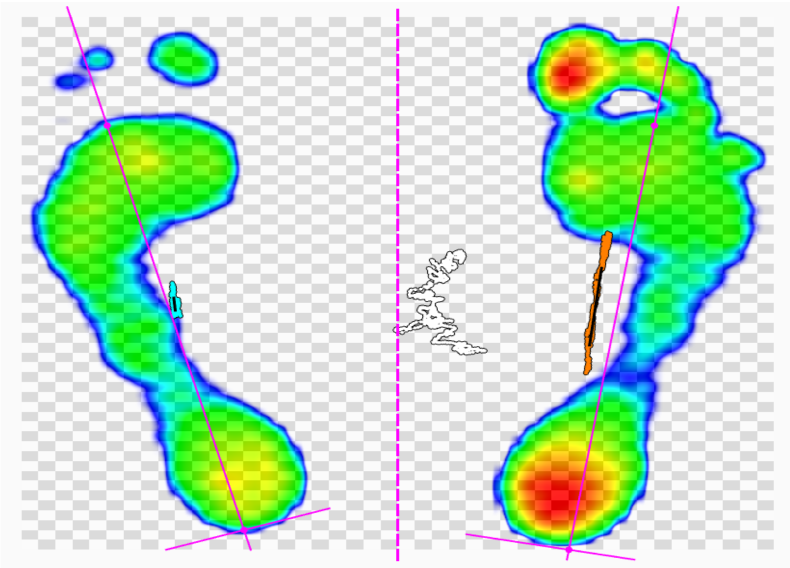
Supplementary figure 1: Screenshot of a COP recording of the Nexus software. On the left, the reflective markers attached to anatomical hallmarks of the feet (2nd metatarsal bone head, malleolus lateralis, heel) together with the 3-dimensional ground reaction force vector at a certain frame. On the left is the image of a video camera of the assessed subject at the same time.

Mobile pressure plate

Force data acquisition: A pressure plate consists of a large(r) number of embedded load sensors (2.6 sensors/cm^2) in order to record plantar (i.e., the part of the foot touching the plate surface) distribution of the uni-dimensional ground reaction force in the vertical direction, or F_Z. The sampling frequency is 500 Hz.

COP calculations: The COP trajectories with AP and ML coordinates were calculated as the point of application of the summed vertical force component, as measured by all available load sensors bearing weight. A single plate can determine the individual-limb and net COP trajectories by selecting either loaded sensors on one geometrical side, or all sensors of the entire plate. These calculations were performed using the system's own software (Footscan version 9, Materialize, BE).

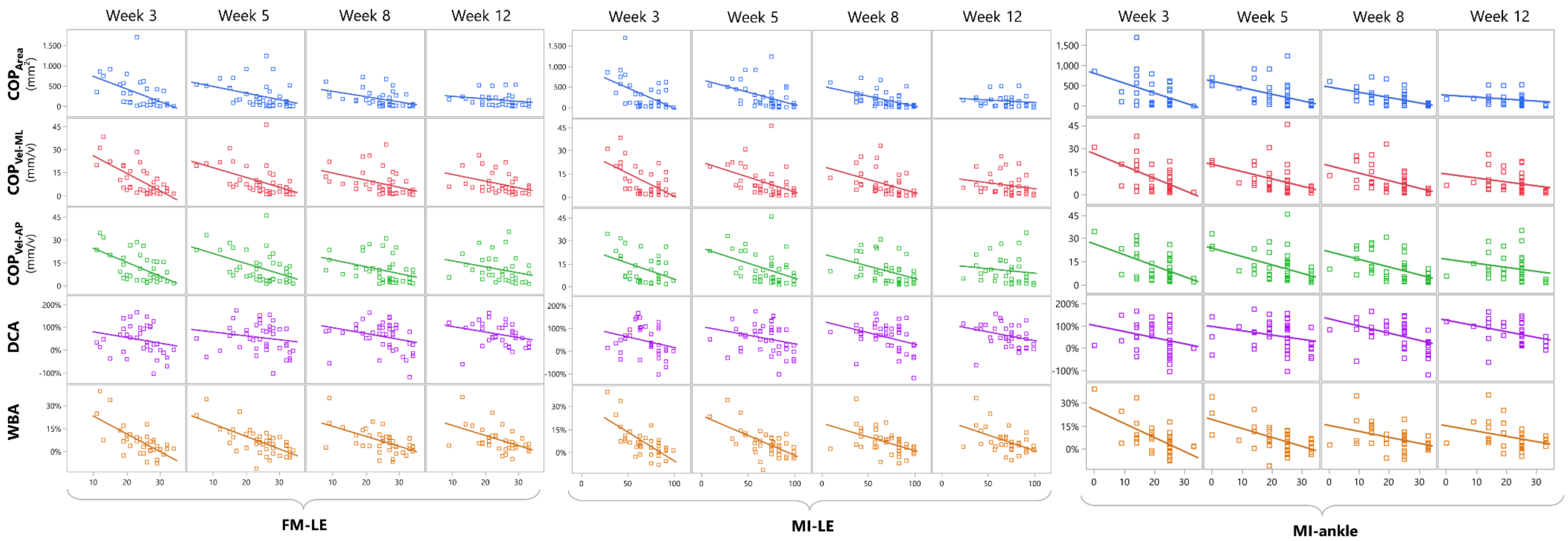
COP axes rotation: The foot orientation was determined using the plantar force distribution in order to algin the COP displacements along the foot axis. For this purpose, the second metatarsal bone and heel were located and new AP/ML axes were defined (see supplemental figure 2).



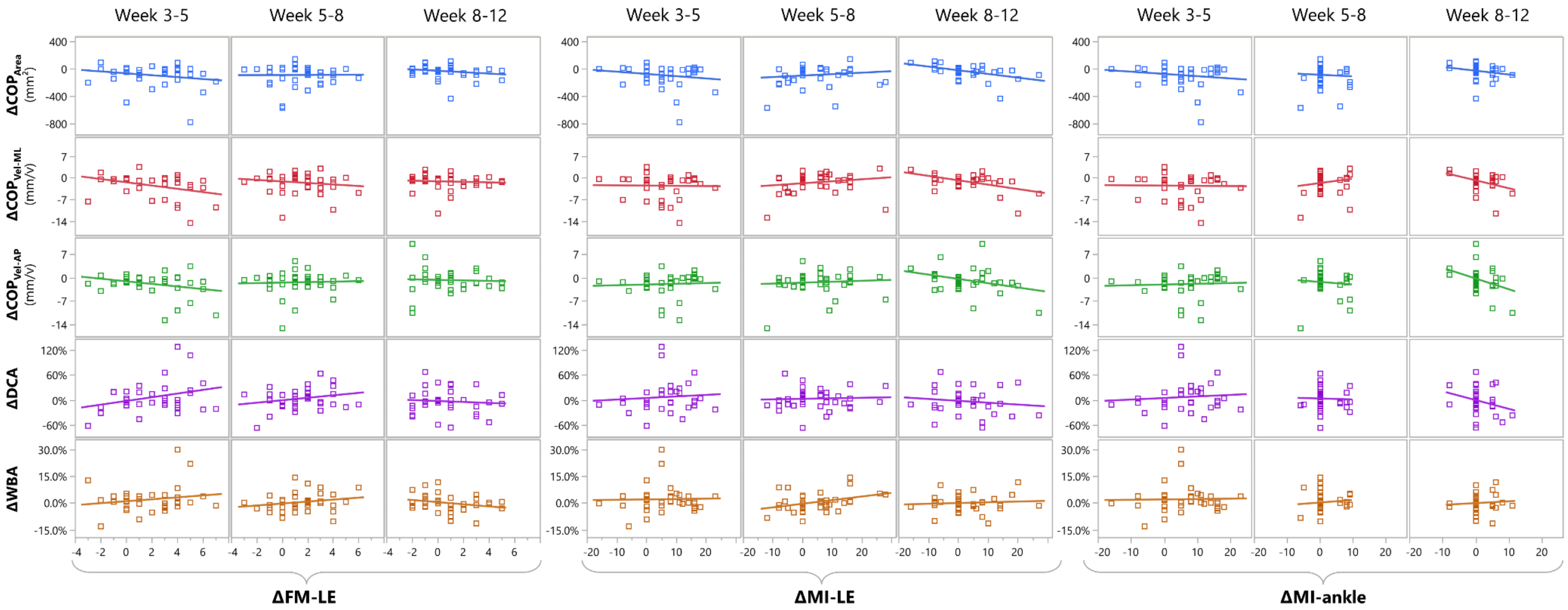
Supplementary figure 2: Screenshot of a COP recording of the Footscan software. The dashed magenta line represents the geometrical vertical center of the plate used to separate sensors for COP calculations of the left or right foot. The solid magenta line show the trial-specific foot orientation determined by the plantar pressure distribution (illustrated here as a heat map). The blue and red trajectories represent, respectively, the COP trajectories along the left and right foot axis. The white trajectory is the net COP trajectory.

APPENDIX C

Supplementary figures 3 and 4 respectively show scatterplots of the *between*- and *within*-subject associations between lower limb motor impairments on the one hand and metrics reflecting steady-state balance during quiet two-legged stance on the other.



Supplementary figure 3: Lower limb motor impairment severity plotted against quiet standing balance at 3, 5, 8 and 12 weeks post-stroke.
Abbreviations: COP, center-of-pressure; COPArea, area of the total COP; COPVel-ML, rms velocity of the total COP in the frontal plane; COPVel-AP, rms velocity of the total COP in the sagittal plane; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry; FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; MI-ankle, Motricity Index ankle item score.
Lower limb muscle synergies and strength are reflected by FM-LE (0-34) and MI-LE (0-100) scores. Strength at the level of the ankles is reflected by MI-ankle (0-33). Lower COPArea, COPVel-ML and COPVel-AP values indicate better postural stability. DCA and WBA values closer to zero indicate symmetry, and a positive value reflects greater contribution of the less-affected leg (and vice versa).



Supplementary figure 4: Improvements in lower limb motor impairments plotted against quiet standing balance across different epochs post-stroke. Abbreviations: Δ, change scores; COP, center-of-pressure; COP_{Area}, area of the total COP; $COP_{Vel\text{-}ML}$, rms velocity of the total COP in the frontal plane; $COP_{Vel\text{-}AP}$, rms velocity of the total COP in the sagittal plane; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry; FM-LE, Fugl-Meyer lower extremity motor score; MI-LE, Motricity Index lower extremity score; MI-ankle, Motricity Index ankle item score.
Improvements in impairments include lower limb muscle synergies and strength, reflected by FM-LE (0-34) and MI-LE (0-100) change scores. Improved strength at the level of the ankles is reflected by MI-ankle change scores (0-33). Lower COP_{Area}, $COP_{Vel\text{-}ML}$ and $COP_{Vel\text{-}AP}$ values indicate better postural stability. DCA and WBA values closer to zero indicate symmetry and a positive value reflects greater contribution of the less-affected leg (and vice versa).

4

CHAPTER 5

5

FEASIBILITY AND EFFECTIVENESS OF REPETITIVE GAIT TRAINING EARLY AFTER STROKE - A SYSTEMATIC REVIEW AND META-ANALYSIS.

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ABSTRACT

Background: Pre-clinical evidence suggests a period early after stroke during which the brain is most receptive to rehabilitation, if provided as high-dose motor training.

Objective: To evaluate the feasibility of repetitive gait training delivered within the first 3 months post-stroke and the effects on gait-specific outcomes.

Methods: PubMed, Web of Science, Cochrane Library, Rehab Data and PEDro databases were searched systematically. Randomized controlled trials were included to descriptively analyze the feasibility and quantitatively investigate the effectiveness of repetitive gait training compared to conventional therapy.

Results: Fifteen randomized controlled trials were included. Repetitive training can safely be provided through body weight support and locomotor assistance from therapists or a robotic device. No difference in drop-out rates was reported despite the demanding nature of the intervention. The meta-analysis yielded significant, but small, effects on walking independence and endurance. Training with end-effector robots appears most effective.

Conclusion: Robots enable a substantial, yet feasible, increase in the quantity of walking practice early post-stroke, which might enhance functional recovery. However, the mechanisms underlying these effects remain poorly understood.

5

Introduction

Stroke is a leading cause of long-term disability worldwide and a dramatic increase of incidence is expected.[1] Economic consequences are enormous,[2] particularly regarding stroke survivors who remain dependent on continuous support.[3] For social participation, regaining of mobility is obligatory.[4] However, more than 20% of stroke survivors do not reach independent walking[5,6] and, even if achieving independence, the great majority struggle to ambulate in the community.[7] These persisting disabilities will aggravate physical inactivity leading to deconditioning and poor long-term outcome.[5,8] If research fails to provide effective rehabilitation, the increasing incidence will inevitably lead to a growing dependent stroke population.

Considering that no therapeutic approach to date is proven to be superior[9] and effect sizes in clinical research are generally low,[10] it seems reasonable to reflect on basic research. Interesting pre-clinical evidence on timing of stroke rehabilitation has been published. In rodents, motor training loses effectiveness if provided delayed, i.e., after seven[11] and 30 days[12] post-stroke, respectively, compared with earlier exposure. This activity-induced recovery pattern matches the temporal pattern of increased gene expression important for neuronal growth and plasticity in the post-stroke brain.[13,14] Thus, it appears that a limited period of heightened plasticity is induced early after stroke, in which the brain is most receptive to rehabilitation.[14] Since this period is time-dependent, it is best described as a sensitive or critical period for stroke rehabilitation.[15]

In human stroke survivors, greatest gait recovery gains occur within the first three months post-stroke[5,16] and rehabilitative interventions outside this period have rather modest effects.[15,17,18] This time-dependent recovery profile corresponds highly to characteristics of a sensitive time-window, which might be reflected in the observed association between earlier rehabilitation and improved outcome.[19,20] This emphasizes the need to develop a rehabilitative approach designed to take advantage of this time-window.

Such an approach should include high-dose training initiated within the first weeks aiming at the recovery of normal function.[15] This is in great contrast with how rehabilitation is provided in current practice.[21,22] Therefore, this review aims to detect therapeutic strategies allowing such intensive therapy in the early phase when patients usually exhibit severe weakness and are unable to walk without significant support. It is hypothesized that highly repetitive gait training has the potential to improve long-term outcome when temporally matching the sensitive time-window.

However, there are concerns that application of rehabilitation too early might slow down recovery[23,24] or even induce infarct expansion.[25] Additionally, clinicians might limit the patient's effort to engage in exercise, since this can lead to short-term increases in spasticity[26] and an increased fall risk.[27] To clarify these aspects, all trials on early repetitive gait training will be collected to investigate feasibility as well as effectiveness.

The following research questions will be addressed:

- Which strategies providing repetitive walking practice to non-ambulatory patients early post-stroke are already investigated in scientific literature?
- Is early-initiated repetitive gait training feasible in terms of safety and patients' acceptance?
- Is repetitive gait training early after stroke more effective than conventional physiotherapy in terms of gait recovery, and do these effects persist?

Methodology

The current review was developed in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[28]

Definitions

According to the World Health Organization (WHO), stroke is defined as rapidly developing signs of disturbance of cerebral functions lasting more than 24 h (unless interrupted by surgery/death), with no apparent nonvascular cause.[29]

The focus here is on the early subacute phase, defined as the first three months post-stroke, i.e., the period during which most spontaneous gait recovery gains are observed.[5,16] Studies initiating gait training within a mean of at most 31 days post-stroke were included, to guarantee that the investigated population was exposed to the intervention protocol within this time-window. Furthermore, participants included in this review were non-ambulatory (i.e., Functional Ambulation Classification[30] (FAC) ≤ 3, or equivalent) as we aim to report interventions which can be provided to patients who are dependent in walking at onset.

The intervention was considered repetitive gait training if an "active motor sequence was performed repetitively within a single training session, and the practice was aimed towards a clear functional goal".[31] In this case, the motor sequence was defined as whole gait cycles and the functional goal as independent walking. The training might be provided with the assistance of therapists or with (electro-)mechanical devices, such as robots. Trials were excluded if training is combined with another intervention (e.g., electrical stimulation) and the effects could not be isolated.

A study was identified as a randomized controlled trial (RCT) if the participants were assigned prospectively to one of two (or more) alternative forms of intervention using random allocation. In included trials all groups spend an equal amount of time on therapy.

Literature Search

In October 2017, the following databases were searched for trials published between January 2000 and October 2017: PubMed, Web of Science, the Cochrane Library, PEDro and Rehab Data. Indexing terms and free-text words of the following key terms and synonyms were used: (Participants) "stroke" and "(sub)acute" or "inpatient"; (Intervention) "exercise therapy" or "task-specific training"; (Outcome) "gait" or "walking"; (Study design) "RCT". A detailed search strategy used in PubMed can be found in supplemental material (Supplemental Table 1). A search revision was scheduled while finalizing the manuscript to avoid missing recently published studies.

Search records were saved in EndNote X8. Duplicates were identified and removed. Afterwards, different screening phases based on abstracts and full-texts were conducted. Disagreement between two reviewers (JS, WS) performing study selection independently were discussed with a third reviewer (ST) to reach consensus.

Studies were included when (I.) patients had been diagnosed with stroke, (II.) the mean stroke interval (i.e., time between stroke onset and randomization) was ≤ 31 days, (III.) patients were non-ambulant (i.e., FAC ≤ 3), (IV.) effects of repetitive gait training were investigated and (V.) compared with conventional physiotherapy, (VI.) the study used an RCT design, and (VII.) the article was written in English, German, or Dutch.

Methodological Quality

The Physiotherapy Evidence Database Scale (PEDro), an 11-item scale, was used to assess methodological quality of included RCTs. All scores were obtained from the PEDro database. The first item, eligibility criteria, does not account for the total score and blinding of patients (item 5) and therapists (item 6) is impossible due to the nature of the intervention. Therefore, the maximum score is considered eight and the following classification is used: a PEDro score of 7-8 is considered good quality, while a score of 5-6 indicates moderate quality. To guarantee high-quality reporting, trials with a high risk of bias, i.e., a PEDro score ≤ 4, were excluded.

Outcomes

The following data were extracted from selected studies: sample size, stroke interval, baseline impairment, type of experimental intervention and characteristics, between-group differences in the occurrence of adverse events and drop-outs, and effects on gait-specific outcomes. In case of missing data or inadequate documentation, the corresponding author was contacted.

Outcomes of this review were reported in correspondence with the proposed research questions. This firstly includes a description of therapeutic strategies allowing non-ambulant stroke patients to repetitively train walking. Secondary, the two feasibility items safety, measured by the incidence of adverse events, and adherence to therapy, defined as the number of dropouts, were investigated. Thirdly, outcomes on effectiveness were investigated and classified according to the domains of the International Classification of Functioning Disability and Health (ICF) model.[32] All included studies had to include the ability to walk independently (i.e., primary outcome) as an outcome measure. Secondary gait-related outcomes were included, such as motor impairments of the affected leg and different measures on walking performance.

Quantitative Analysis

The Review Manager software (RevMan 5.3) was used for the quantitative synthesis on the comparative effectiveness. Therefore, the number of participants in both groups together with the means of post-intervention and follow-up outcome scores and their standard deviations were entered in RevMan 5.3 by one reviewer (JS) and cross-checked by another reviewer (WS or ST). If the scores were provided in medians and interquartile ranges, an algorithm developed by Wan et al.[33] was used to estimate means and standard deviations. Summary effect sizes (SES) were calculated with 95% confidence interval (95%CI) based on the effect sizes of individual studies. The mean differences (MD) were calculated since identical measures were used per comparison. When a dichotomized outcome on walking independence was reported, an odds ratio was additionally calculated. The I^2 statistic was used to determine between-study heterogeneity in results. If heterogeneity was high (i.e., $I^2 > 50\%$), a random-effects model was used instead of a fixed-effects model. In each comparison, a sub-analysis on the intervention type was performed. If at least three RCTs could be included in a sub-group, the results were reported separately. In addition, if results of two or more subgroups were given, the subgroup difference was established using a χ^2 test. Finally, the level of evidence drawn from the quantitative analysis were graded using a classification adapted from the Scottish Intercollegiate Guideline Network (SIGN) guidelines,[34] where the methodological quality of included RCTs and consistency of results (based on the I^2 test for heterogeneity) will be taken into account (see Table 1).

	Conclusion based on …
A	At least 3 RCTs with a low risk of bias with consistent results and a clinical meaningful effect.
B	At least 2 RCT with a low risk of bias but inconsistent results, or at least 2 RCTs with a moderate risk of bias with consistent results.
C	One RCT with a low risk of bias, or several RCTs with a moderate risk of bias with inconsistent results.
D	Lower.

Table 1. Rating the level of evidence adapted from the Scottish Intercollegiate Guideline Network (SIGN) guidelines.

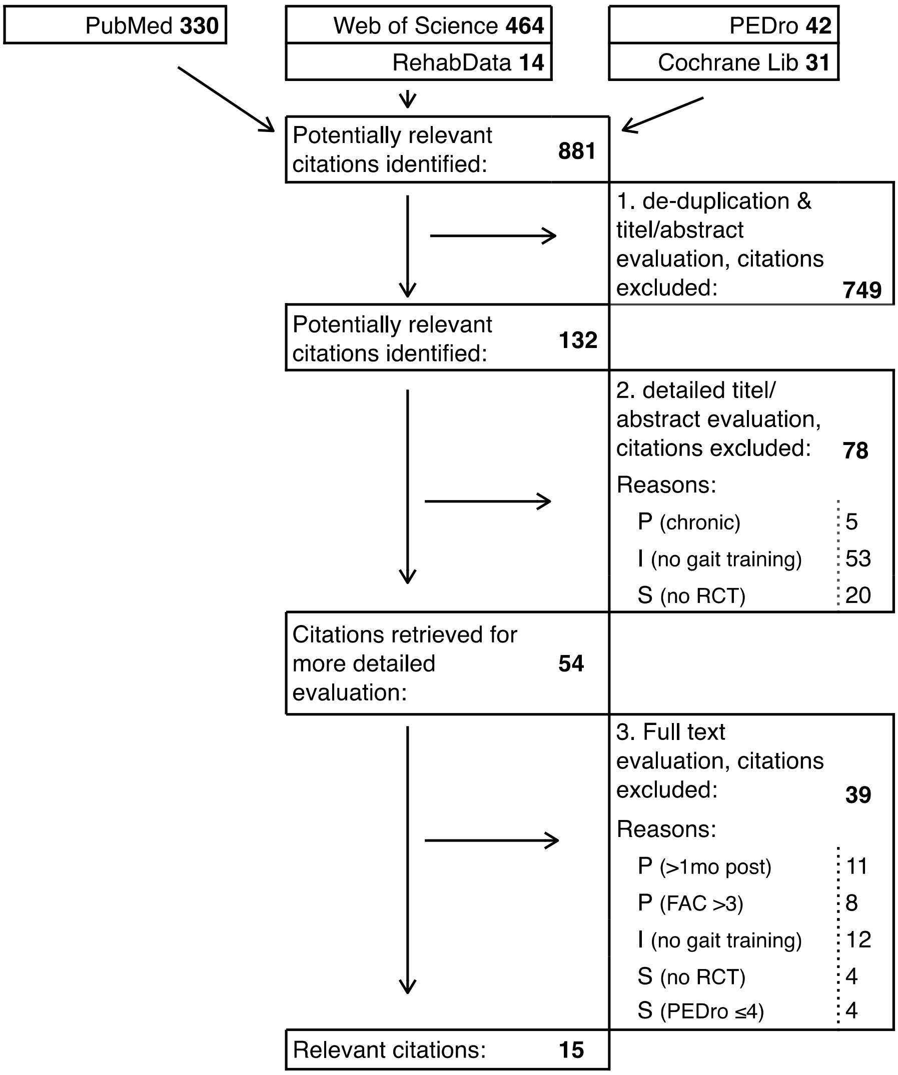
Results

Literature Search

In PubMed, the search strategy led to 330 hits on 24 October 2017 and a similar strategy was used in Web of Science. After identifying the two main interventions, i.e., body weight supported treadmill training (BWSTT) and robot-assisted gait training (RAGT), in other databases (Cochrane Library, Rehab Data, PEDro) the reviewers explicitly searched for those interventions. After de-duplication and a first phase screening on eligibility, 132 unique studies were included for detailed screening on abstract and afterwards on full-texts. Finally, 15 studies were included (Figure 1). A revision in August 2018 did not reveal additional eligible studies.

Methodological Quality

In the final screening phase, four studies were excluded due to insufficient quality. Of the remaining 15 studies, eight presented good (PEDro score 8[35-37] or 7[38-41]) and seven moderate quality (PEDro score 6[42-47] or 5[48,49]; Table 2). A detailed scoring is shown in Supplemental Table 2.



µFigure 1. Flow diagram of study identification and selection process.
Abbreviations: P, participants; I, intervention; S, study design

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ID	MQ	N	Stroke interval, days (SD)	Baseline motor impairment MI (SD) [0-99]	Type intervention	Frequency, duration of training	Additional time spent walking in the experimental group
		Experimental / Control group					
Peurala et al. 2009	5	17 / 20	8.6 (2.3) / 7.8 (3.0)	n/r	RAGT EE	5x/w, 3w	20min x 15 = 300min
Tong et al. 2006 Ng et al. 2008	7 6	15 / 20	16 (7.0) / 18.9 (8.7)	52.3 (21.2) / 51.6 (13.1)	RAGT EE	5x/w, 4w	20min x 20 = 400min
Morone et al. 2011 2012	6 7	12* / 12* 12 / 12	16.3 (11.3)* / 20 (12.8)* 21.9 (10.7) / 20 (15.7)	16.1 (11.4)* / 16.3 (9.5)* 52.0 (10.3) / 51.3 (12.7)	RAGT EE	5x/w, 4w	20min x 20 = 400min
Chua et al. 2016	7	53 / 53	27.2 (11.3) / 29.8 (14.1)	n/r	RAGT EE	6x/w, 8w	20min x 48 = 960min
Pohl et al. 2007	8	77 / 78	29.4 (12.6) / 31.5 (13.3)	32.3 (22.6) / 33.4 (24.0)	RAGT EE	5x/w, 4w	20min x 20 = 400min
Chang et al. 2012	7	20 / 17	16.1 (4.9) / 18.2 (5.0)	46.8 (9.1) / 47.3 (12.1)	RAGT Exo	5x/w, 2 w	40min x 10 = 400min
Han et al. 2016	5	30 / 26	21.6 (8) / 18.1 (9.8)	n/r	RAGT Exo	5x/w, 4w	30min x 20 = 600min
Schwartz et al. 2009	6	37 / 30	21.6 (8.7) / 23.6 (10.1)	n/r	RAGT Exo	3x/w, 6w	30min x 18 = 540min
Ochi et al. 2015	7	13 / 13	26.1 (8.0) / 22.9 (7.4)	n/r	RAGT Exo	5x/w, 4w	20min x 20 = 400min
Franceschini et al. 2009	6	52 / 45	16.7 (9.8) / 14.4 (7.3)	44.0 (31.3) / 51.0 (26.8)	BWSTT	5x/w, 4w	20min x 20 = 400min
Ada et al. 2010 Dean et al. 2010	8 8	64 / 62	18 (8) / 18 (7)	n/r	BWSTT	5x/w until discharge	30min each session
Nilsson et al. 2001	7	36 / 37	22 (range 10–56) / 18 (range 8–53)	n/r	BWSTT	5x/w until discharge	30min each session

Table 2. Characteristics of included studies regarding the methodological quality, recruited population and applied intervention.

* indicates the “low motricity group”, i.e., the group with more severe motor impairments at baseline.

Note, Tong et al. 2006 and Ng et al. 2008, Morone et al. 2011 and 2012, and Ada et al. 2010 and Dean et al. 2010 are, respectively, dependent studies as they investigated on the same dataset.

Abbreviations: MQ, methodological quality as assessed with the PEDro scale (…/10); SD, standard deviation; MI, the Motricity Index subscale for the lower limb; RAGT, robot-assisted gait training; BWSTT, body-weight supported treadmill training; EE, End-effector device; Exo, Exoskeleton device; n/r, not reported.

Outcomes

In the 15 studies, a total of 915 participants were treated and evaluated; RAGT was provided to 286 participants and BWSTT to 152 participants, while 425 participants were allocated to the control groups.

Descriptive analysis of the Intervention

All participants were provided with repetitive gait training or conventional therapy as an add-on to usual care, depending on the group to which they were allocated. In general, usual care included 25 to 60 min of daily physiotherapy and occupational therapy.

To allow non-ambulant patients in the experimental group to repetitively practice gait, various forms of manual and (electro)mechanical assistance were provided. Participants' body weight and trunk were (partly) supported by an overhead harness system, while stationary practicing walking on a treadmill or while being attached to moving footplates. In a single study, the trunk is not suspended in a harness, but a robotic device supports the legs and trunk for stance stability to allow full weight-bearing by the patient.[46]

Body weight supported training can be divided into BWSTT and RAGT depending on the kind of locomotor assistance provided. During BWSTT, patients train on a treadmill while therapists manually assist stance stability, swing initiation and forward progression of the paretic leg in a cyclical motion.[36,37,41,47] RAGT involves a similar stationary set-up while patients are not manually assisted by therapists, but with a robot. Two different kinds of robots can be classified based on the motion they apply to the patient (Figure 2):

- The Gait Trainer[35,39,40,42-44,48] is an end-effector device, meaning that motion is applied to the feet of the patient only by two footplates whose driven movement simulates stance- and swing-phase of a "normal" gait pattern. This kind of assistance differs from treadmill-based training, as during the whole gait-cycle the feet are in contact with the footplates and there is no foot clearance during swing.
- The exoskeleton Lokomat[38,45,49] is a robotic-driven orthosis consisting of actuators applying motion to the hip and knee joints of the patient to guide locomotion in a pre-programmed kinematic trajectory based on characteristics of a healthy symmetrical gait pattern. There is an exception to this division. Ochi et al.[46] investigated a treadmill-based system including robotic arms which guide thighs and legs to reproduce a physiological gait pattern. As this

5

system resembles characteristics of before-mentioned exoskeletons (i.e., precise control of hip and knee kinematics), it will be accounted as such in the following analyses.

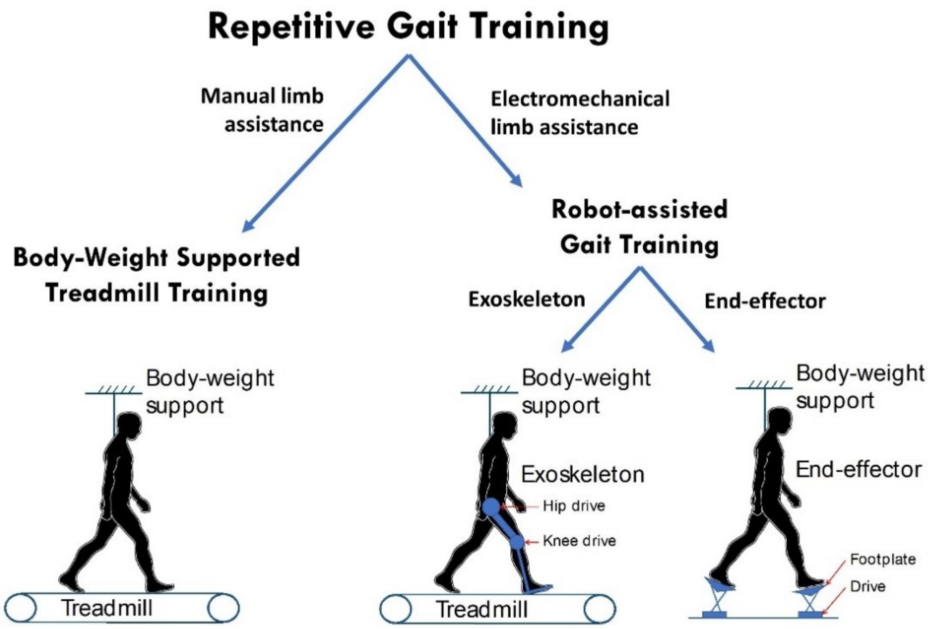

Figure 2. Graphic illustration of identified interventions.

The training modalities are compared to a control group which is provided with conventional physiotherapy. This includes, generally speaking, pre-gait exercises aiming at paretic leg strengthening and sitting balance. If possible, manual-assisted over-ground balance and gait training was provided. However, the exact content of the control intervention is poorly documented and described throughout the included studies.

Few studies provided detailed information on the therapy dose. Ada et al.[36] documented that participants were able to walk 129 m during the first session of BWSTT compared with only 26 m in the control group. Tong et al.[39] documented that participants performed about 500 to 1,000 steps during a session using an end-effector robot, and during conventional therapy 50 to 100 steps only. Pohl et al.[35] found that participants walked with the same device 851 to 1076 steps, similar to results of Morone et al.[43] In addition, Peurala et al.[48] found that, with robot assistance, participants were able to initially walk 20 min without needing resting breaks, while none in the control group were able to. A similar documentation on exoskeletons is lacking, but authors consistently declared that the exoskeleton allowed patients to practice walking at much higher doses compared to the control condition.[45,49]

Overall therapy dose, as measured by the total augmented time spent walking in the experimental group, is found to vary between 300 to 960 min. Most studies provided additional 400 min (or 6.7 h) of walking practice in 20 sessions over four weeks, meaning that five training sessions were provided weekly (Table 2).

	Adverse events	Drop outs	Activity level † (i.e., walking ability)				Body function level †	
	Exp/Ctr		Indepen-dence	≥3 mo Follow-up	Speed	Endurance	Motor Control	Muscle Strength
Peurala et al. 2009	0	5 / 3	x	x	x	x		
Tong et al. 2006 Ng et al. 2008	0	0 / 4	✓	✓	✓			x
Morone et al. 2011 2012	4 / 3	12 / 9	✓* x	✓* x	x	✓* x		x
Chua et al. 2016	0	7 / 13	x		x	x		
Pohl et al. 2007	0	5 / 6	✓	✓	✓			✓
Chang et al. 2012	0	1 / 3	x				✓	x
Han et al. 2016	0	0 / 4	x				x	
Schwartz et al. 2009	0	4 / 2	✓					
Ochi et al. 2015	0	0 / 0	✓		x		x	x
Franceschini et al. 2009	0	9 / 3	x	x	x	x		x
Ada et al. 2010 Dean et al. 2010	0	4 / 2	x					
Nilsson et al. 2001	0	4 / 3	x		x		x	

Table 3. Extracted data from included studies on feasibility and effectiveness on gait-specific outcomes, as documented in the published article.

Tong et al. 2006 and Ng et al. 2008, Morone et al. 2011 and 2012, and Ada et al. 2010 and Dean et al. 2010 are, respectively, dependent studies as they investigated on the same dataset. Abbreviations: *, the low motricity group, i.e., the group with more motor impairments at baseline; †, results on gait-specific outcome are reported as stated in the original article, these might differ from results of the meta-analysis due to differences in statistical methodology; (x), neutral or uncertain effect; (✓), beneficial effect or likely to be beneficial.

Descriptive analysis of the feasibility

In total, 53 patients dropped out of the experimental group, while 55 out of the control group (see Table 3). The majority of dropouts were unrelated to the intervention (e.g., scheduling interference). In a single study, adverse events were reported without any difference between experimental and control groups.[43] In addition, few studies reported minor events caused by training such as discomfort due to the harness,[47] hypotension,[43] pain,[36,43] or pressure sores[45] which led to a temporal discontinuity of the intervention. However, no study documented a significant difference between groups in the occurrence of such events (Table 3).

Quantitative analysis of the effectiveness

The following outcome measures on the comparative effectiveness of repetitive gait training were detected and classified according to the ICF.

1. Categorization:

Activity Level: The measurements assessing the ability to walk are classified under the activity domain “walking” (ICF d450).

- *Walking Independence:* Independence, the primary outcome, is either measured with the FAC, a 5-item scale measuring the degree of assistance required to walk, or by dichotomized outcome where the number of patients achieving independence (e.g., FAC ≥ 4) is scored.
- *Walking Speed:* The time is measured while participants walk over a 5- or 10-m distance at a comfortable pace to calculate walking speed.
- *Walking Endurance:* Endurance is assessed by asking the participant to walk the greatest possible distance during a period of 6 min.

Body Function Level:

- *Motor Control:* The motor subscale for the lower extremity of the Fugl-Meyer assessment (FM-LE) is classified under the domain “control of voluntary movements functions” (ICF b760).
- *Muscle Strength:* The (Medical Research Council) Motricity Index subscale for the lower extremity (MI-LE) measures strength of major leg muscle groups and is classified as “muscles power functions” (ICF b730).

The results of the meta-analysis for each outcome, as defined above (Table 4), are described below. Forrest plots were derived from RevMan (Supplemental figures 1-7).

2. Results:

Activity Level:

- *Walking Independence*: Post-intervention FAC scores were reported in 10 RCTs. Pooling yielded a nonsignificant heterogeneous SES (10 RCTs; N = 671 [exp 338; ctr 333]; MD = 0.38 [random]; 95%CI [-0.03; 0.78]; $P = 0.07$; $I^2 = 78\%$). There is a significant subgroup difference ($P = 0.002$) and the sub-analysis revealed end-effector training to be effective only (5 RCTs, N = 385 [exp 187; ctr 195]; MD = 0.73 [random]; 95%CI [0.17; 1.30]; $P = 0.01$; $I^2 = 75\%$).
  At follow-up (≥ 3 months), pooling of seven RCTs resulted in a significant heterogeneous SES (7 RCTs; N = 538 [exp 266; ctr 272]; MD = 0.57 [random]; 95%CI [0.14; 1.01]; $P = 0.01$; $I^2 = 66\%$). If pooling outcome of end-effector studies only, a heterogeneous SES is identified (5 RCTs; N = 381 [exp 186; ctr 195]; MD = 0.72 [random]; 95%CI [0.16; 1.28]; $P = 0.007$; $I^2 = 69\%$).
  Additionally, dichotomous outcome was pooled to calculate an odds ratio. Follow-up data was entered if provided and otherwise post-intervention data was used. This yielded significant heterogeneous results (8 RCTs; N = 627 [exp 312; ctr 315]; OR = 1.99 [random]; 95%CI [1.13; 3.53]; $P = 0.02$; $I^2 = 60\%$). If pooling end-effector studies only, a greater, but nonsignificant, SES is identified (5 RCTs; N = 382 [exp 187; ctr 195]; MD = 2.15 [random]; 95%CI [0.88; 5.28]; $P = 0.1$; $I^2 = 75\%$). Taking the inconsistency into account, there is level B evidence for improved walking independence after repetitive (robot-assisted) gait training.
- *Walking Speed:* Walking speed was assessed in nine RCTs and pooling yielded a nonsignificant homogenous SES (9 RCTs; N = 672 [exp 342; ctr 330]; MD = 0.05 [fixed]; 95%CI [-0.00; 0.11]; $P = 0.06$; $I^2 = 42\%$). No significant subgroup difference was found ($P = 0.41$).
- *Walking Endurance:* Endurance was evaluated in four RCTs. When pooling data, a significant homogenous SES (4 RCTs; N = 406 [exp 206; ctr 200]; MD = 24.36 [fixed]; 95%CI [3.58; 45.14]; $P = 0.02$; $I^2 = 43\%$) is found. Taking the inconsistent results into account, there is level B evidence for improved walking endurance after repetitive gait training. If

pooling end-effector trials only, a homogeneous significant SES is found (3 RCTs; N = 309 [exp 154; ctr 155]; MD = 32.08 [fixed]; 95%CI [8.30; 55.86]; *P* = 0.008; I^2 = 44%).

Body Function Level:

- *Motor Control:* Four RCTs assessed the FM-LE and pooling yielded a nonsignificant homogeneous SES (4 RCTs; N = 179 [exp 91; ctr 88]; MD = 0.52 [fixed]; 95%CI [-1.52; 2.59]; *P* = 0.62; I^2 = 28%). If pooling exoskeleton trials only, a nonsignificant heterogeneous SES is found (3 RCTs; N = 119 [exp 63; ctr 56]; MD = 0.76 [fixed]; 95%CI [-1.83; 3.36]; *P* = 0.56; I^2 = 51%).
- *Muscle Strength:* For a comparison on the MI-LE, results of 5 RCTs were pooled. This resulted in a non-significant heterogeneous SES (5 RCTs; N = 364 [exp 185; ctr 179]; MD = 3.64 [random]; 95%CI [-2.88; 10.17]; *P* = 0.27; I^2 = 56%). If isolating effects of end-effector trials, a significant homogeneous SES is identified (3 RCTs; N = 230 [exp 113; ctr 117]; 95%CI [2.08; 13.93]; *P* = 0.008; I^2 = 8%).

	Activity level (*i.e.,* walking ability)					Body function level	
	Walking Independence						
	Post-intervention (FAC, 0-5)	Follow-up (FAC, 0-5)	Follow-up (FAC, OR)	Walking Speed (5/10mWT, m/s)	Walking Endurance (6minWT, m)	Motor Control (FM-LE, 0-34)	Muscle Strength (MI-LE, 0-99)
Repetitive Gait Training	MD=0.38 [-0.03, 0.78]; *P*=.07; N=338/333 *	**MD=0.57 [0.14, 1.01]; *P*=.01; N=266/272**	**OR=1.99 [1.13, 3.53]; *P*=.02; N=312(65%)/ 315(50%)**	MD=0.05 [-0.00, 0.11]; *P*=.06; N=342/330	**MD=24.36 [3.58, 45.14]; *P*=.02; N=206/200**	MD=0.52 [-1.54, 2.59]; *P*=.62; N=91/88	MD=3.64 [-2.88, 10.57]; *P*=.27; N=185/179
- RAGT [Exo]	MD=-0.27 [-0.57, 0.03]; *P*=.08; N=63/56	?	?	?	?	MD=0.76 [-1.83, 3.36]; *P*=.56; N=63/56	?
- RAGT [EE]	**MD=0.73 [0.17, 1.30]; *P*=.01; N=187/195**	**MD=0.72 [0.16, 1.28]; *P*=.01; N186/195**	OR=2.15 [0.88, 3.53]; *P*=.10; N=187(61%)/ 195(43%)	**MD=0.08 [0.01, 0.15]; *P*=.03; N=171/176**	**MD=32.08 [8.30, 55.86]; *P*=.008; N=154/155**	?	**MD=8.00 [2.08, 13.93]; *P*=.008; N=113/117**
- BWSTT	?	?	?	MD=0.00 [-0.10, 0.10]; *P*=.99; N=122/111	?	?	?

Table 4. Results of the quantitative analysis on the comparative effectiveness of repetitive gait training. This includes gait-specific outcome on both body function and activity level. Sub-analyses based on the intervention type are performed for each comparison and results are analyzed if at least 3 RCTs could be included.

Effect sizes in **bold** present statistically significant (P<0.05) results in effectiveness in favor of repetitive gait training.

Abbreviations: *, a significant (*P*<0.05) subgroup differences was identified; RAGT, robot-assisted gait training; Exo, Exoskeleton; EE, End-effector; BWSTT, body-weight supported treadmill training; FAC, Functional Ambulatory Categories; 5/10mWT, 5 or 10 m walk test; 6minWT, 6 min walk test; FM-L, Fugl-Meyer motor assessment lower extremity subscale; MI-L, Motricity Index lower extremity subscale; MD, mean difference with 95% confidence interval; OR, Odds Ratio with 95% confidence interval and percentage of participants regaining walking independence; N, number of participants; ?, unknown effect due to lack of data (<3 RCTs).

Discussion

No between-group difference in the occurrence of adverse events and drop-outs was found despite the demanding nature of the intervention. This suggests that it is feasible to provide repetitive training early after stroke by the use of an overhead harness system for support of body weight, and manual or robotic assistance in forward progression of the paretic leg. Statistically significant effects on walking independence (at follow-up) and endurance were found in favor of repetitive training when compared to conventional therapy, according to level B evidence. Sub-analyses revealed that these effects are mainly based on studies investigating RAGT effects provided with an end-effector robot.

Dose-response relation in stroke rehabilitation.

In the context of neurological rehabilitation, repetitive training leads to task-specific improvements[10,31] and associated neuroplastic re-organization[50] if a sufficient dose of practice is provided. In animal models, synaptic changes in the motor cortex are observed after 400, but not after 60 reach-movements[51] and gait training is effective only if at least 1,000 steps are performed during a treadmill session.[52] Corresponding findings in clinical research are in favor of a dose-response relation in stroke rehabilitation.[17,53] Despite this solid association between larger quantities of practice and greater gains, inpatient rehabilitation is described as a time of being physically inactive[54,55] and the practice dose is far less than doses provided in previously mentioned stroke models; patients walk for a mean of 250 steps,[21] while non-ambulatory patients walked for as little as 6 to 16 steps during a therapeutic session aiming at gait.[56]

Technological advances can be of great value in providing more intensive rehabilitation as robots let non-ambulatory patients train at much higher doses.[57] For example, the Gait Trainer allows to execute approximately 1,000 steps in a session, while assistance of a single therapist is usually sufficient.[35,39,43] In line with a dose-response relation, training with such a device appears effective in improving walking independence and endurance post-intervention. This implies the importance of practice repetitions when designing effective interventions[58] and, in more general terms, the significance of motor learning in stroke rehabilitation.[14,50,59]

The observed dose-response relationship is not linear, indicating other factors to have an influence.[53] Morone et al.[43,44] compared responsiveness to training between groups who differ in baseline scores on the MI-LE (MI-LE ≈ 16 vs. 52). Outcomes clearly demonstrate that only the more-impaired patients benefit,[43,44] which is supported by Pohl et al.[35] as they found large effects in a more-affected population as well (MI-LE ≈ 32 at baseline; Table 2). Interestingly, the initial muscle strength of the paretic leg (e.g., assessed with the MI-LE[6]) measured within the first days to weeks post-stroke is associated to walking ability at six months.[5,6,60] Therefore, it appears that robot-assisted training was most effective in those patients with an initial poor prognosis. This might be related to a greater treatment contrast, since the more-affected patients do not engage in intensive rehabilitation under conventional conditions.[56] As suggested by Morone et al.,[57] future research should not address *if* RAGT is effective, but rather *who* may benefit.[43,57]

What drives improved walking ability after repetitive training?

It is essential to consider that the task performance in the context of stroke rehabilitation can improve either via restitution of impairments or compensation strategies.[15,61-63] While the included participants potentially improved their ability to walk, we do not know *how* these changes were achieved. The FAC does not reflect whether patients "returned towards more normal patterns of motor control" (i.e., behavioral restitution), or learned to "accomplish the goal through a new approach by the use of intact muscles, joints and effectors".[62,64] Since participants improved their ability to walk without greater normalization of motor control and strength of the paretic leg (see Table 4), it seems that it is rather through compensation that the included patients improved.

Compensation is frequently observed in the recovery of standing balance[65-67] and walking[68] as patients adopt an asymmetric pattern to shift the kinetic control towards the less-affected side, while normalization of motor control of the paretic leg is almost lacking.[69,70] However, robots provide practice in a symmetrical pattern, which at first sight appears paradoxical. In future trials, analyses on the quality of the gait pattern, including interlimb coordination in spatiotemporal and kinetic parameters, should be included to provide definitive evidence on mechanisms underlying effectiveness of early training.[64,71] This knowledge will have major implications for practice and designing robots for rehabilitation (i.e., trying to improve impairments or teaching compensation strategies).[15,72]

Future directions for robots in rehabilitation.

Despite evidence in support of repetitive training, small effect sizes are found. These are statistically significant, but the clinical importance is questionable. For example, an improvement of 24 m on the 6-min walk test does not exceed the established minimal clinically important difference of 50 m.[73]

It should be considered that interventions investigated to date are treadmill- or footplate-based. This means that massed practice of the same action is provided while the device controls balance via a supporting harness and gait via the pre-set belt speed.[74,75] Consequently, the patient is simply exposed to repetitive monotonous movement. However, animal models established that it is not such exposure to movement, but skill learning that guides neuroplastic changes.[50] This suggests that stroke rehabilitation requires a different concept of RAGT, where the patient is constantly challenged in engaging environments and through variable practice.[59]

The introduction of novel mobile exoskeletons might allow to combine high-dose practice through robotic assistance with the challenging nature of over-ground walking, since the patient has to actively initiate each step and control their balance, meaning that every step taken is treated as a novel problem to solve.[59,74] However, research on the usage of such devices is just beginning.

The need to change the current scientific approach.

Only 15 studies, of which three are dependent follow-up studies met the inclusion criteria. Those are in majority phase I or II trials with small samples. Therefore, this review agrees with Stinear et al.[76] who found that less than 10% of clinical trials are initiated in the first 30 days post-stroke. A priority shift in research towards the first weeks is required.[15,62]

This research requires a new approach.[62,77,78] First, stratification seems important, since a growing body of evidence suggests that not all patients have the same potential to recover.[6,79] Applying prognostic models may help to discriminate between these groups and to identify those patients who are most likely to benefit,[80] e.g., by assessing muscle strength of the paretic leg when enrolling participants.[6] Second, our quantitative analysis is based on post-intervention data, which means that the process of recovery is measured as a single outcome score on an arbitrary time-point. Considering that such trials are taking place in the background of spontaneous neurological recovery, a time-dependent process responsible for most improvements on body function and activity level,[63,81] assessments of participants should be performed repetitively and at fixed time-points relative to stroke onset.[77] This allows to encapsulate the process rather than simply the outcome of recovery. Third, most trials describe characteristics of the interventions poorly. A documentation on the dose in terms of repetitions is a far more accurate outcome compared to time scheduled for therapy.[23,53] This would allow to quantify the treatment contrast between groups to analyze a dose-response relationship.[53] Forth, this review highlights the need to shift the selection of outcome measures from scales simply measuring task accomplishment to those measuring the quality of movement, to gather evidence on *how* patients improve when engaging in task practice interventions.[14,15,63]

Conclusion

In total, 15 eligible studies were identified, which are in general pilot studies with small sample sizes. Consequently, well-designed motor rehabilitation trials starting in the first month post-stroke remain scarce. Repetitive gait training appears feasible and safe. Such training can lead to long-term functional improvements if provided early, but these observed effects are small. In sub-analyses, RAGT provided with an end-effector appears most effective and it seems that the more impaired patients benefit most. However, analyses on body function level yielded neutral effects and, consequently, the mechanisms underlying these functional gains after augmented gait training remain poorly understood. In the context of walking recovery after stroke, this review suggests that clinical research on early motor rehabilitation, including robot-assisted training, is still in its infancy.

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APPENDIX A

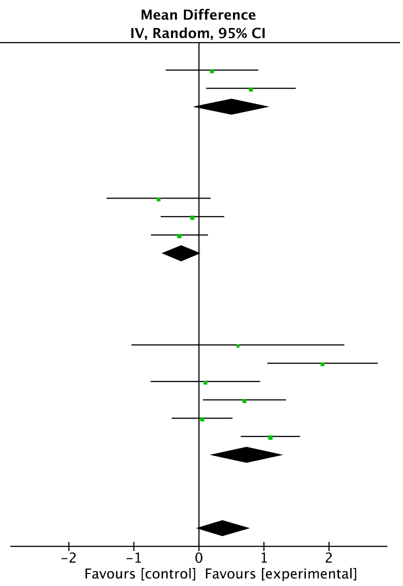
Forrest plots of effectiveness.

Summary effect sizes (SES) are calculated and illustrated based on immediate post-intervention and follow-up data on gait functions after (comparison 1) repetitive gait training compared to conventional PT, (comparison 2) RAGT compared to conventional PT, including a sub-analysis between different devices (End-effector versus Exoskeleton) and (comparison 3) BWSTT compared to conventional PT.

Abbreviations: RAGT, robot-assisted gait training; BWSTT, body weight supported treadmill training; FAC, Functional Ambulation Categories; IV, inverse variance; CI, confidence interval; df, degrees of freedom; HM, high motricity group; LM, low motricity group.

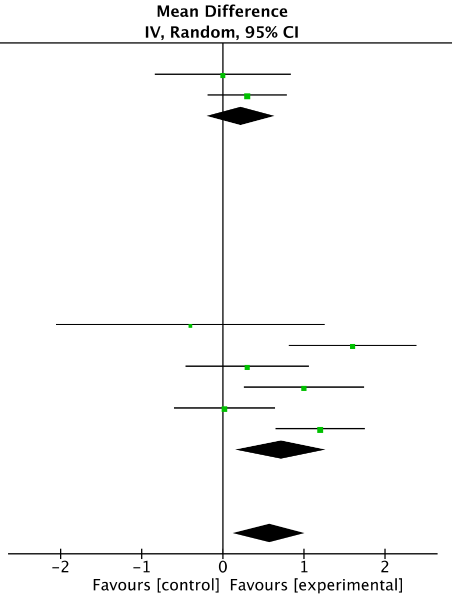
Supplemental figure I. *Walking independence ('raw' FAC scores) post-intervention.*

	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.3.1 BWSTT								
Nilsson 2001	2.8	1.5	36	2.6	1.6	37	9.1%	0.20 [−0.51, 0.91]
Franceschini 2009	3	1.5	52	2.2	1.9	45	9.2%	0.80 [0.11, 1.49]
Subtotal (95% CI)			**88**			**82**	**18.3%**	**0.51 [−0.08, 1.09]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.41$, df = 1 (P = 0.23); $I^2 = 29\%$								
Test for overall effect: Z = 1.69 (P = 0.09)								
1.3.2 RAGT Exoskeleton								
Han 2016	1.33	1.21	30	1.95	1.75	26	8.5%	−0.62 [−1.42, 0.18]
Chang 2012	1.3	0.7	20	1.4	0.8	17	10.6%	−0.10 [−0.59, 0.39]
Ochi 2015	3	0.1	13	3.3	0.8	13	10.9%	−0.30 [−0.74, 0.14]
Subtotal (95% CI)			**63**			**56**	**30.0%**	**−0.27 [−0.57, 0.03]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.22$, df = 2 (P = 0.54); $I^2 = 0\%$								
Test for overall effect: Z = 1.75 (P = 0.08)								
1.3.3 RAGT End−effector								
Peurala 2009	2.9	3	16	2.3	1.6	19	4.2%	0.60 [−1.04, 2.24]
Morone 2011 (LM)	4	0.9	12	2.1	1.2	12	8.1%	1.90 [1.05, 2.75]
Morone 2011 (HM)	3.8	1.1	12	3.7	1	12	8.2%	0.10 [−0.74, 0.94]
Ng 2008	3.2	0.8	17	2.5	1.2	21	9.6%	0.70 [0.06, 1.34]
Chua 2016	2.28	1.15	53	2.23	1.3	53	10.8%	0.05 [−0.42, 0.52]
Pohl 2007	3.2	1.4	77	2.1	1.5	78	10.8%	1.10 [0.64, 1.56]
Subtotal (95% CI)			**187**			**195**	**51.7%**	**0.73 [0.17, 1.30]**
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 20.01$, df = 5 (P = 0.001); $I^2 = 75\%$								
Test for overall effect: Z = 2.54 (P = 0.01)								
Total (95% CI)			**338**			**333**	**100.0%**	**0.38 [−0.03, 0.78]**
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 45.33$, df = 10 (P < 0.00001); $I^2 = 78\%$								
Test for overall effect: Z = 1.80 (P = 0.07)								
Test for subgroup differences: $Chi^2 = 12.22$, df = 2 (P = 0.002), $I^2 = 83.6\%$								



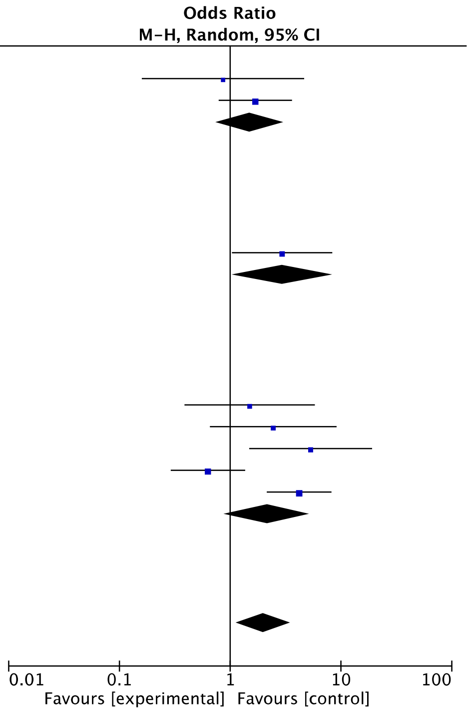
Supplemental figure II. *Walking independence ('raw' FAC scores) follow-up.*

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 BWSTT								
Nilsson 2001	3.3	1.7	28	3.3	1.6	32	11.6%	0.00 [−0.84, 0.84]
Franceschini 2009	4.3	0.8	52	4	1.5	45	16.1%	0.30 [−0.19, 0.79]
Subtotal (95% CI)			**80**			**77**	**27.7%**	**0.22 [−0.20, 0.65]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.37$, df = 1 (P = 0.54); $I^2 = 0\%$								
Test for overall effect: Z = 1.04 (P = 0.30)								
1.4.2 RAGT Exoskeleton								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.4.3 RAGT End-effector								
Peurala 2009	3.3	3.3	16	3.7	0.8	19	5.2%	−0.40 [−2.06, 1.26]
Morone 2012 (LM)	4.7	0.5	12	3.1	1.3	12	12.2%	1.60 [0.81, 2.39]
Morone 2012 (HM)	4.3	0.9	12	4	1	12	12.5%	0.30 [−0.46, 1.06]
Ng 2008	4	1	16	3	1.3	21	12.8%	1.00 [0.26, 1.74]
Chua 2016	3.02	1.55	53	3	1.72	53	14.3%	0.02 [−0.60, 0.64]
Pohl 2007	3.8	1.7	77	2.6	1.8	78	15.3%	1.20 [0.65, 1.75]
Subtotal (95% CI)			**186**			**195**	**72.3%**	**0.72 [0.16, 1.28]**
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 15.91$, df = 5 (P = 0.007); $I^2 = 69\%$								
Test for overall effect: Z = 2.54 (P = 0.01)								
Total (95% CI)			**266**			**272**	**100.0%**	**0.57 [0.14, 1.01]**
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 20.58$, df = 7 (P = 0.004); $I^2 = 66\%$								
Test for overall effect: Z = 2.57 (P = 0.01)								
Test for subgroup differences: $Chi^2 = 1.94$, df = 1 (P = 0.16), $I^2 = 48.4\%$								



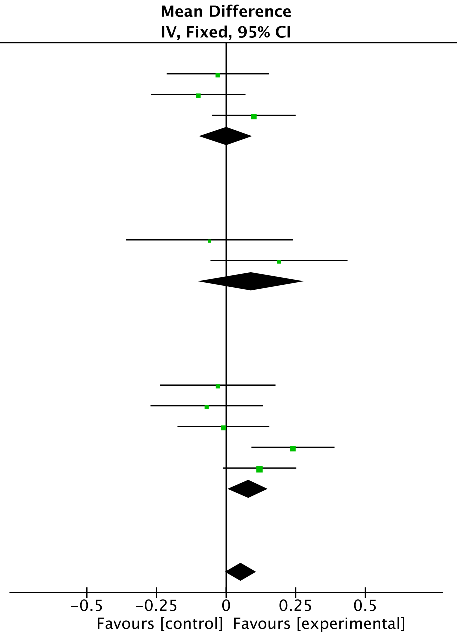
Supplemental figure III. *Walking independence (dichotomized FAC scores) post-intervention/follow-up.*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 BWSTT						
Nilsson 2001	25	28	29	32	7.6%	0.86 [0.16, 4.66]
Ada/Dean 2010	43	60	36	60	16.0%	1.69 [0.79, 3.62]
Subtotal (95% CI)		**88**		**92**	**23.6%**	**1.50 [0.75, 3.02]**
Total events	68		65			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0\%$						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.5.2 RAGT Exoskeleton						
Schwartz 2009	20	37	8	28	12.8%	2.94 [1.04, 8.36]
Subtotal (95% CI)		**37**		**28**	**12.8%**	**2.94 [1.04, 8.36]**
Total events	20		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.5.3 RAGT End-effector						
Peurala 2009	10	16	10	19	9.9%	1.50 [0.39, 5.81]
Ng 2008	11	17	9	21	10.2%	2.44 [0.65, 9.13]
Morone 2012	19	24	10	24	10.6%	5.32 [1.48, 19.06]
Chua 2016	20	53	26	53	15.9%	0.63 [0.29, 1.36]
Pohl 2007	54	77	28	78	17.1%	4.19 [2.14, 8.21]
Subtotal (95% CI)		**187**		**195**	**63.6%**	**2.15 [0.88, 5.28]**
Total events	114		83			
Heterogeneity: $Tau^2 = 0.75$; $Chi^2 = 15.71$, df = 4 (P = 0.003); $I^2 = 75\%$						
Test for overall effect: Z = 1.67 (P = 0.10)						
Total (95% CI)		**312**		**315**	**100.0%**	**1.99 [1.13, 3.53]**
Total events	202		156			
Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 17.43$, df = 7 (P = 0.01); $I^2 = 60\%$						
Test for overall effect: Z = 2.37 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 1.17$, df = 2 (P = 0.56), $I^2 = 0\%$						



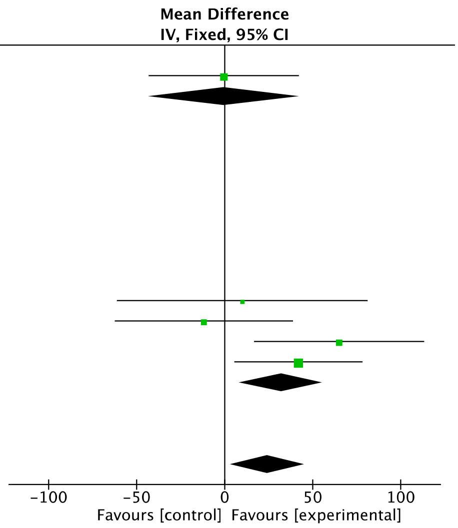
Supplemental figure IV. *Walking speed (5/10-meter walk test, m/s) post-intervention.*

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 BWSTT								
Franceschini 2009	0.57	0.46	52	0.6	0.46	45	9.2%	−0.03 [−0.21, 0.15]
Nilsson 2001	0.7	0.3	32	0.8	0.4	34	10.7%	−0.10 [−0.27, 0.07]
Ada/Dean 2010	0.57	0.36	38	0.47	0.28	32	13.7%	0.10 [−0.05, 0.25]
Subtotal (95% CI)			**122**			**111**	**33.6%**	**0.00 [−0.10, 0.10]**
Heterogeneity: Chi² = 3.14, df = 2 (P = 0.21); I² = 36%								
Test for overall effect: Z = 0.02 (P = 0.99)								
1.6.2 RAGT Exoskeleton								
Schwartz 2009	0.31	0.37	37	0.37	0.77	30	3.4%	−0.06 [−0.36, 0.24]
Ochi 2015	0.38	0.43	12	0.19	0.07	13	5.1%	0.19 [−0.06, 0.44]
Subtotal (95% CI)			**49**			**43**	**8.5%**	**0.09 [−0.10, 0.28]**
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%								
Test for overall effect: Z = 0.92 (P = 0.36)								
1.6.3 RAGT End−effector								
Morone 2011 (HM)	0.49	0.21	12	0.52	0.3	12	7.2%	−0.03 [−0.24, 0.18]
Chua 2016	0.56	0.45	53	0.63	0.6	53	7.6%	−0.07 [−0.27, 0.13]
Morone 2011 (LM)	0.36	0.11	12	0.37	0.27	12	11.4%	−0.01 [−0.17, 0.15]
Ng 2008	0.43	0.21	17	0.19	0.26	21	13.9%	0.24 [0.09, 0.39]
Pohl 2007	0.44	0.47	77	0.32	0.36	78	17.8%	0.12 [−0.01, 0.25]
Subtotal (95% CI)			**171**			**176**	**57.8%**	**0.08 [0.01, 0.15]**
Heterogeneity: Chi² = 9.10, df = 4 (P = 0.06); I² = 56%								
Test for overall effect: Z = 2.13 (P = 0.03)								
Total (95% CI)			**342**			**330**	**100.0%**	**0.05 [−0.00, 0.11]**
Heterogeneity: Chi² = 15.62, df = 9 (P = 0.08); I² = 42%								
Test for overall effect: Z = 1.90 (P = 0.06)								
Test for subgroup differences: Chi² = 1.78, df = 2 (P = 0.41), I² = 0%								



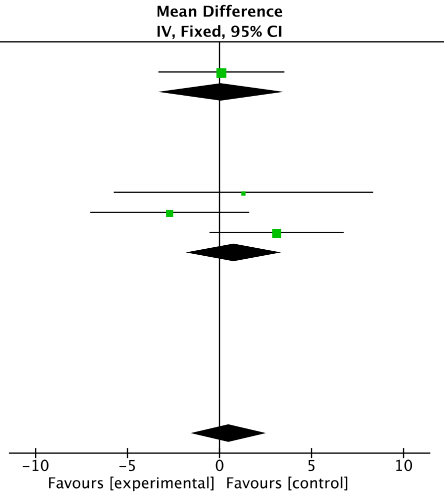
Supplemental figure V. *Walking endurance (6-min walk test, m) post-intervention.*

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 BWSTT								
Franceschini 2009	169.7	86.2	52	170.2	122.1	45	23.7%	−0.50 [−43.18, 42.18]
Subtotal (95% CI)			**52**			**45**	**23.7%**	**−0.50 [−43.18, 42.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.02 (P = 0.98)								
1.7.2 RAGT Exoskeleton								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.7.3 RAGT End−effector								
Morone 2011 (HM)	161	89	12	151	89	12	8.5%	10.00 [−61.21, 81.21]
Chua 2016	145.1	121	53	156.9	144	53	16.8%	−11.80 [−62.44, 38.84]
Morone 2011 (LM)	156	78	12	91	35	12	18.4%	65.00 [16.63, 113.37]
Pohl 2007	134.4	125.5	77	92.5	104.9	78	32.5%	41.90 [5.46, 78.34]
Subtotal (95% CI)			**154**			**155**	**76.3%**	**32.08 [8.30, 55.86]**
Heterogeneity: Chi² = 5.31, df = 3 (P = 0.15); I² = 44%								
Test for overall effect: Z = 2.64 (P = 0.008)								
Total (95% CI)			**206**			**200**	**100.0%**	**24.36 [3.58, 45.14]**
Heterogeneity: Chi² = 7.02, df = 4 (P = 0.13); I² = 43%								
Test for overall effect: Z = 2.30 (P = 0.02)								
Test for subgroup differences: Chi² = 1.71, df = 1 (P = 0.19), I² = 41.5%								



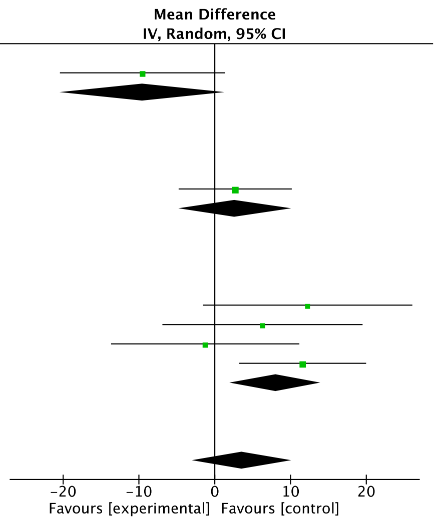
Supplemental figure VI. *Motor control (Fugl-Meyer Assessment motor subscale for the lower extremity) post-intervention.*

	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
1.1.1 BWSTT								
Nilsson 2001	25.4	5.9	28	25.3	7.6	32	36.5%	0.10 [−3.32, 3.52]
Subtotal (95% CI)			**28**			**32**	**36.5%**	**0.10 [−3.32, 3.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
1.1.2 RAGT Exoskeleton								
Ochi 2015	10.3	9.97	13	9	8.3	13	8.6%	1.30 [−5.75, 8.35]
Han 2016	13.43	8.34	30	16.14	8.13	26	22.9%	−2.71 [−7.03, 1.61]
Chang 2012	22.7	5.7	20	19.6	5.6	17	32.1%	3.10 [−0.55, 6.75]
Subtotal (95% CI)			**63**			**56**	**63.5%**	**0.76 [−1.83, 3.36]**
Heterogeneity: Chi^2 = 4.08, df = 2 (P = 0.13); I^2 = 51%								
Test for overall effect: Z = 0.58 (P = 0.56)								
1.1.3 RAGT End−effector								
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**91**			**88**	**100.0%**	**0.52 [−1.54, 2.59]**
Heterogeneity: Chi^2 = 4.17, df = 3 (P = 0.24); I^2 = 28%								
Test for overall effect: Z = 0.49 (P = 0.62)								
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.76), I^2 = 0%								



Supplemental figure VII. *Muscle strength (Motricity Index subscale for the lower extremity) post-intervention.*

	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.2.1 BWSTT								
Franceschini 2009	61	31.26	52	70.53	23.36	45	16.6%	−9.53 [−20.43, 1.37]
Subtotal (95% CI)			**52**			**45**	**16.6%**	**−9.53 [−20.43, 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.71 (P = 0.09)								
1.2.2 RAGT Exoskeleton								
Chang 2012	56.2	11	20	53.5	12	17	21.9%	2.70 [−4.77, 10.17]
Subtotal (95% CI)			**20**			**17**	**21.9%**	**2.70 [−4.77, 10.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
1.2.3 RAGT End−effector								
Morone 2011 (LM)	65.08	19.28	12	52.83	14.99	12	12.9%	12.25 [−1.57, 26.07]
Ng 2008	74.7	22.1	17	68.4	18.7	21	13.6%	6.30 [−6.90, 19.50]
Morone 2011 (HM)	77.17	16.76	12	78.42	14.18	12	14.5%	−1.25 [−13.67, 11.17]
Pohl 2007	53.8	25.1	72	42.2	26.1	72	20.4%	11.60 [3.24, 19.96]
Subtotal (95% CI)			**113**			**117**	**61.5%**	**8.00 [2.08, 13.93]**
Heterogeneity: Tau^2 = 3.15; Chi^2 = 3.27, df = 3 (P = 0.35); I^2 = 8%								
Test for overall effect: Z = 2.65 (P = 0.008)								
Total (95% CI)			**185**			**179**	**100.0%**	**3.64 [−2.88, 10.17]**
Heterogeneity: Tau^2 = 36.05; Chi^2 = 11.38, df = 5 (P = 0.04); I^2 = 56%								
Test for overall effect: Z = 1.09 (P = 0.27)								
Test for subgroup differences: Chi^2 = 7.75, df = 2 (P = 0.02), I^2 = 74.2%								



APPENDIX B

Supplemental table I. Search strategy used in PubMed.

Search Strategy in PubMed	Results
((("stroke"[Mesh] OR "stroke"[All Fields]) OR ("cerebrovascular accident"[All Fields] OR ("cerebrovascular"[All Fields] AND "accident"[All Fields]))) AND ("acute"[All Fields] OR "sub-acute"[All Fields] OR "subacute"[All Fields] OR "early"[All Fields] OR "inpatient"[All Fields] OR "in-patient"[All Fields])) AND (("exercise"[Mesh] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[All Fields] OR ("exercise"[All Fields] AND "therapy"[All Fields])) OR ("physical therapy modalities"[MeSH Terms] OR "physical therapy"[All Fields] OR ("physical"[All Fields] AND "therapy"[All Fields]) OR "active therapy"[All Fields] OR ("active"[All Fields] AND "therapy"[All Fields])) OR ("rehabilitation"[All Fields] OR "rehabilitation"[MeSH Terms]) OR "training"[All Fields] OR "treadmill"[All Fields] OR ("task-specific"[All Fields] OR "taskspecific"[All Fields] OR ("task"[All Fields] AND ("specific"[All Fields] OR "specificity"[All Fields])))) AND ("walking"[Mesh] OR "walking"[All Fields] OR "locomotion"[Mesh] OR "early Ambulation"[Mesh] OR "ambulation"[All Fields] OR "gait"[Mesh] OR "gait"[All Fields] OR "mobility"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields] OR "RCT"[All Fields])	24/10/2017: 331 Hits

APPENDIX C

Supplemental table II. Detailed scoring on methodological quality using the PEDro scale.

	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimates and variability	**Score**
Peurala et al. 2009	X	X	X	X						X	X	**5**
Chang et al. 2012	X	X	X	X			X	X		X	X	**7**
Tong et al. 2006	X	X		X			X	X	X	X	X	**7**
Ng et al. 2008	X	X		X				X	X	X	X	**6**
Morone et al. 2011	X	X		X			X		X	X	X	**6**
Morone et al. 2012		X		X			X	X	X	X	X	**7**
Han et al. 2016	X	X		X			X			X	X	**5**
Schwartz et al. 2009	X	X		X			X		X	X	X	**6**
Ochi et al. 2015	X	X	X	X			X			X	X	**6**
Chua et al. 2016	X	X	X	X			X		X	X	X	**7**
Pohl et al. 2007	X	X	X	X			X	X	X	X	X	**8**
Franceschini et al. 2009	X	X		X			X		X	X	X	**6**
Ada et al. 2010	X	X	X	X			X	X	X	X	X	**8**
Dean et al. 2010	X	X	X	X			X	X	X	X	X	**8**
Nilsson et al. 2001	X	X	X	X			X	X		X	X	**7**
	14/15	15/15	8/15	15/15	0/15	0/15	13/15	8/15	10/15	15/15	15/15	

5

CHAPTER 6

6

EXOSKELETON-ASSISTED TRAINING TO ENHANCE LOWER LIMB MOTOR RECOVERY IN EARLY SUBACUTE STROKE: DOES TIMING MATTER? A PILOT RANDOMIZED TRIAL

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Submitted for peer-review.

ABSTRACT

Background: The course of lower limb motor recovery (e.g., muscle synergies) in the first 5 weeks poststroke suggests a time-sensitive period for impairment-focused therapies, such as exoskeleton-type robots that promote symmetric gait.

Objective: (1) To compare early robotic training (ERT) with usual care against usual care alone on restoring intralimb muscle synergies and interlimb symmetry during functional tasks; (2) To investigate whether ERT is superior to delayed robotic training (DRT) starting after the proposed sensitive period.

Methods: This observer-blinded, randomized pilot trial with cross-over design involved 19 non-ambulatory adults included within 14 days poststroke. Those allocated to ERT (N=10) received immediately 4 weeks of training (16 sessions, 4x/week) with the Ekso GT® above usual care and were compared with DRT subjects (N=9) who received usual care alone. After a 3-week washout, the interventional roles exchanged; DRT subjects received the same robotic protocol starting at week 8 poststroke and ERT subjects received usual care as the controls. Outcomes included change in Fugl-Meyer lower extremity scores (FM-LE) reflecting muscle synergies, weight-bearing asymmetry (WBA) and dynamic control asymmetry (DCA) while quiet standing, and functional ambulation categories (FAC) classifying walking independence. To explore trends in effectiveness, between-group differences were estimated at α-levels 0.05 and 0.15.

Results: A trend toward faster FAC recovery favoring ERT over usual care alone (α=0.15, β=0.79, 85%CI[0.03;1.55]) was not accompanied by between-group differences in FM-LE recovery, or WBA and DCA (objective 1). No differences were found favoring restorative effects of ERT over DRT (objective 2).

Conclusion: This pilot study shows the feasibility of a trial investigating a wearable exoskeleton as an adjunct therapy early poststroke. However, our preliminary findings suggest that motor recovery was not enhanced by 4 weeks training to reduce compensations, irrespective of timing of application poststroke.

6

Introduction

Approximately 65-80% of stroke survivors eventually regain the ability to walk independently within the first 3-6 months poststroke.[1-3] However, neurological recovery from motor impairments affecting the lower limb (e.g., muscle synergies) seems to plateau within 5-8 weeks poststroke, which parallels spontaneous recovery as observed for the paretic upper limb.[4,5] Unfortunately, in most cases, recovery is incomplete and synergistic co-activation persists when performing functional tasks.[6,7] As a consequence, people with stroke typically prefer asymmetric postures[6,8,9] and stepping patterns[10,11] when regaining walking by compensating with the less-affected limb.

The critical recovery period,[4,5] with associated enhanced levels of brain plasticity,[12,13] suggests an ideal timing for impairment-focused therapies. Therefore, the question arises if we can prevent compensations by symmetry-oriented training in patients unable to walk at onset. Exoskeleton-type robots may be an ideal therapeutic tool for addressing this question by their ability to "normalize" hemiparetic gait by mimicking symmetrical step trajectories of able-bodied controls.[14,15] However, despite a trend favoring robotic training over conventional therapies on achieving walking independence in early subacute stroke,[16,17] hardly any exoskeleton trials delivered their intervention in the initial 5 weeks post-stroke. Moreover, these trials often lack objective biomechanical outcomes that adequately reflect normalization of a task performance,[18] such as symmetry in standing balance control[8,19] and spatiotemporal step parameters while walking.[10,20] Following the Stroke Rehabilitation and Recovery Roundtable (SRRR),[21-23] these outcomes are prerequisite to better understand intervention-related performance changes by distinguishing behavioral restitution from compensatory task improvements.

Acknowledging the lack of early-starting exoskeleton trials, a pilot study was conducted. In addition to exploring the feasibility of study procedures, our aim was to investigate preliminary effects of a 4-week early robotic training (ERT) intervention using the Ekso GT® wearable exoskeleton[24,25] with usual care (ERT+UC) against early usual care (EUC) alone on enhancing intralimb motor recovery and restoring interlimb symmetry during functional tasks. Inspired by the recent CPASS study[26,27] on the time dependence of upper limb training effects after stroke, a second aim was to investigate whether timing within the critical recovery period matters. Therefore, we investigated whether effects of additional robotic training are more pronounced when applied in the first 5 weeks poststroke than delayed robotic training with usual care

(DRT+UC) starting at 8 weeks poststroke, using mere usual care as the control intervention at both timings.

Regarding objective 1, we hypothesized that ERT+UC is superior to EUC in improving muscle synergies, as reflected by Fugl-Meyer lower extremity motor scores (FM-LE) beyond spontaneous recovery.[4,5] Due to significant impairment reductions, we further expected normalization (i.e., more equal limb contributions) in terms of weight-bearing asymmetry (WBA) and dynamic control asymmetry (DCA) while quiet standing, and step length asymmetry (SLA) while walking. Regarding objective 2, we expected that DRT+UC applied from 8 weeks poststroke would be less effective in improving muscle synergies and, thereby, restore interlimb symmetry relative to delayed usual care (DUC), than ERT+UC compared with EUC. This would support preclinical evidence for a time-sensitive period for enhancing behavioral restitution through timely motor training.[13,28]

Methods

This study is part of the TARGEt research project (Temporal Analyses of the Responsiveness of hemiplegic Gait and standing balance early poststroke) and was funded by the Research Foundation Flanders (FWO), Belgium. This study was approved by the medical ethics committee of the University Hospital Antwerp (No. 18/25/305; Belgium trial registration no. B300201837010). The protocol was registered online (ClinicalTrials.gov, no. NCT03727919), and the findings were reported according to CONSORT guidelines adapted for pilot trials.[29]

Patient selection

Adults referred to the neurology wards of the Antwerp University Hospital (Edegem, BE) and GZA hospitals St Augustinus (Wilrijk, BE) and St Vincentius (Antwerp, BE) with suspicion of stroke were screened. Potential candidates were identified as being 18–90 years old, having a first-ever, CT- or MRI-confirmed cortical, subcortical, or midbrain infarct or hemorrhage, and exhibiting one-sided weakness.

Information about the study was presented to each potential candidate. Once informed consent was given, eligibility was confirmed if participants required inpatient rehabilitation care, exhibited persistent leg weakness (i.e., Motricity Index leg score [MI-LE] ≤ 75) and walking dependency (i.e., Functional Ambulation Categories [FAC] ≤ 1) at the time of inclusion, and had no other significant orthopedic or neurological condition or any contraindications for using the exoskeleton (e.g., bodyweight > 95 kg, severe hypertonia/contracture).

Design

The current study was an observer-blinded randomized trial with a cross-over design (Figure 1). At baseline (i.e., ≤ 14 days poststroke), participants were allocated to either the ERT or DRT study arms. Randomization was concealed by using sealed opaque envelopes and executed by an uninvolved person. Randomization was blocked (2-by-2 ratio) and stratified according to the prognosis for achieving walking independence (i.e., FAC ≥ 4). Following the validated EPOS model,[2,30] a favorable prognosis was defined as having sitting balance (i.e., Trunk Control Test - sitting item [TCT-sit] > 25) and leg strength (ie, MI-LE ≥ 25). A poor prognosis was assigned if either function was impaired.

The experimental intervention was a 4-week robotic training regime (16 45-min sessions, 4x/week) delivered additional to usual care. The ERT arm received this intervention immediately after inclusion and up to week 5 poststroke (i.e., ERT+UC), whereas the DRT group received EUC to serve as controls. After a 3-week washout, the intervention roles exchanged. The DRT group received delayed robotic training following the same standardized protocol between weeks 8 and 12 poststroke (i.e., DRT+UC), whereas the ERT group received DUC. Thus, between-group comparisons for estimating treatment effects were ERT+UC vs. EUC before washout (i.e., early period), and DRT+UC vs. DUC after washout (i.e., delayed period).

Measurements were performed at baseline and at weeks 5, 8, and 12 poststroke. Intake and biomechanical evaluations were administered by the study coordinator (JS), whereas a trained assessor (EE or RLC) who was blinded to treatment allocation performed clinical follow-up assessments of a specific subject. Biomechanical evaluations of quiet standing balance started once participants could stand independently for 30 s (i.e., BBS unsupported standing item [BBS-stand] ≥ 2). Walking evaluations started when participants could walk under supervision (i.e., FAC ≥ 3).

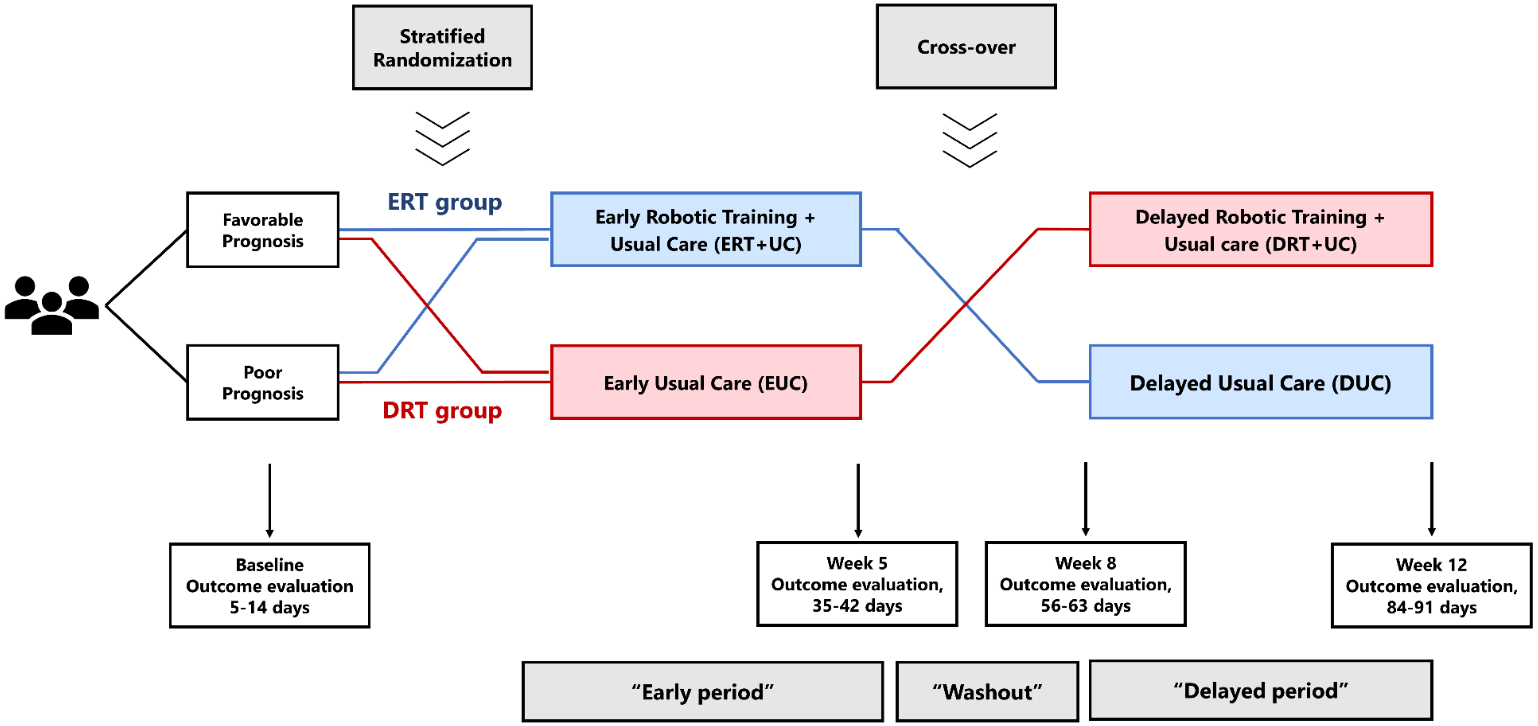

Figure 1. Design of the clinical trial. Participants underwent stratified randomization within 14 days poststroke (i.e., baseline) to either the ERT or DRT study arm, based on their prognosis for achieving walking independence (i.e., FAC ≥ 4). During the early period, ranging from baseline to week 5 poststroke, ERT participants underwent early robotic training (16 sessions, 4x/week) with usual care (ERT+UC), whereas the DRT participants received EUC alone to serve as controls. After a 3-week washout, DRT participants started delayed robotic training with usual care (DRT+UC) following the same standardized protocol from 8 weeks poststroke, whereas ERT participants served as controls by receiving delayed usual care (DUC). Serial measurements were performed in each participant at baseline and at weeks 5, 8, and 12 after stroke.

Robotic device

We used an Ekso GT® (Ekso Bionics, CA, USA) exoskeleton, consisting of motorized limbs that provide bilateral angular motion at the hip and knee joints in the sagittal plane and a passive spring-loaded joint maintaining the ankles in a neutral position via footplates to assist foot clearance. The legs can be moved with full or partial assistance to encourage active patient involvement and progress training difficulty during overground walking. Stepping automaticity was set to "ProStep", such that a step was triggered when the opposite limb was sufficiently weight-loaded, as determined by sensors embedded in the footplates. This mode was chosen to further encourage patient involvement and simulate symmetrical weight-shifting of a healthy gait pattern. Spatiotemporal parameters such as step height and length or swing speed were adjusted in symmetrical patterns to fit the patients' biometrics. Within these global guidelines, therapists were free to individualize settings to guarantee safety and improve training efficacy according to their expertise.

Intervention

Robotic training

Licensed therapists provided robotic training. Each session lasted approximately 45 min to provide sufficient time for practice, besides preparation and resting breaks. Practice started with establishing a symmetric stance with equal weight-bearing and progressed toward stepping with the goal to achieve, eventually, ~20 min time on task and ~1,000 steps per session. Sessions were scheduled daily for 4 weeks, 4x/week. The experimental intervention therefore consisted of 16 sessions, or a 12-h scheduled therapy time above usual care, which was not modulated.

Usual care

Usual care was provided continuously and until discharge. Although usual care was not standardized, it typically consisted of daily 60-min sessions of physiotherapy and occupational therapy following the Bobath concept, 5x/week, besides nursing care. In general, physiotherapy targeted lower limb voluntary movement control and independent mobility (e.g., transferring or walking), and occupational therapy focused on upper limb function and daily activities (e.g., dressing or eating). Additional speech or cognitive therapy was provided based on patients' needs and wishes.

Outcomes

Intervention characteristics

The time spent actively training in an upright position and the steps performed per session were recorded. Intervention-related adverse events and negative side effects were monitored.

Clinical outcomes

FM-LE (0-34) was used to measure muscle synergies. FM-LE is a widely used valid and reliable measure of poststroke motor impairment.[31,32] Increasing scores reflect improvements in dissociating willed movement from abnormal muscle synergies.

The FAC measures the ability to walk without manual support or supervision, such that a score can be assigned even in a non-ambulatory state. We treated FAC as a continuous (0-5) and binary outcome (FAC-bi, 0-1), categorizing participants into dependent and independent walkers using a cut-off ≥ 4.

Biomechanical outcomes

Biomechanics samples were collected at the M²OCEAN laboratory of the University of Antwerp, following standardized protocols for measuring quiet standing balance[33] and walking[34] performance. Data analysis was performed using custom-written MATLAB (version 2018a) algorithms.

Steady-state balance was evaluated during quiet two-legged standing for 40 s using two force plates (type OR 6-7, AMTI, MA, USA). Data were low-pass filtered (Butterworth 2nd order, cut-off 12.5 Hz). The first 10 s were removed, and three trials were averaged to maximize reliability.[35] The root mean square of the center-of-pressure (COP) velocities at both limbs combined was calculated as a measure of anteroposterior (COPvel-ap) and mediolateral (COPvel-ml) postural stability.[19] Weight-bearing asymmetry (WBA) is calculated as the percentage bodyweight on the less-affected side minus 50%. The dynamic control asymmetry (DCA) reflects each limb's balance control contribution as a symmetric index of the individual-limb COPvel-ap.[19] With respect to WBA and DCA, 0% indicates perfect symmetry, and positive values reflect a larger compensatory contribution by the less-affected limb. Because COP signals are sensitive to errors when applied forces are low, DCA was set arbitrarily to 160% (i.e., largest asymmetry recorded) if < 20% bodyweight was recorded on the less-affected limb.

Motion capture (VICON Motion Systems Ltd, Oxford, UK) was used to evaluate step parameters during barefoot walking at comfortable speeds over a 10-m walkway. Foot markers (heel, ankle, 2nd toe) were labeled and low-pass filtered (Butterworth 2nd order, cut-off 6 Hz). Foot-strike and foot-off events were determined using a coordinate-based algorithm[36] for at least 8 strides in the walkway center. We calculated step lengths (i.e., difference in ankle position between foot-strike and foot-off) and walking speed during each stride, and averaged results were expressed as a symmetry ratio (i.e., SLA) with the larger value in the numerator per recommendation.[20] SLA reflects kinetic asymmetries and a compensatory reliance on the less-affected side for body propulsion.[37,38]

Sample size

Expecting an attrition rate of 25%, we aimed to enroll 40 participants to achieve 15 participants per study arm, as recommended for pilot studies.[39] We scheduled 20 months of recruitment, expecting to recruit 2 participants per month.

Statistics

Expecting an attrition rate of 25%, we aimed to enroll 40 participants to achieve 15 participants per study arm, as recommended for pilot studies.[39] We scheduled 20 months of recruitment, expecting to recruit 2 participants/month.

Statistics

To test whether recovery time courses were different between groups, linear mixed models were applied, including fixed effects for GROUP [ERT+UC, DRT+UC], TIME [baseline, week 5, week 8, week 12], and GROUPxTIME interaction, and a subject-specific random intercept. This yielded β-coefficients with their standard error (SE) and confidence interval (CI) reflecting a *time*-effect within groups and an *interaction*-effect reflecting between-group differences across three epochs: the early period ranging from baseline to week 5 (i.e., ERT+UC vs. EUC), washout from weeks 5 to 8, and the delayed period ranging from weeks 8 to 12 (i.e., DRT+UC vs. DUC). All models were tested for normality assumptions using Q-Q plots. Homoskedasticity was checked using a plot of residuals by predicted values. FAC-bi scores were descriptively analyzed.

To deal with the potential absence of biomechanical data in non-ambulatory participants, thereby limiting time course analyses, we additionally compared between-group differences with respect to COPvel-ap, COPvel-ml, WBA, DCA, SLA, and gait speed cross-sectionally at each time point. To calculate the mean difference (MD) with CI, independent sample Welch's t-tests (assuming unequal variance) were used. T-tests were applied if data of at least 50% of the sample were available at a specific time point.

By lack of established thresholds of clinically meaningful differences, we decided that a 15% difference in outcomes would be required to confirm our hypotheses. It was understood that the trial would not be adequately powered to detect this with statistical significance. To protect against premature rejection of a potential benefit, we therefore relied on descriptives and trends by CIs of varying widths, per recommendation.[40] Thus, we not only used the two-tailed traditional α-rate (Type I error, false-positive) of 0.05 but also included results based on a α-rate of 0.15. This resulted in an 85% CI, besides the traditional 95% CI.

All statistical analyses were performed using JMP Pro v16 (SAS, NC, USA). Because this was a pilot study, the preliminary analyses were restricted to participants who completed the intervention (i.e., on-treatment analyses).

Results

Recruitment

Figure 2 shows the inclusion flow. Between December 2018 and November 2021, approximately 1,200 patients were screened for eligibility upon hospital admission. Screening was interrupted from February 2020 to September 2021 because of restricted hospital access due to COVID-19 measures. During the 15 months of actively recruiting, 140 potential candidates were identified, and 26 participants were enrolled (1.73 participants/month). The main exclusion reasons were "too mild impairments" (i.e., NIHSS motor leg item < 1 and/or FAC > 3) and "short length of stay" resulting in immediate discharge. The trial was eventually stopped due to expiration of funding.

Of the 26 enrolled patients, 19 successfully participated (attrition rate 28%) in the ERT (N = 10) or DRT (N = 9) groups, and seven dropouts were registered: three subjects no longer adhered to eligibility criteria after exhibiting a second stroke (N = 2) or another sudden-onset disease (N = 1), two subjects were unavailable after discharge (N = 1) or isolation due to an infectious disease (N = 1), and two subjects wished to discontinue robotic training.

The 19 included participants had a median age of 64 (IQR = 24) years and a bodyweight of 70 (28) kg. Nine were female (47%), 16 had an ischemic stroke (84%), and 13 suffered left-sided weakness (68%). Median baseline FM-LE and MI-LE scores were 14 (13) and 37 (20), respectively. In terms of TCT-s and BBS-s, 13 participants had sitting balance (68%) and one participant (5%) could stand at baseline. Eleven participants had a favorable prognosis for walking (58%), and 8 had a poor prognosis (42%). The ERT and DRT arms were comparable in these baseline variables (Table 1).

	ERT N=9	DRT N=10	*P*
Demographics and Stroke Information			
Age (years)	60.0 (29.3)	69.0 (27.5)	.968
Sex (female/male, % female)*	4/6, 40%	5/4, 56%	.656
Body-weight (kg)	66.9 (31.8)	70.7 (17.0)	.345
Paretic body side (left/right, % left)*	6/4, 60%	7/2, 78%	.628
Stroke type (ischemic/hemorrhage, % ischemic)*	9/1, 90%	7/2, 78%	.582
Care characteristics			
Length of stay in inpatient rehabilitation (weeks)	15.0 (9.5)	19.0 (10.0)	.619
Discharge destination after rehabilitation (home/nursing facility or other hospital, % home)*	6/4, 56%	8/1, 89%	.291
Clinical characteristics			
FM-LE (0-34)	15.0 (12.0)	11.0 (13.5)	.561
MI-LE (0-99)	42.0 (30.0)	33.0 (32.5)	.736
FAC (0-5)	0.0 (0.0)	0.0 (0.5)	.580
TCT-sit: Able to sit 30 s? (yes/no, % yes)*	6/4 (60%)	7/2 (78%)	.628
BBS-stand: Able to stand 30 s? (yes/no, % yes)*	1/9 (10%)	0/9 (0%)	1
Prognosis of walking ability (favorable/poor, % yes)*	6/4 (60%)	5/4 (56%)	1
Intervention characteristics			
Time between stroke onset and intervention initiation (days)	15.5 (5.3)	58 (7)	<.001
Number of training-sessions (n)	16 (0)	16 (1)	.210
Time practicing in an upright position per session (min)	22.7 (5.7)	20.8 (5.9)	.367
Practice steps taken per session (n)	856 (183)	866 (210)	.968

Table 1. Baseline characteristics of participants and intervention characteristics. Values are medians with IQR for continuous scales or n for binary scales (marked with *). Acknowledging the limited sample, non-parametric tests were used to compare the groups at baseline. Hence, P-values were derived from two-way Wilcoxon rank sum tests for continuous variables and Fisher's exact tests for binary variables (*).

Measurements were applied at baseline, ranging from 7 to 14 days poststroke; at week 5, ranging from 36 to 44 days; at week 8, ranging from 57 to 63 days; and at week 12, ranging from 84 to 94 days.

Intervention

Two of the seven dropouts were treatment-related as participants, one in each group, felt too exhausted to train above usual care. Among the subjects who completed training, 17 received all 16 sessions, and two received 14 sessions due to scheduling issues. Over the entire 300 robotic sessions, 10 cases (3%) of negative side effects were documented (ERT: N=6 vs. DRT: N=4) including minor joint pain and sore muscles, leading to a temporal training intensity reduction. No adverse events occurred.

Median practice time per session in ERT vs. DRT was 22.7 (5.7) vs. 20.8 (5.9) min, and the practice steps per session were 856 (183) vs. 866 (210).

Preliminary Treatment Effects on Clinical Outcomes

A figure with mean and individual time courses (Figure 3) yields overall parallel recovery courses between groups, yet a tendency toward faster FAC gains during the early period favoring ERT+UC over EUC.

Table 2 summarizes *time*- and *interaction*-effects. As shown, there was a significant *time*-effect regarding FM-LE during the early period within the ERT and DRT arms at $\alpha = 0.05$ ($\beta = 5.50$, 95%CI [3.12; 7.88] and $\beta = 5.56$, 95%CI [3.05; 8.06]). Change leveled off during washout and was significant at $\alpha = 0.15$ ($\beta = 2.00$, 85%CI [0.27; 3.57] and $\beta = 2.44$, 85%CI [0.62; 4.27]). The *interaction*-effect did not contribute to FM-LE change.

Regarding FAC, there was a significant *time*-effect at $\alpha=0.05$ within the ERT and DRT arms during the early period ($\beta = 1.90$, 95%CI [1.18;2.62] and $\beta = 1.10$, 95%CI [0.36;1.87]) and washout ($\beta = 0.90$, 95%CI [0.18;1.62] and $\beta = 0.89$, 95%CI [0.13;1.64]). The *interaction*-effect contributed significantly to FAC change at $\alpha=0.15$ during the early period ($\beta = 0.79$). The 85%CI ([0.03;1.55]) excluded 0 and crossed the 15% threshold (i.e., 0.75 points) favoring ERT+UC over EUC. FAC-bi scores in the ERT vs. DRT arms were 1 (10%) vs. 0 (0%) at week 5; 5 (50%) vs. 1 (11%) at week 8; and 6 (60%) vs. 5 (56%) at week 12.

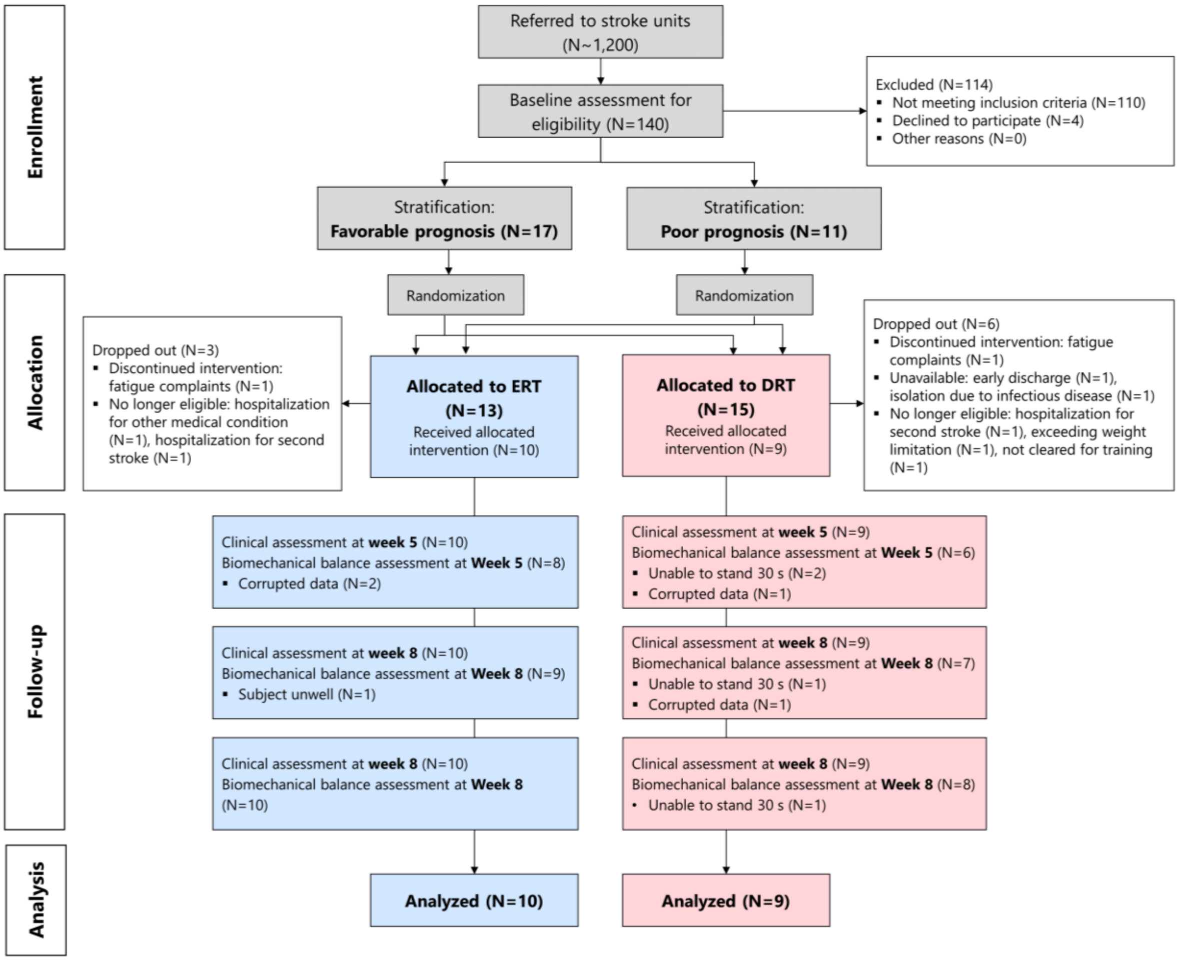

Figure 2. CONSORT flow diagram of the inclusion and follow-up.

The first two boxes show the two-phase recruitment process. Of the 140 potential candidates, 26 were eventually enrolled. After stratifying the participants, random allocation was performed to the ERT or DRT study arms. Eventually, 19 participants successfully underwent the intervention and follow-up measurements and were included in the on-treatment analysis.

Preliminary Treatment Effects on Biomechanical Outcomes

At week 5, two quiet standing measurements were impossible because of poor balance, and three had to be excluded because of corrupted data. At week 8, one participant refused, and one measurement was lost because of an software error. A single participant could not perform the measurements at weeks 8 and 12. Consequently, eligible balance data in ERT vs. DRT were N = 8 (80%) vs. N = 6 (67%) at week 5; N = 9 (90%) vs. N = 7 (78%) at week 8; and N = 10 (100%) vs. N =

8 (89%) at week 12. Time course analyses yielded a *time* effect at $\alpha = 0.15$ during washout for COPvel-ap change in ERT ($\beta = -3.04$, 85%CI [-5.59;-0.48]) and COPvel-ml change in DRT ($\beta = -3.09$, 85%CI [-5.50;-0.68]). In the same period, a WBA reduction was found in the DRT group ($\beta = -4.1$, 95%CI[-7.5;-0.6]) with an *interaction* effect ($\beta = 5.4$, 95%CI [0.6;10.2]). MDs regarding the standing balance outcomes were non-significant at weeks 5, 8, and 12 (Table 3).

Regarding walking, two (11% of the entire sample) and seven (37%) subjects with FAC ≥ 3 could perform the standardized task at the week 5 and 8 assessment, respectively. At week 12, 14 participants reached FAC ≥ 3 whereas four required support to perform the task. Therefore, 10 participants (53%), five in each group, could be tested at week 12, allowing for a between-group comparison. This yielded non-significant MDs in SLA and gait speed (Table 3).

Discussion

In this pilot study, exercising with an exoskeleton as an adjunct to usual care for four weeks was well tolerated by non-ambulatory patients (i.e., FAC < 2). Only two of 21 participants (9.5%) who received this intervention withdrew because of exhaustion, and no adverse events were documented. This suggests feasibility of this intervention in a sufficiently powered phase II trial.

Between-group comparisons in our limited sample yielded a trend toward faster reacquisition of independent walking (FAC) favoring ERT+UC over EUC, which is in line with a general trend in the literature.[16,17] However, regarding objective 1, this potential benefit was not accompanied by greater motor recovery following FM-LE, and both groups exhibited similar postural stability (COPvel-ap, COPvel-ml) and preference to keep (WBA) and control (DCA) their standing balance predominantly on the less-affected side. Consequently, we found no preliminary evidence supporting our hypotheses regarding objective 2 that restorative effects of additional robotic training are pronounced when applied in the first 5 weeks poststroke (i.e., ERT+UC vs. EUC) than an equal treatment contrast starting at 8 weeks poststroke (i.e., DRT+UC vs. DUC).

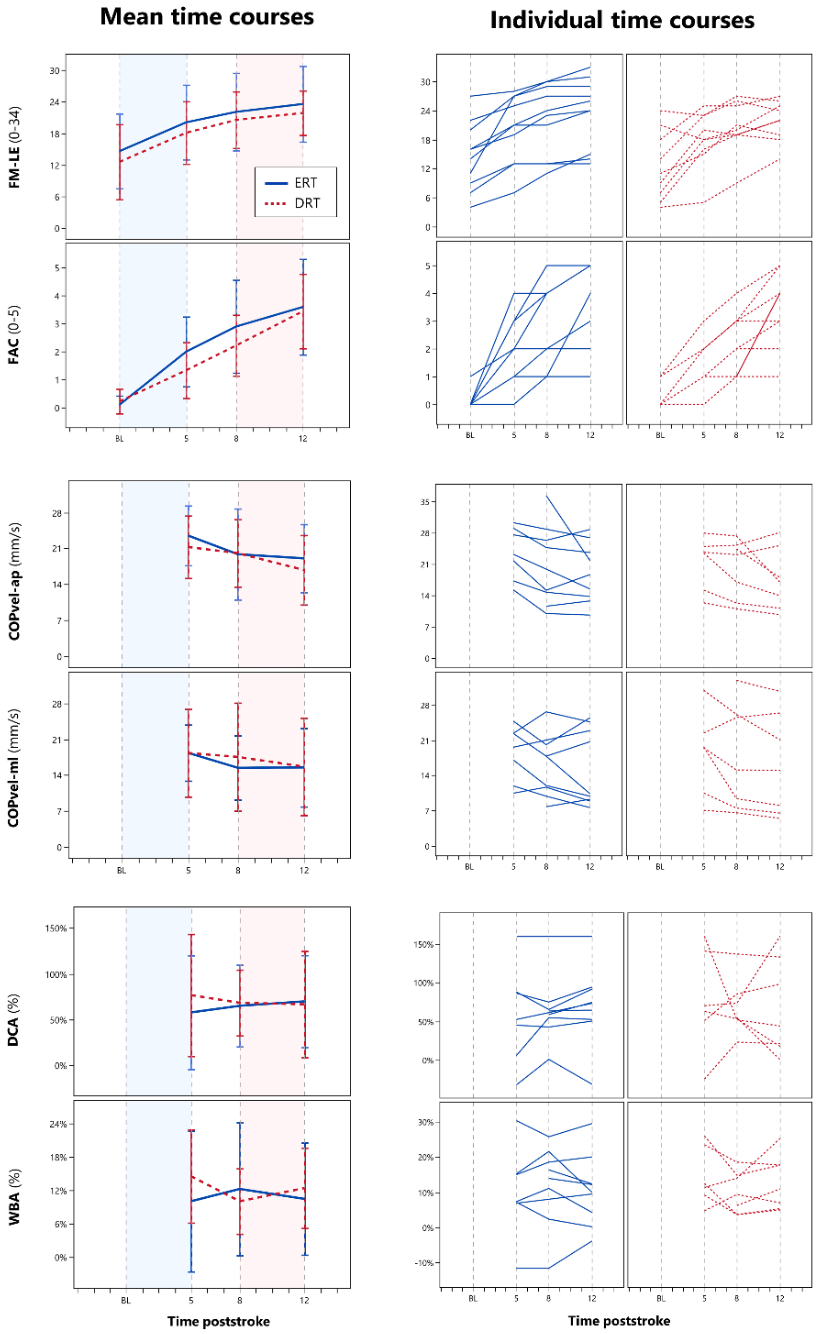

Figure 3. Time courses of muscle synergies (FM-LE), walking independence (FAC), and postural stability (COPvel-ap, COPvel-ml) and interlimb asymmetries (DCA, WBA) during quiet standing.

Abbreviations: FM-LE, Fugl-Meyer Lower Extremity motor scores; FAC, Functional Ambulation Category; ERT, early robotic training next to usual care group; DRT, delayed robotic training next to usual care group. The line graphs on the left depict group-specific means and their standard deviations as error bars. Graphs on the right show individual recovery curves. Blue solid lines represent subjects in the ERT group (N=10), red dotted lines represent the DRT group (N=9). X-axis represent the time poststroke in weeks with fixed measurement time-points at baseline (BL, <14 days poststroke) and weeks 5, 8, and 12 poststroke.

		Early period: Baseline to Week 5			Washout: Weeks 5–8			Delayed period: Week 8–Week 12		
		Time [ERT]	Time [DRT]	Interaction [Difference]	Time [ERT]	Time [DRT]	Interaction [Difference]	Time [ERT]	Time [DRT]	Interaction [Difference]
FM-LE [0-34]	β(SE)	**5.50*(1.86)**	**5.56*(1.25)**	-0.06(1.72)	**2.00$^{\times}$(1.19)**	**2.44$^{\times}$(1.25)**	-0.44(1.72)	1.50(1.86)	1.33(1.25)	0.17(1.72)
	95% CI	**3.12; 7.88**	**3.05; 8.06**	-3.51; 3.40	**-0.38; 4.38**	**-0.06; 4.95**	-3.90; 3.01	-0.88; 3.88	-1.18; 3.84	-3.29; 3.63
	85% CI	**3.77; 7.23**	**3.73; 7.38**	-2.57; 2.46	**0.27; 3.73**	**0.62; 4.27**	-2.96; 2.07	-0.23; 3.23	-0.49; 3.16	-2.35; 2.68
FAC [0-5]	β(SE)	**1.90*(0.36)**	**1.11*(0.38)**	**0.79$^{\times}$(0.52)**	**0.90*(0.36)**	**0.89*(0.38)**	0.01(0.52)	**0.70$^{\times}$(0.36)**	**1.22*(0.38)**	-0.52(0.52)
	95% CI	**1.18; 2.62**	**0.36; 1.87**	**-0.25; 1.83**	**0.18; 1.62**	**0.13; 1.64**	-1.03; 1.05	**-0.02; 1.42**	**0.46; 1.98**	-1.56; 0.52
	85% CI	**1.38; 2.42**	**0.56; 1.66**	**0.03; 1.55**	**0.38; 1.42**	**0.34; 1.49**	-0.75; 0.77	**0.18; 1.22**	**0.67; 1.77**	-1.28; 0.24
COPvel-ap [mm/s]	β(SE)	NA	NA	NA	**-3.04$^{\times}$(1.72)**	-1.55(1.79)	-1.49(2.48)	-1.60(1.56)	-2.65(1.69)	1.05(2.30)
	95% CI				**-6.58; 0.51**	-5.25; 2.15	-6.61; 3.63	-4.82; 1.61	-6.12; 0.82	-3.69; 5.78
	85% CI				**-5.59; -0.48**	-4.22; 1.11	-5.18; 2.21	-3.92; 0.71	-5.15; -0.15	-2.37; 4.46
COPvel-ml [mm/s]	β(SE)	NA	NA	NA	-1.14(1.56)	**-3.09$^{\times}$(1.62)**	1.95(2.25)	-0.52(1.41)	-1.47(1.53)	0.95(2.08)
	95% CI				-4.35; 2.08	**-6.43; 0.26**	-2.69; 6.59	-3.43; 2.40	-4.62; 1.68	-4.44; 5.24
	85% CI				-3.45; 1.18	**-5.50; -0.68**	-1.39; 5.29	-2.61; 1.58	-3.74; 0.80	-2.14; 4.04
DCA [%]	β(SE)	NA	NA	NA	7.6(16.1)	-2.9(16.8)	10.5(23.2)	5.0(14.6)	-0.9(15.7)	5.9(21.5)
	95% CI				-25.4; 40.7	-37.5; 31.7	-37.3; 58.3	-25.1; 35.0	-33.3; 31.7	-38.2; 50.0
	85% CI				-16.2; 31.5	-27.8; 22.0	-26.0; 37.8	-16.8; 26.7	-24.3; 22.4	-26.0; 37.8
WBA [%]	β(SE)	NA	NA	NA	1.3(2.2)	**-4.1$^{\times}$(2.3)**	**5.4$^{\times}$(3.2)**	-1.5(2.0)	2.6(2.2)	-4.1(3.0)
	95% CI				-3.3; 5.9	**-8.9; 0.7**	**-1.3; 12.0**	-6.0; 2.7	-1.9; 7.1	-12.3; 2.0
	85% CI				-2.0; 4.6	**-7.5; -0.6**	**0.6; 10.2**	-4.5; 1.5	-0.6; 5.9	-8.6; 0.3

Table 2. *Time*- and *interaction*-effects on change in muscle synergies (FM-LE), walking independence (FAC), and postural stability (COPvel-ap, COPvel-ml) and interlimb asymmetries (DCA, WBA) while standing. Abbreviations: ERT, early robotic training group; DRT, delayed robotic training group; FM-LE, Fugl-Meyer Lower Extremity motor scores; FAC, Functional Ambulation Category; COPvel-ap, net COP velocity in the anteroposterior sway direction; COPvel-ml, net COP velocity in the mediolateral sway direction; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry; NA, not analyzed by insufficient data. Estimated regression coefficients (β), their standard error (SE), and confidence interval (CI) at certainty levels of 95% and 85% are shown. *Time* effects represent change within the ERT (N=10) and DRT (N=9) groups. An *interaction* represents differences in change between groups. Marked β-coefficients reflect a significant *time* or *interaction* effects with *, α = 0.05 and $^{\times}$, α = 0.15. CIs in bold do not include zero, the value expected under the null hypothesis.

Table 3. Mean scores and differences in biomechanical outcomes of quiet standing balance and walking.

	Baseline			Week 5			Week 8			Week 12		
	ERT (SD)	DRT (SD)	MD (95%CI) (85%CI)	ERT (SD)	DRT (SD)	MD (95%CI) (85%CI)	ERT (SD)	DRT (SD)	MD (95%CI) (85%CI)	ERT (SD)	DRT (SD)	MD (95%CI) (85%CI)
Quiet standing												
Data available (yes/no, %)	1/9, 10%	0/9, 0%		8/2, 80%	6/3, 67%		9/1, 90%	7/9, 78%		10/0 100%	8/1, 89%	
COPvel-ap [mm/s²]	NA	NA	NA	23.50 (5.81)	21.28 (6.08)	2.27 (-5.11; 9.56) (-2.92; 7.37)	19.87 (8.87)	20.08 (6.56)	-0.21 (-8.86; 8.45) (-6.33; 5.92)	19.07 (6.64)	16.81 (6.76)	2.26 (-4.69; 9.21) (-2.69; 7.21)
COPvel-ml [mm/s²]	NA	NA	NA	18.39 (5.48)	18.37 (8.56)	0.02 (-9.29; 9.34) (-6.42; 6.47)	15.45 (6.26)	17.57 (10.53)	-2.12 (-12.33; 8.11) (-9.25; 5.02)	15.51 (7.64)	15.67 (9.48)	-0.16 (-9.22; 8.90) (-6.58; 6.27)
DCA [%]	NA	NA	NA	57.75 (62.19)	76.60 (66.68)	-18.84 (-98.56; 60.87) (-74.74; 37.06)	64.96 (44.60)	68.28 (35.99)	-3.32 (-48.33; 41.70) (-35.19; 28.55)	69.84 (50.27)	66.63 (58.06)	3.20 (-53.63; 60.04) (-37.16; 43.57)
WBA [%]	NA	NA	NA	10.03 (12.63)	14.52 (8.37)	-4.49 (-17.50; 8.53) (-13.62; 4.64)	12.24 (11.94)	10.02 (5.89)	2.21 (-8.35; 12.78) (-5.20; 9.26)	10.45 (10.08)	12.39 (7.20)	-1.95 (-19.96; 7.07) (-8.36; 4.46)
Walking												
Data available (yes/no, %)	0/10, 0%	0/9, 0%		1/10, 10%	1/9, 11%		4/6, 40%	3/6, 33%		5/5, 50%	5/4, 55%	
Walking speed [m/s]	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.74 (0.32)	0.56 (0.26)	0.17 (-0.25; 0.60) (-0.12; 0.47)
SLA [ratio]	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.065 (0.052)	1.050 (0.053)	0.015 (-0.062; 0.092) (-0.038; 0.069)

Abbreviations: ERT, early robotic training group; DRT, delayed robotic training group; MD, mean difference; CI, confidence interval; NA, not analyzed by insufficient data; COPvel-ap, net COP velocity in the anteroposterior sway direction; COPvel-ml, net COP velocity in the mediolateral sway direction; DCA, dynamic control asymmetry; WBA, weight-bearing asymmetry; SLA, step length asymmetry; SD, standard deviation.

Values shown are means with SD for the ERT (N=10) and DRT (N=9) groups and MD between groups with CIs at a certainty level of 95% and 85%.

Motor recovery was not enhanced by robotic training, irrespective of an early timing poststroke.

By measuring subjects serially at fixed times poststroke, we found, *within* groups, spontaneous recovery of muscle synergies (FM-LE) mainly in the first 5 weeks. This is consistent with recovery courses documented in large observational studies.[4,5] This repeated-measurement protocol further allowed us to precisely determine an additive treatment effect on the backdrop of spontaneous recovery.[44] However, this yielded no signal favoring FM-LE recovery with robotic training, irrespective of timing within (i.e., "early") or after (i.e., "delayed") the critical recovery period.

In the literature, the period of the first 5 weeks after stroke has been argued to be a sensitive rehabilitation period for enhancing behavioral restitution due to a heightened plasticity milieu.[12,13,28] However, this notion is inspired by animal models showing increased training responsiveness early poststroke relative to a delayed deliverance,[13,28] whereas only few clinical trials have addressed this issue of timing.[26,41] Consequently, it is inconclusive *if* such a sensitive period exists in patients and *when* to intervene. Defining this period is further hindered by a lack of "gold standard" interventions that interact with mechanisms of spontaneous recovery to successfully reduce impairments.[13,42] In that sense, our findings question, similar to systematic reviews on upper[43] and lower limb[17,25] robotics, the role of exoskeletons as a restorative therapy for improving motor functions of the paretic limb.

Earlier walking reacquisition after robotic training may be related to benefits associated with more physical activity.

The observed trend toward faster independent walking favoring ERT+UC above EUC must be related to factors other than motor impairment reductions. Therefore, it is important to emphasize that our comparisons were unequally dosed. Relative to the control condition, our robotic intervention consisted of 14-16 additional sessions, containing 800-900 steps and 20-25 min active practice time each. This exceeds step counts documented during conventional therapies, ranging between 12 and 249 steps per session in non-ambulatory inpatients.[44-46] Hence, robotics appear a feasible method to provide more exercise in patients whose ability to participate in conventional therapies is limited. Therefore, a faster walking reacquisition may have simply resulted from more physical activity and associated benefits (e.g., improved mood and confidence or prevention of deconditioning[47,48]), independent of the actual movements performed by the exoskeleton.

It may be questioned whether applied doses were sufficient and engaging enough to enhance motor recovery. Recent stroke rehabilitation trials[49-51] illustrate dosing above 2,000 steps per session with task variability, delivered over longer periods, and at greater cardiovascular exertion as critical factors for improving walking capacity in those with some walking function at baseline. This is consistent with the thousands of challenging repetitions performed in the abovementioned animal models. In comparison, exoskeletons deliver the same pre-programmed trajectories each time. As the device eventually provides the necessary assistance to complete the movement, each step is a "success" notwithstanding abnormal muscle activation and torques exerted by the patient.[52,53] Consequently, patients may not receive an adequate "error signal" to learn the desired trajectories outside the robotic milieu. Another limitation of current exoskeletons may be the lack of dynamic actuation of the ankles, such that ankle movements for controlling balance and propulsion forces (i.e., "push off") to achieve step length might have been insufficiently trained. Therefore, future studies may explore combined interventions by starting exercises with robots, if otherwise not feasible, to advance toward unrestricted training. This may provide greater opportunity to investigate learning-dependent effects on promoting neurological recovery early poststroke by delivering even larger doses with task progression and variability, greater motivation, and feedback.

Do current robotic designs allow adaptive learning to reduce walking disability after stroke?

Another question arising from our preliminary findings is *what* therapeutic movements should be promoted. Exoskeletons typically steer the limbs symmetrically following the long-held assumption that facilitating "normal" movement is ideal for enhancing poststroke recovery.[54,55] In contrast, our findings suggest that patients learn in an adaptive way. When asked to stand upright, participants placed 10-15% more weight on their less-affected leg, with a 50-70% greater contribution to balance control in terms of DCA and little tendency to change. Asymmetries appear enforced, not restored.

SLA could only be collected by week 12, limiting a similar time course analysis regarding walking. The slow gait speeds (< 0.5 m/s) suggest that the surprisingly symmetric scores reflect a cautious gait by reducing step lengths on both sides due to fear of falling,[56,57] rather than "true" normalization of performance. Furthermore, few studies[58,59] have shown strong correlations between standing balance asymmetries, including DCA and WBA, and asymmetric gait after stroke, suggesting common underlying causes. Thus, our findings are consistent with observational studies[6,8-10] (including a study from our group[60]) showing that asymmetries favoring the less-affected limb hardly change within the first 3-6 months poststroke, despite continuous improvements in functional balance and walking outcomes. Adding to this evidence, our preliminary findings suggest that 4 weeks of exoskeleton-assisted training is not effective in reducing this compensatory behavior in those with persistent hemiparesis.

The Ekso GT® used in this study is a mobile exoskeleton that allows training overground instead of being treadmill-bound (e.g., Lokomat).[24] Due to its recent introduction, only few randomized trials have investigated effectiveness on enhancing recovery in early subacute stroke, either as an adjunct therapy[61] or embedded in usual care.[62] This yielded, however, neutral effects relative to equally-dosed conventional therapy in terms of the 6-min walk test[61] and FAC[62] (see review[25]). Although speculative, this lack of superiority may result from a mismatch between enforced symmetrical patterns by exoskeletons and compensatory strategies preferred by patients. Therefore, more longitudinal research with serially-applied kinematics and kinetics is warranted to elucidate adaptive learning mechanisms of balance and gait as a basis for designing robots that either target impairments or aim for early safety and independence by allowing compensations, to harness a potentially beneficial effect on walking reacquisition. Additionally, studies should investigate EMG responses to robotic assistance to better understand motor control of hemiparetic patients under movement restrictions and whether this strategy promotes or impedes learning.

Limitations

Our pilot study was small and slightly unbalanced in median FM-LE scores at baseline (ERT: 15 (12) vs. DRT: 11 (13.5)), which may have confounded recovery courses.[1,4] Despite this potentially favorable prognosis for the ERT arm, no consistent between-group differences were found. Unfortunately, recruitment was slower than expected (1.73 vs. 2 subjects/month) and shortened due to the COVID-19 pandemic. Efforts to recruit patients in an inpatient rehabilitation setting during the pandemic were unsuccessful because patients arrived “too late” (i.e., > 14 days poststroke) to participate. This is similar to a recruitment analysis of the CPASS trial,[63] with a low recruitment rate of 1-2 subjects per month in an acute hospital setting also applying perfusion therapies.

Other limitations include, as emphasized, our definition of the sensitive period, which is somewhat arbitrary, not knowing the exact moment to intervene. We hypothesized that enhanced plasticity parallels the critical recovery window of the first 5 weeks after stroke, as previously suggested.[12,28] Furthermore, our outcome FM-LE suffers a known measurement error,[31] which may have affected responsiveness to show treatment effects. Additionally, we were restricted to a standing task for assaying interlimb symmetry. Therefore, protocols for collecting gait biomechanics more broadly in this population by allowing footwear and orthotics,[10] or even light support,[64] should be validated to facilitate data acquisition in early trials. Finally, we did not document usual care and performance beyond the protocolized intervention. Therefore, we cannot determine the actual amount of exercise each participant performed or how robotic training may have competed with usual care for patients' time and energy.

Despite these shortcomings, our findings do not support initiating a phase II trial following our specific protocol. This resource-demanding protocol (i.e., acute hospital network for recruitment, robotic rehabilitation facilities, and biomechanics laboratories due to a lack of validated portable systems[23]) demands a strong rationale and preliminary evidence indicating a high chance of finding clinically meaningful results. Therefore, our recommendation is mainly guided by the absence of any clear signal in this pilot favoring motor recovery by exoskeletons to facilitate symmetric gait.

Conclusion

This pilot study tested the feasibility and preliminary effects of four weeks training with a wearable exoskeleton as an adjunct to usual care in non-ambulatory patients, applied either early (i.e., within 5 weeks) or delayed (i.e., after 8 weeks) after stroke onset. While adherence to the intervention was deemed sufficiently high, we identified barriers to patient recruitment and biomechanical data collection that may limit a definitive trial. Outcomes collected in this limited sample yielded no greater recovery from intralimb muscle synergies (FM-LE) favoring ERT+UC over EUC, despite a trend toward faster walking reacquisition following FAC. Furthermore, an early or delayed timing of robotic training did not matter for enhancing FM-LE recovery or reducing compensations with the less-affected limb. Our findings therefore suggest lack of generalization of learning symmetric gait in the robotic milieu to real-world performance, despite a high dose and early timing that are seen important for maximizing rehabilitation effects. With that, the surplus value of therapeutic robots that emphasize "normal" movement kinematics for stroke rehabilitation is further questioned.[65-67]

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DECLARATION OF INTEREST: We have no conflicts of interest to report.

ETHICS STATEMENT: This study is part of the TARGEt project and was approved by the medical ethics committee of the University Hospital Antwerp (No. 18/25/305; Belgium trial registration no. B300201837010).

INFORMED CONSENT: Each subject provided written informed consent before participation.

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CHAPTER 7

7

GENERAL DISCUSSION

People with stroke typically have one-sided sensorimotor impairments that affect balance and increase the risk of falls.[1,2] Therefore, improving balance control while sitting, transferring, standing, and walking is a cornerstone of stroke rehabilitation when aiming to improve a patient's ability to perform activities of daily life and enable home discharge.

As outlined in **chapter 1**, reacquisition of balance skills in hemiplegic patients involves a complex interplay of behavioral restitution (i.e., recovery of motor performance toward *normal* behavior, or impairment reductions) and compensation (i.e., *alternate* movements to improve functional tasks), which depends on the amount of spontaneous recovery from impairments in the first 3 months post-stroke. Unfortunately, this dichotomy in recovery is poorly understood because of a lack of early-starting longitudinal studies with repeated measurements that adequately delineate these mechanisms, thereby reflecting the recovery of quality of movement (QoM). Thus, it remains unknown *what* patients exactly learn when regaining balance control to accomplish functional tasks and *how* they should be trained to reduce disabilities and prevent falls in the long term. This includes the design of technological applications for neurorehabilitation, such as robotics.

According to this knowledge gap, the current thesis investigated the psychometric properties of testing devices for measuring QoM during a standing balance task (**chapter 2**), the time course of recovery (**chapters 3 and 4**), and the effects of early exercise therapies post-stroke on promoting lower limb motor recovery and functionals tasks as quiet standing and walking (**chapters 5 and 6**). Though, the main theme was to investigate associations between neurological recovery of intralimb muscle synergies and strength, and behavioral change in balance control during quiet two-legged standing throughout the first 3 months post-stroke. These aims align with recommendations by an international group of neurorehabilitation experts – the Stroke Recovery and Rehabilitation Roundtable initiative (SRRR)[3-6] – and this final chapter summarizes and discusses the main findings to provide recommendations for further research.

Main Findings

- Despite its sufficient test-retest reliability, the portable pressure plate yielded center-of-pressure (COP) measures of quiet standing balance that are strongly associated with, but not equivalent to, floor-mounted force plates as the "gold standard". The pressure plate systematically underestimated force plate outcomes if tested in the same subjects (N =

19) and under the same conditions. This suggests that using the same pressure plate is a valid alternative to monitor the time course of standing balance recovery *within* subjects, whereas comparison *between* subjects when using different instruments must be avoided (**chapter 2**).

- Velocity-based measures of COP appear to be particularly reliable and are advised for describing postural stability and the dynamic control asymmetry (DCA) during quiet standing. Averaging three immediate test-retest repetitions yielded excellent reliability in these measures, irrespective of the choice of measuring plate (**Chapter 2**). This protocol was feasible for acquiring data in a typical inpatient rehabilitation cohort from 3 weeks post-stroke onwards (**chapter 4**).
- In 48 first-ever stroke survivors, recovery of postural stability displayed a time-dependent course in the first 8 weeks post-stroke and, thereby, paralleled spontaneous recovery of muscle synergies following the Fugl Meyer lower extremity motor scores (FM-LE) and strength following the Motricity Index (MI-LE). However, time-dependent recovery of lower limb muscle synergies and strength was not significantly associated with improvements in postural stability, nor with changes in DCA and weight-bearing asymmetry (WBA). These findings suggest that intralimb motor improvements hardly contributed to recovery in standing balance, and time-dependent improvements in postural stability rather reflect behavioral compensation (**chapter 4**).
- Asymmetries in DCA and WBA were significantly different from normative values obtained from age-matched healthy controls. This finding suggests that subjects did not "normalize" qualitative aspects of their standing balance in the first 12 weeks after stroke, despite improvements in the ability to maintain postural stability (**chapter 4**).
- Metrics that reflect interlimb asymmetries were quite invariant over time early post-stroke and strongly associated with using compensations by keeping (WBA) and controlling (DCA) balance predominantly with the less-affected leg (**chapters 4 and 6**).
- In a pilot study involving 19 stroke subjects, those (N= 10) who received a 4-week exoskeleton training program as an adjunct to usual care within the first 5 weeks post-stroke showed faster recovery of independent walking following the Functional Ambulation Categories (FAC) than those who received usual care alone (**chapter 6**). This finding agrees with a meta-analysis (15 studies, 915 subjects) suggesting that more

intensive task practice started in the first month after stroke is safe and may enhance walking recovery at the ICF level of activities (**chapter 5**).

- However, faster walking reacquisition after robotic training was not accompanied by enhanced motor recovery (FM-LE) or "normalization" of interlimb symmetry during quiet standing (WBA and DCA), despite practicing symmetric limb movements with the exoskeleton (**chapter 6**). These preliminary findings suggest that a restorative therapy by a wearable exoskeleton is not effective, even if applied in a proposed time-sensitive period of enhanced plasticity post-stroke (**chapter 6**).

Instrumented assessment methods for quantifying standing balance performance post-stroke.

The COP moves continuously when standing, which reflects, in kinetic terms, the summed neuromuscular response of both legs to maintain our center of mass (COM) in a steady position.[7,8] Therefore, the amount of COP movements can be used as a proxy measure of body sway, or postural stability. Previous studies[9-11] yielded gradual posture stabilization in the subacute phase post-stroke, whereas our protocol with repeated measurements in time shows that sway reductions are restricted to the first 5 to 8 weeks post-stroke (**chapters 4 and 6**). Addressing the qualitative changes underlying improved body sway control requires posturographic assessments with dual force plates to separate the limbs. Previous studies have shown reduced interlimb coordination in COP movements relative to age-matched healthy controls,[12,13] with a greater contribution by the less-affected limb as reflected by, for example, DCA.[10,14] This compensatory behavior was even found in patients who suffered a minor stroke.[14]

In **chapter 4**, we elaborated on these findings by showing in 48 first-ever stroke survivors that interlimb asymmetries in terms of DCA and WBA yield little tendency to diminish over time, thus dissociating from motor recovery of FM-LE and MI-LE. The sole use of clinical scales is obviously insufficient to address recovery of QoM during a standing task. In other words, using kinetics and kinematics applied in a repeated and standardized way is the only way to delineate between "true" neurological recovery and compensation when achieving complex skills.[3,15] From this perspective, the recently conducted third round of the SRRR - including the balance and mobility task force - recommends COP-based metrics of interlimb coordination as study outcomes to inform *what* is changing in a patient's motor performance when balance improves (see addendum of this thesis).

Can a pressure plate be used as a portable alternative to force plates for measuring COP?

Floor-mounted force plates by established brands such as AMTI (MA, USA) are currently seen as the gold standard for obtaining reliable COP measures in healthy[16] and stroke subjects.[17,18] However, these devices are expensive and difficult to transport, making them impractical for clinical trials. To perform serial measurements within subjects irrespective of location of residence (i.e., hospital, rehabilitation center, nursing home, or home), we used a pressure plate as a portable alternative to force plates. Thereby, we aimed to "bring the lab to the patient" rather than the reverse.

Chapter 2 describes a head-to-head comparison between these instrumented plates in 19 healthy adults. Despite its sufficient reliability and strong associations with gold standard force plates, our findings yielded concerns regarding the criterion validity of the pressure plate by a consistent underestimation of COP values. A bias relative to force plates has also been reported for the recently introduced Balance Tracking System (BTrackS),[19] whereas mixed results have been found for using the Wii Balance Board to measure COP.[20] The latter has been most extensively studied as a low-cost clinical tool for monitoring standing balance,[20] including a validation study in stroke patients.[21] However, an obvious limitation of this commercial gaming device is that its production has been discontinued.

Hence, we currently do not possess portable instrumentation that can adequately replace laboratory-grade force plates. Consequently, it is strongly advised to use the *same* instrumentation for assessing recovery in a specific patient. These measurements should ideal be performed in well-equipped laboratories, awaiting further research into the psychometric properties of portable plates in a stroke population.

Other ambulant systems for quantifying balance and walking performance post-stroke.

Other technologies that enable movement quantification independent of laboratories include wearable inertial sensors.[22] Emerging evidence supports the validity of using these devices to assess body motion kinematics, including sway when standing.[23] Validation of sensor-based sway measurements while standing in stroke subjects, including smartphone technology,[24] has just started.[25] However, as emphasized, body sway measurements alone are insufficient to adequately separate the limb's balance contribution to address QoM post-stroke. Rather, wearable sensors appear suitable for measuring the quality of stepping kinematics during more dynamic tasks, such as reactive balance and walking.

Mechanisms underlying the time course of standing balance recovery post-stroke.

Referring back to the conceptual model in **chapter 1** (Figure 3), neuronal restitution means a restoration of brain networks to their original state. As discussed, these mechanisms may involve reperfusion-driven salvation of penumbral tissue and reversal of diaschisis, which are seen mainly responsible for neurological recovery from impairments after stroke onset.[26] Significant recovery has been demonstrated across neurological domains in the first 5 to 8 weeks post-stroke, including upper and lower limb muscle synergies,[27,28] sensory deficits,[29] neglect,[30] and aphasia,[31] supporting the claim of common repair mechanisms. Likewise, we found recovery from lower limb muscle synergies (i.e., FM-LE) and strength deficits (i.e., MI-LE) to be mainly restricted to the first 5 weeks post-stroke (**chapters 4 and 6**).

As emphasized, our longitudinal analysis also shows that improved discrete intralimb movements, as reflected by FM-LE and MI-LE, cannot be extrapolated to an improved contribution of the most-affected leg to balance while quiet standing (**chapter 4**). Compensation with the less-affected leg seemingly develops as soon as stroke patients achieve independent standing and is *optimized*, not *normalized*, with subsequent task practice. Our findings are consistent with prior reports. In fact, as summarized in **chapter 3**, all available recovery studies conducted in the first 3 to 6 months post-stroke show that interlimb asymmetries remain unchanged in most patients, despite continuous improvements in their ability to control balance and perform functional tasks as walking.[10,11,32-34] Early skill reacquisition is seemingly a matter of both, reperfusion-driven repair in the affected cerebral tissue and reorganization in intact tissue (i.e., neuronal substitution) to direct behavioral compensation.

Neuroimaging studies of post-stroke balance recovery require fine-grained behavioral measurements.

Our findings have implications for functional magnetic resonance imaging (fMRI) and other neuroimaging studies, as brain activity changes over the course of post-stroke recovery might easily be misinterpreted as reflecting behavioral restitution when task improvements were actually compensatory.[15,35] Previously, excessive task-related fMRI activation increases have been demonstrated in the ipsi- and contralesional motor areas early post-stroke,[36] whereas overactivity in secondary motor areas and the contralesional cortex persists in cases of corticospinal tract (CST) damage.[37,38] These cortical activation shifts and associated plastic changes may therefore reflect compensatory skill learning in patients with more impairments. However, there is currently no precise understanding that distinguishes neuronal mechanisms associated with either behavioral restitution or compensation.[39]

However, caution should be exercised when interpreting cortical mechanistic findings from upper limb studies to the lower limb, given the difference in motor control of unilateral arm-hand movements, and more “automated” bilateral leg movements when balancing and walking.[40,41] This field of research is just emerging, facilitated by technical advances in the use of noninvasive ambulant systems for measuring brain activity while performing upright tasks, e.g., electroencephalogram (EEG) or functional near-infrared spectroscopy (fNIRS), instead of being bound to a lying position in an MRI scanner. So far, the historical view that balance is a pure subcortical function[42] has been opposed by several experiments showing rich cortical responses to unexpected platform translations[43,44] or sway instability during quiet standing.[45] However, *how* the cortex is involved in balance control is still debated (see reviews[46-48]). This knowledge is warranted because it may serve as a framework for elucidating how cortical damage to motor regions and their subcortical projections contribute to balance deficits and falls in people with stroke.

Effects of using compensation on balance and falls after stroke.

It should be emphasized that our task design for assaying quiet standing (**chapters 4 and 6**) obviously allowed for compensation. Participants were not encouraged nor restricted in choosing their postural strategy and adopted, on average, an asymmetric weight-bearing as typically preferred in this population.[32,33] Therefore, we cannot rule out a latent capacity to use the unloaded hemiplegic leg for controlling balance that patients may have avoided due to, for example, fear of falling. To address this issue, Marigold et al.[49] investigated balance responses to unexpected platform translations in subjects with chronic stroke during various loading conditions. They showed that forced loading did not alter delayed or reduced electromyography (EMG) responses in paretic leg muscles. Contrary to healthy subjects,[49-51] imposing symmetric weight-bearing did obviously not normalize balance regulations with the most-affected leg. This rather suggests an adaptive role for asymmetric weight-bearing, which is pronounced in those with more impairments (**chapter 4**), by relying on the less-affected side when the use of the most-affected leg for improving balance has already saturated.[14]

Ideal, we would have included various loading conditions to investigate patients' capacity to utilize their hemiplegic leg when it is forced in a longitudinal way. This is an important issue for neurorehabilitation. Traditional frameworks, such as neurodevelopmental treatment (NDT) or Bobath therapy, assume that teaching patients to stand with symmetric weight-bearing is an ideal strategy to enhance balance recovery and avoid falls.[52] While systematic reviews discourage the use of NDT in neurorehabilitation,[52-54] their emphasis on restoring "normal" movement kinematics finds entrance to modern therapies. For example, the LEAPS study[55] – the largest lower limb rehabilitation trial after stroke – explicitly stated in their protocol[56] that restoring "upright symmetrical posture with spatial-temporal symmetry of the stepping pattern" was a prioritized treatment goal of their weight-supported treadmill training intervention.

Exercise interventions for improving standing balance and mobility early post-stroke.

In line with a general trend in the literature on a greater amount of task practice and an improved recovery from disabilities,[57,58] a meta-analysis summarized in **chapter 5** (15 studies, 915 subjects) found that starting higher training intensities within the first month post-stroke is safe and likely important for enhancing recovery of walking ability. This may involve robotics[59-61] that enable non-ambulatory patients to exercise at higher doses and in more symmetric, qualitative stepping patterns, when otherwise not feasible. Hence, current robotic designs combine, similar to the LEAPS trial,[55,56] elements of evidence-based intervention by enabling larger practice doses while emphasizing kinematics following traditional frameworks, such as NDT.

Critical appraisal of current robotic designs for neurorehabilitation application.

We hypothesized that the first 5 weeks post-stroke – the critical period of most spontaneous neurological recovery[27,28] - is an ideal timing for investigating normalization effects of training with an exoskeleton-type robot. Contrary to our expectations, we found in a restricted sample of 19 moderate-to-severely impaired patients that robotic exercises were generally ineffective in enhancing neurological recovery from intralimb muscle synergies following FM-LE, irrespective of timing within or beyond the proposed sensitive period. With that, we were unable to prevent compensations with the less-affected leg for achieving functional tasks as quiet standing (**chapter 6**). From this perspective, enforcing normal symmetric movements by an exoskeleton may be seen as unwanted performance; kinematics of each successive practice step are "corrected", irrespective of synergistic movements produced by the patients. As a result, the enforced symmetrical pattern hardly allows adaptations in which patients learn to optimally deal with existing deficits.

In the last decade, wearable exoskeletons, such as those used in **chapter 6**, were announced with great enthusiasm by allowing overground training instead of treadmill-based training (e.g., Lokomat).[62] However, their introduction, including the Ekso GT[63,64] and Hybrid Assistive Limb,[65,66] did not live up to the expectations in first randomized trials. In fact, neutral results for improving functional outcomes (e.g., FAC or gait speed) in subacute stroke relative to conventional therapies corroborate a highly ambiguous evidence base regarding earlier exoskeletons, with some trials yield benefits of using the Lokomat above therapist-assisted approaches,[67] whereas others found even the contrary.[68] Thus, fine-tuning current robotic designs seems an unsuccessful strategy for improving their effectiveness. Rather, as George Hornby recently argued, it may be time to "rethink the tools in the toolbox" altogether.[69]

Is there a sensitive period for motor rehabilitation after stroke?

Our findings are in contrast with rodent models of stroke rehabilitation that do show augmented treatment responses to early vs. delayed motor exercises, suggesting a learning-dependent exploitation of the neuroplastic milieu.[70,71] However, in these models, neuronal changes associated with reaching training were observed beyond the peri-infarct area and in contralesional sensorimotor areas, indicating neuronal substitution.[70,72] In addition, kinematic analyses of foot pallet reaching using high-speed cameras showed dexterity abnormalities in rodents similar to those seen in patients with abnormal flexor synergies.[73] Hence, it remains unknown whether larger treatment gains to earlier interventions in these models actually reflect behavioral restitution of synergies or simply more effective compensatory movements.[39]

Clinical rehabilitation trials that specifically address the issue of timing in a similar way remain scarce.[4,74] Few exceptions include the recent CPASS trial.[75] In this trial, Dromerick and colleagues showed that arm-hand training was generally more beneficial before 3 months post-stroke than a later deliverance.[75] In contrast, the previously mentioned LEAPS trial[55] found equal treatment responses to weight-supported treadmill training irrespective of an timing at 2 or 6 months post-stroke. Both trials, CPASS and LEAPS, obviously hypothesized that earlier exposure to exercise is beneficial due to optimal conditions of neuroplasticity,[56,76] but chose to test this hypothesis with clinical outcomes that are heavily confounded by compensation (i.e., the Action Research Arm Test[77] and walking speed[78]). This makes the conflicting evidence very difficult to interpret from the perspective of a sensitive period. Therefore, it remains unknown *if* and *how* heightened neuroplasticity augments treatment responses in patients early after stroke onset.

Future perspectives for research

Our results have been discussed with reference to current gaps in the literature. Now, targets for further research are summarized that are considered important to advance our understanding of how behavioral restitution or compensatory learning contributes to post-stroke recovery of balance and mobility, and to what extend these mechanisms can be modulated by rehabilitation interventions.

1.) *Need for better understanding of the time course of recovery of QoM during various balance tasks in association with dynamics of brain activation.*

Translational research in a longitudinal manner with multimodal repeated measurements is needed to advance our understanding of the time course of sensorimotor deficits post-stroke and their interrelationship with behavioral compensation for improving balance to accomplish meaningful tasks. These studies should expand our findings by, first, starting their measurements before 3 weeks post-stroke to show early-onset performance changes in those who achieve standing relatively fast. Second, two-legged standing balance should be tested under various loading conditions. This may elucidate whether a patient’s preferred control asymmetry is modifiable by forced weight-bearing, and whether this loading effect differs between subgroups of patients with varying impairment severities and corticospinal integrity. The addition of physiological (e.g., Transcranial Magnetic Stimulation) or anatomical (e.g., diffusion MRI) measures of CST damage may help to phenotype these groups based on their capacity to show restitution. Third, longitudinal studies should expand to tasks that go beyond quiet standing, e.g., synergistic muscle coordination disrupts reactive stepping responses,[79] which contributes to perturbation-induced falls.[80] This may shed light on common compensatory strategies to address the question of whether a preferred asymmetric posture is generally beneficial for avoiding falls in daily life.[81]

Unravelling the inter-relationship between neuronal changes in brain activation and recovery in performing functional tasks is a particularly challenging task for future research. This requires the development of robust and feasible protocols for measuring, for example, EEG or fNIRS activation patterns while collecting kinematic and kinetic data to associate the former with standing balance improvements in terms of behavioral restitution or compensation. As emphasized, these multimodal measurements should be applied first in healthy controls to build a solid physiological framework for investigating the mechanisms of impaired balance control after cortical damage due to stroke.

2.) *Need for an ambulant measurement system for quantifying QoM independent of laboratories with robust and standardized assessment protocols.*

There are hardly any assessments protocols available for measuring interlimb coordination in COP movements in clinics. To make longitudinal studies as described above possible, it is advised to develop and validate ambulant posturographic systems. Regarding quiet standing balance, pressure-sensitive systems as investigated in **chapter 2,** and portable force plates, that are becoming increasingly commercially available, appear promising. Future studies should test their psychometric properties for quantifying COP in stroke patients against gold standard force plates. Wearable sensor-based systems should be explored for measuring, in kinematic terms, the quality of stepping responses and gait asymmetries. So far, the reliability and accuracy of such systems to address QoM during these dynamic tasks are largely unknown.

The introduction of portable assessment systems should go hand-in-hand with highly standardized protocols to ensure reliable observations for describing time courses within subjects, and to facilitate pooling across studies. This will facilitate large qualitative datasets. Acknowledging an obvious trend for increasing the trial duration and more reliable COP outcomes,[16] we propose a protocol including three 40-s quiet standing trials and recommend the use of velocity-based COP metrics because they are generally more reliable than displacement-based measures (**chapter 2**). However, available reliability studies are largely restricted to healthy controls, with a focus on traditional descriptors of postural sway.[16] Generalization to measuring COP symmetry in people with post-stroke hemiplegia should be investigated. To our knowledge, only a single recent reliability study addressed this issue so far.[18]

Exploring novel performance metrics that reflect the continuum of steady-state, anticipatory, and reactive balance requires datasets of age-matched control subjects' performance. Healthy individuals usually exhibit some deviations from perfect symmetry (**Chapter 2**). To account for this natural variation when making interpretations of abnormal movement in people after stroke, large-scale datasets of healthy performance on highly standardized balance tasks should be made available, ideal open access.

3.) *Need for performance assays that reflect behavioral restitution of lower limb motor impairment.*

The observed dependency on using compensations for improving balance post-stroke, despite significant motor improvements (**chapter 4**), suggests persistent impairments that are insufficiently captured by FM-LE and MI-LE. This agrees with kinematic observations of reaching movement abnormalities in subjects with minor upper limb deficits.[82,83] This obvious ceiling effect of traditional scales warrants finer-grained measurements that isolate highly controlled, single-joint movement outside a functional task context in a challenging way, without any contamination by compensations. These so-called performance assays are defined as "tests that quantify aspects of rudimentary motor control performance" and the assumption is that these tests best capture the true upper bound of neurological recovery.[3]

This field of research has hardly been explored, but a promising direction has been provided by Madhavan et al.[84,85] who developed an instrumented kinematic visuomotor tracking task that assayed the ability to match continuous dorsi- and plantarflexion ankle movements to a trajectory (e.g., sinusoidal wave). This is obviously more challenging than merely asking patients to lift their feet off the ground, as scored by the FM-LE and MI-LE. Another example includes the LECOMOT test focusing on coordination at the level of the knee joint.[86-88] However, performance assays on ankle coordination are interesting because these muscles are highly relevant to balance control[7] and walking,[89] and appear to be particularly dependent on corticospinal pathways during tasks.[90] Therefore, these tests may serve as markers of CST function, similar to finger extension tests for predicting the extent of upper limb recovery.[91] This may eventually assist phenotyping patients as emphasized above. Translation to clinically feasible testing protocols and their reliability and accuracy for quantifying ankle coordination after stroke should be explored.

4.) *Need for better understanding of predictors of response to high-dosed balance and mobility training early post-stroke.*

Understanding the time courses of recovery and their underlying mechanisms is a prerequisite for investigating novel interventions and optimizing existing exercise therapies based on sound neurobiological hypotheses for either restricting or supporting compensations. More specifically, future trials should address whether impairment-focused therapies that aim to restore, for example, symmetric weight-bearing are counterproductive for improving balance and avoiding falls in subgroups of patients selected by performance assays or physiological markers of CST function. This may help prospectively choosing patients who are most likely to respond to either a restorative or adaptive intervention. Importantly, fine-grained behavioral measures are needed to delineate treatment responses by enhancing behavioral restitution from learning more-effective compensation. This is the only way to understand *if* and *how* rehabilitation effects are pronounced early post-stroke.

Importantly, trials should be ambitious in the intensity and dose of interventions to show the full potential of patients for improving tasks that they wish to master. Next to the obvious strategy of increasing the amount of therapy time, evidence-based guidelines may help to direct how we deliver therapies within the boundaries of current healthcare regulation. A recent multicenter trial by Klassen et al.[100] conducted within the critical period for neurological recovery, found it safe, feasible, and potentially effective to double (2196 steps/session) the dose of conventional walking practice within 1-h therapy sessions. This should be seen as a starting point for adequately dosing interventions in future early rehabilitation trials. An additional resource-efficient strategy to enhance the intensity of exercise therapies includes active involvement of the caregiver as a “co-therapist”, but this intervention has been insufficiently explored in the early rehabilitation phase.[101]

5.) Need for reconsideration of robotic designs that focus on correcting kinematics.

As described by Nikolai A. Bernstein (1986-1966) in his seminal book *The Coordination and Regulation of Movements*, “practice [...] does not consist of repeating the means of solution [...] time after time, but involves the process of solving this problem again and again by techniques we have changed and perfected from repetition”.[92] In other words, learning occurs by letting patients make kinematic errors during practice. This corresponds to emerging evidence on the efficacy of allowing rather than restricting movement variability to improve walking performance after stroke.[68,69] This requires a new approach of delivering task practice by shifting the focus away from correcting kinematics to mimic healthy trajectories, toward robots that provide safety yet freedom to explore adaptive movements. This may eventually allow patients to acquire compensation strategies, if needed, to facilitate the transfer of what is learned in the robotic milieu to real-world performance. From this perspective, better knowledge about recovery mechanisms and their time courses post-stroke is important to inform adequate robotic designs. We argue that this approach is the only way to make this technology relevant to the field stroke rehabilitation, rather than continuing trials that test current devices against usual care with little chance of achieving meaningful results.

Conclusion: Connecting the dots

Post-stroke recovery of quiet standing balance seemingly depends to a large extent on compensation rather than behavioral restitution of motor functions in the most-affected leg. More specifically, stroke patients employ a substitution strategy by relying on the kinetic regulation of the less-affected side’s ankle strategy to control their COM when standing. This strategy appears to develop early and parallel to spontaneous neurobiological recovery. In other words, the nervous system “does not wait” until the full extent of true neurological recovery is achieved and instead uses its inherent adaptability for compensatory learning to optimally cope with remaining deficits.

There may be similarities to observations of the paretic upper limb. To overcome abnormal synergistic co-activation during reaching, patients often learn to bend and rotate the scapula and romp[93,94] while fixating the forearm and hand position[95] as shown by a series of experiments led by Mindy F. Levin. Likewise, patients may have learned to stiffen the hemiplegic leg to bear some weight without collapsing, while the dynamic control is shifted toward the less-affected leg altogether. Both strategies reduce the degrees of freedom to be controlled, thus simplifying the motor control demands to complete the task. Asymmetric weight-bearing may then reflect an attempt to optimize this strategy by increasing the efficacy of the less-affected ankle strategy in those with more impairments.[14,51]

The innate ability of the brain to undergo plastic changes and re-organize raises the question of how to capitalize on enhanced plasticity early post-stroke, as shown recently for the first time in human patients.[96] Animal models have shown that skill training rather than mere exposure to repetitious movement directs neuroplastic changes in the motor system.[97] This corresponds to a large amount of clinical evidence emphasizing the amount and intensity of task practice as a critical factor for enhancing recovery from disabilities in patients undergoing neurorehabilitation.[57,58,98,99] The important question arising from this thesis is whether therapies that allow compensations are optimal for directing brain remodeling to improve balance and avoid falls in the long term, under the condition of being sufficiently dosed. This knowledge is important to promote the transition from traditional rehabilitation frameworks to modern evidence-based therapies.

To progress recovery and rehabilitation studies with serial measurements, a strong case is made for developing and validating easy-to-use ambulant measurement systems with highly standardized protocols. This is seen as a prerequisite to follow-up patients irrespective of their location of residence and to build toward large-scale epidemiological studies of post-stroke recovery.

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ADDENDUM

STANDARDIZED MEASUREMENT OF BALANCE AND MOBILITY POST-STROKE - CONSENSUS-BASED CORE RECOMMENDATIONS FROM THE THIRD STROKE RECOVERY AND REHABILITATION ROUNDTABLE.

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ABSTRACT

Background: Mobility is a key priority for stroke survivors. Worldwide consensus of standardized outcome instruments for measuring mobility recovery after stroke is an essential milestone to optimize the quality of stroke rehabilitation and recovery studies, and to enable data synthesis across trials.

Methods: Using a standardized methodology, which involved convening of 13 world-wide experts in the field of mobility rehabilitation, consensus was established through an a priori defined survey-based approach followed by group discussions. The group agreed on balance and mobility-related definitions and recommended a core set of outcome measure instruments for lower extremity motor function, balance and mobility, biomechanical metrics, and technologies for measuring quality of movement.

Results: Selected measures included the Fugl-Meyer Motor Assessment lower extremity subscale for motor function, the Trunk Impairment Scale for sitting balance, and the Mini Balance Evaluation System Test (Mini-BESTest) and Berg Balance Scale (BBS) for standing balance. The group recommended the Functional Ambulation Category (FAC, 0-5) for walking independence, the 10-metre Walk Test (10mWT) for walking speed, the 6-Minute Walk Test (6MWT) for walking endurance, and the Dynamic Gait Index (DGI) for complex walking. A FAC score of less than three should be used to determine the need for an additional standing test (FAC < 3, add BBS to Mini-BESTest) or the feasibility to assess walking (FAC < 3, 10mWT, 6MWT, and DGI are 'not testable'). Additionally, recommendations are given for prioritized kinetic and kinematic metrics to be investigated that measure recovery of movement quality of standing balance and walking, as well as for assessment protocols and preferred equipment to be used.

Conclusions: The present recommendations of measures, metrics, technology, and protocols build on previous consensus meetings of the International Stroke Recovery and Rehabilitation Alliance to guide the research community to improve the validity and comparability between stroke recovery and rehabilitation studies as a prerequisite for building high-quality, standardized 'big data' sets. Ultimately, these recommendations could lead to high-quality, participant-specific datasets to aid the progress towards precision medicine in stroke rehabilitation.

Introduction

Stroke is a major disabling condition in the adult population worldwide and recovery of post-stroke mobility is largely dependent on the ability to regain lower extremity function, sitting and standing balance.[1] The International Classification of Functioning, Disability and Health (ICF) framework2 defines 'mobility' as: 1) changing and maintaining body position (d410-d429), 2) carrying, moving and handling objects (d430-d449), 3) walking and moving (d450-d469), and 4) moving around using transportation (d470-d489).[2] These functions determine independence in mobility and are often chosen as a rehabilitation priority by stroke survivors.[3] Consequently, improving mobility is selected as a primary objective in stroke recovery and rehabilitation trials.[4,5] Although epidemiological studies remain scarce,[6] prospective cohort studies suggest that 80%[7] to 95%[8] of people with stroke regain walking independence, with or without the use of walking aids, within the first 3-6 months post-stroke.[6] This percentage drops to 60% in individuals unable to walk in the first week post-stroke.[9] Besides the strong time-dependency of using outcome measurement instruments (OMI) in the first three months,[10] recovery of walking has been significantly associated with factors such as an intact corticospinal tract,[11] muscle strength of the most affected lower extremity,[11] continence,[11] sitting,[12] standing balance,[13] and cognition.[11]

Currently, the comparison or pooling of existing prognostic stroke studies and trials applying similar interventions is hindered by the heterogeneity of mobility-related OMI.[11,14] For example, many different distances are used in the literature to measure walking speed such as the 3-, 5-, 7-, 8-, 10-, or 12-metres.[15] Each walking speed test is based on different testing protocols resulting into different psychometric properties.[15] Standardization of OMI allows for meta-synthesis of data from different studies needed for adequate power exploration of the many complex body functions that underpin independent mobility. Thus, there is an urgent need for a recommended core set of OMI allowing synthesis and comparison of participant data. Ultimately, these recommendations could lead to high-quality, participant-specific datasets to aid the progress towards precision medicine in stroke rehabilitation.

So far, no overarching recommendations for using the same OMI and biomechanical metrics for balance and mobility exists in the stroke research community. Existing recommendations[15-16] that guide clinical practice are too elaborate, as they recommend without substantiating multiple OMI for the same construct16 whereas recommendations on biomechanical metrics are lacking for measuring balance and mobility. Consensus on measuring the fine-grained movement quality measures that are sensitive and specific, able to capture small behavioral changes, is imperative, not only for distinguishing behavioral restitution from compensation in stroke recovery and rehabilitation trials, but also to make proper interpretation of longitudinal neuroimaging studies (e.g., fMRI, DTI and EEG) that may underly functional recovery post stroke.[18]

The International Stroke Recovery and Rehabilitation Alliance aims to facilitate breakthroughs for stroke survivors through global collaborations on specific themes.[19] Through this initiative, we invited international experts in the field of stroke mobility to take part in the third Stroke Recovery and Rehabilitation Roundtable (SRRR3). The SRRR3 builds on achieved consensus on defining different time points post-stroke,[20] recommended core set of OMI (SRRR1[21]) and biomechanical metrics to measure quality of upper extremity movement (SRRR2[18]). These metrics allow us to differentiate between recovery achieved from behavioral restitution or compensation.[22] Furthermore, the achieved consensus is based on different ICF constructs and includes recommendations on standardized assessment protocols, and equipment for quantitative assessment of mobility. Therefore, the work in this SRRR3 addressed the following questions to aid future stroke rehabilitation and recovery studies:

1. Which baseline characteristics for participants should be added to the SRRR1 recommendations in the field of lower extremity motor function, balance, and mobility?
2. At what time points within the first six months post-stroke should lower extremity motor function, balance, and mobility outcomes be measured?
3. How should constructs of lower extremity motor function, balance, and mobility be defined?
4. Which core set of OMI and accompanying assessment protocols should be recommended for investigating lower extremity motor function, balance, and mobility post-stroke?
5. Which biomechanical metrics should be recommended for quantifying quality of balance and mobility recovery post-stroke?
6. Which types of technological equipment should be recommended for measuring quality of balance and mobility recovery post-stroke?

Methods

Consensus building

The SRRR3 started with a ‘preparatory group’ of four members (GK-GV-TVC-CH) who formulated the research questions (GK-GV), prepared evidence tables and designed questionnaires (TVC-CH). Two methodological experts (KB-LC) were consulted and all 11 stroke research experts from North America (3), Europe (7) and Asia (1) accepted the invitation to join the ‘core group’. Established experts as well as emerging leaders were selected based on their professional background (physiotherapy and movement sciences) and impact of their scientific publications in the fields of balance and/or mobility post-stroke. None of the invited experts of the core group had a conflict of interest. A 5-stage process following a voting-based graph-theory was undertaken to form consensus (Figure 1),[23] consisting of three online questionnaires followed by three online meetings and one hybrid meeting to discuss the six research questions. The methods employed were the same as in previous SRRR.[18,21]

Stage 1	• Preparatory work completed by preparatory group • First questionnaire completed by core group • Results discussed during online consensus meeting
Stage 2	• Second questionnaire completed by core group • Results discussed during online consensus meeting
Stage 3	• Third questionnaire completed by core group • Results discussed during online consensus meeting
Stage 4	• Face-to-face consensus meeting
Stage 5	• First draft of final manuscript provided by preparatory group and reviewed by core group • Second draft of manuscript reviewed by core group and advisory group

Figure 1. Stages of consensus building

Stage 1

Prior to administering the online questionnaires, the preparatory group performed a scoping review to identify current OMI being used in stroke research, by compiling the evidence of 60 reviews on mobility interventions and on measurement properties. Subsequently, a summary of balance and mobility-related definitions, measurement properties of OMI and biomechanical metrics in stroke rehabilitation were extracted from 220 studies (167 clinical and 53 biomechanical studies) and presented in a tabular overview (Appendix 1 available online, see journal website). Relevant studies were only included when OMI and assessment protocols were published in a peer-reviewed journal and at least one of the following measurement properties was reported: reliability, validity, internal consistency, ceiling/floor effects, responsiveness, minimal detectable change, minimal important clinical difference, measurement error. Tables were structured in agreement with the international consensus guidelines of COSMIN[24] and COMET.[25] The tables in Appendix 1 representing the candidate measurement instruments were part of the first online consensus meeting with the consensus group. While completing each questionnaire, the expert of the core group was able to consult these resource tables. Questionnaires were created and administered using QualtricsXM software (QualtricsXM PlatformTM, Utah, US), and focused on finding consensus for research questions 2 to 6 presented in the introduction of this paper. For each question, different answers were presented to elicit individual panel members' preferred ranking of presented answers. Therefore, the core group were asked to rank the provided answers (e.g., definitions, OMI, equipment) from highest to lowest priority within each ICF construct, based on their expert opinion and the measurement properties presented in the tables.

The first questionnaire included an option 'other' or 'user-specific answer' where experts could provide a unique response not included in the provided ranking options. The results were summarized by two members of the preparatory group who did not participate in the questionnaire (TVC-CH) and data analyses were performed by an independent statistician (LC) who was not involved in the consensus meetings. Individual responses were combined into one group-level ranked list, by aggregating individual rank-ordered lists using a robust graph theory-based voting system,[23,26] which was implemented as a decision-support tool in Microsoft Excel. The analysis of the voting-based graph-theory resulted in Condorcet's of ranked outcomes, from 'most preferred' to 'least preferred'. In cases of a clear 'most preferred' option (or winner, with no equal number of votes), the core group achieved consensus in stage 1. Results of the data analysis were discussed during a subsequent 2-hour online consensus meeting within the core group.

Stages 2 & 3

To resolve disagreements from stage 1, a second online questionnaire was created with alterations in ranked answer options for questions without a ‘most preferred’ winner. For these questions, the following methods were used: A) when response options received the same ranking (tied with an equal number of votes), answers were again presented with either the same or altered ranking options, based on the received feedback from the core group during the consensus meeting, and B) when a new, user-specific answer was proposed by an expert, the “most preferred” option (in case of a ’winner’) or all options were offered together with the new, user-specific answer. Data analysis was performed as described in stage 1 and followed by a second online meeting. The same methodology was adopted in stage 3.

Stage 4

A 2-day hybrid (in-person and online) meeting was held (Vienna, Austria, December 2022), where core group members discussed the results of stage 3 and reviewed the structure of the first draft of the manuscript. In addition, potential experts in the field of stroke research for the ‘advisory group’ were selected to review the recommendations and manuscript. The advisory group was chosen based on their track record of publications in the field of post-stroke balance and/or mobility, as well as their professional background in movement science, physiotherapy, or bioengineering. None of the invited experts of the advisory group had a conflict of interest.

Stage 5

The first draft of the final recommendations was provided by the preparatory group and reviewed by the core members. The pre-final draft of the recommendations was reviewed by the core and advisory group.

Results

Consensus approach

During SRRR3, we agreed to focus on the evaluation of 'balance' and 'mobility' defined by the core groups as 'the act of maintaining, achieving or restoring a state of control during any posture or activity' and by ICF as 'changing and maintaining body position' and 'walking and moving'.[2] The structure of the three questionnaires and the responses received from the core group are included as Supplementary Table 1 (available online, see journal website).

Recommendations for demographic and stroke information to collect for all research participants: SRRR1 ***– SRRR3 Balance and Mobility***
1. Age: years and category: 18 - 55, 56 - 74, ≥ 75 years 2. Sex: male / female / other 3. Ethnicity: self-description **4. Body mass (kg) or body mass index (kg/m²)** 5. Medical history • Vascular risk factors (coronary artery disease, atrial fibrillation, diabetes, hypertension, clinical obesity, smoking and alcohol use, hyperlipidaemia) • Renal or cardiac failure • Prior stroke or transient ischaemic attack (TIA) • Co-morbid conditions (cognitive decline, osteoarthritis, other neurological disease) 6. Premorbid function • Modified Rankin Scale (mRS) • **Number of (self-reported) falls within 1 year prior to diagnosis, specify type of falls** 7. Education: year count 8. Premorbid walking status: independent with or without gait aid / with assistance / unable 9. Premorbid living arrangements • Living alone: Y / N • Living at home / supported accommodation 10. Stroke severity: National Institutes of Health Stroke Scale (NIHSS) 11. Active hand movement at stroke onset?: Y / N 12. Ability to walk independently at stroke onset?: Y / N • **Independent with walking aid(s) and / or orthoses?: Y/ N;**   ○ **If Yes: Specify type of walking aid(s) and / or orthoses** 13. Stroke type: ischaemic / haemorrhagic 14. Stroke sub-type: lacunar / large artery / other (e.g., carotid dissection) / undetermined 15. Stroke location: • Cortical: internal capsule / middle cerebral artery / frontal lobe • Subcortical: thalamus / basal ganglia • Midbrain: pons / medulla / cerebellum • Brainstem 16. Thrombolysis / reperfusion therapy: Y / N 17. Imaging: • Confirmed stroke on imaging: Y / N • CT obtained: Y / N • MRI obtained: Y / N 18. Recommended OMI at baseline
Recommended characteristics in bold are added to already agreed upon items from SRRR1[21]; Y: yes, N: no, kg: kilograms, m: metre, OMI: outcome measurement instruments

Box 1. SRRR1 and SRRR3 recommendations for baseline characteristics* in lower limb motor function, balance and mobility studies.

Agreed baseline characteristics for lower extremity motor function, balance, and mobility studies.

Box 1 shows in bold the recommended baseline characteristics that should be collected in addition to the minimal core set (SRRR1) within the first 24 hours after stroke in studies investigating recovery of balance and/or mobility post-stroke.

Agreed timing of assessments

Timing of assessments was in accordance to SRRR1, as the time course of upper and lower extremity motor recovery is similar within the first six months post-stroke.[27] Minimal time points are therefore within the first week (day 5), at 12 and 26 weeks (months 3 and 6) post-stroke, with recommended time points at weeks 5 and 8. As it is suggested that recovery or decline of mobility may take longer than six months,[28] we recommend to repeat the same OMI in the chronic phase. However, no specific time points were recommended, as this was beyond the scope of SRRR3. In agreement with SRRR1, the time points of measurements should always refer to time post-stroke onset and not the time of admission or enrolment in the trial.

Agreed measurement properties.

Content validity was our top prioritized item guiding our choice of OMI for the different constructs of recovery post-stroke and was defined according to COSMIN as “the degree to which a measurement is an adequate reflection of the construct to be measured”.[24] Additionally, we agreed that OMI have to be reliable and sensitive to change in the proposed construct to be recommended for studies.

Agreed definitions of underlying constructs of lower extremity motor function, balance, and mobility.

Box 2 shows in alphabetic order the agreed definitions of the different a priori chosen constructs related to balance and mobility post-stroke, and other commonly used terms. We defined ‘balance’ as ‘steady-state’, ‘proactive’, and ‘reactive’ balance but rejected the distinction between ‘static’ and ‘dynamic’ balance, as the act of balancing is always dynamic in its nature. Performance assay was defined as ‘an isolated core motor execution capacity tested outside of a functional task context’.[18]

Construct	Definition
Balance	The act of maintaining, achieving or restoring a state of control during any posture or activity.[29]
Balance – steady-state	The ability to control the centre of mass relative to the base of support in fairly predictable and non-changing conditions.[30]
Balance – proactive	The ability to activate muscles (in the legs and trunk) for balance control in advance of potentially destabilizing voluntary movements.[30]
Balance – reactive	The ability to recover a stable position following an unexpected balance perturbation.[30]
Centre of mass	The point on an object where all the mass can be considered to act.[31]
Centre of pressure	The point on the base of support at which the ground reaction forces can be considered to act.[32]
Fall	An event which results in a person coming to rest unintentionally on the ground or lower level (adapted from Tinetti et al, 1988[33]). The core group recommends that in stroke recovery and rehabilitation trials, researchers must always report the type of falls that are excluded.
Lower extremity	Refers to the part of the body from the hip to the toes. The lower extremity includes the hip, knee, and ankle joints, and the bones of the thigh, shank, and foot; and the muscles and ligaments spanning over these joints. (no reference)
Mobility	The International Classification of Functioning, Disability and Health (ICF) framework defines 'mobility' as: 1) changing and maintaining body position (d410-d429), 2) carrying, moving and handling objects (d430-d449), 3) walking and moving (d450-d469), and 4) moving around using transportation (d470-d489).[2]
Muscle synergy	A systematic coupling/co-articulation across different joints or fixed pattern of co-activation of muscles.[34-36]
Sitting	To be in a position in which the lower part of the body is resting on a seat or other type of support, with the upper part of the body vertical. (Cambridge Dictionary)
Sitting balance	The act of maintaining, achieving or restoring a state of control during sitting. (adapted from Pollock et al.[29])
Standing	To be on your feet, in a vertical position. (Oxford Dictionary)
Standing balance	The act of maintaining, achieving or restoring a state of control during standing. (adapted from Pollock et al.[29])
Walking	Moving along a surface on foot, step by step, so that one foot is always on the ground, such as when strolling, sauntering, walking forwards, backwards, or sideways.[2]

Box 2. SRRR3 agreed definitions of constructs in the field of lower extremity motor function, balance and mobility post-stroke in an alphabetic order.

Agreed core set of OMI for measuring lower extremity motor function, balance, and mobility.

Box 3 presents the core set of OMI for lower extremity motor function, balance and mobility in stroke recovery and rehabilitation studies within the first six months post-stroke. For measuring motor function of the most affected lower extremity, we recommend the Fugl-Meyer Motor Assessment lower extremity subscale[37] (FMA-LE). The SRRR3 was unable to give recommendations with respect to a specific performance assay.

We recommend the Trunk Impairment Scale[38] (TIS) for assessment of sitting balance and a shortened version of the Balance Evaluation Systems Test[39] (Mini-BESTest) for measuring standing balance. Although the Mini-BESTest shows excellent measurement properties even in mildly impaired participants and includes items assessing steady-state, proactive, and reactive balance, it has significant floor effects.[40] Therefore, the addition of the Berg Balance scale[41,42] (BBS) to the Mini-BESTest is recommended for individuals requiring physical assistance for walking ability (defined as Functional Ambulation Category[43] (FAC) < 3). When the BBS is selected, we recommend that it be used throughout the research trial, even in cases where the FAC improves to ≥ 3.

The FAC was recommended to classify walking ability and walking independence. In case of a FAC score ≥ 3, the 10-m walk test (10mWT), 6-min Walk Test (6MWT), and Dynamic Gait Index[44] (DGI) are recommended for assessing walking speed, walking endurance, and complex walking, respectively, and should ideally be performed without the use of a walking aid. However, the use of a walking aid is permitted and should always be documented. In case of a FAC < 3 (i.e., physical assistance by another person is required), further performance on walking tests should be documented as 'Not Testable' instead of assigning a value of 'zero', acknowledging that the inability to walk is not the same as having a walking speed of zero. The proportion of participants able to walk independently and safely (FAC ≥ 4) or not (FAC < 4), should also be reported.

As shown in protocols provided in Appendix 2, the 10mWT should be tested at a comfortable pace on a straight and level 14-m walkway, a 10-m timed distance and a 2-metre acceleration deceleration distance, respecitvely.[45,15] The 10mWT should be administered three times and based on the average time taken to walk 10 m in s. Walking speed (m/s) should be the reported outcome. The 6MWT should be administered once on a straight 30-m walkway with standardized encouragement phrases each minute,[15,46] and without a practice trial.[47] The total distance walked should be reported in m. When a walking aid and/or orthosis is used to perform walking tests, the type of aid and/or orthosis should be documented, and the same aid should be used during retest. For safety reasons, the evaluator should walk on the affected side, but slightly behind the participant. The detailed assessment protocols with full instructions and scoring sheet of all OMI can be found in Appendix 2 (available online, see journal website).

Outcome	**Outcome measurement instrument**	
Construct	**FAC < 3**	**FAC ≥ 3**
Lower extremity motor function	FMA-LE	FMA-LE
Sitting balance	TIS	TIS
Standing balance	Mini-BESTest and BBS	Mini-BESTest
Walking – walking speed	Not testable	10mWT
Walking – walking endurance	Not testable	6MWT
Walking – complex walking	Not testable	DGI
Walking – independence	FAC	FAC

FMA-LE: Fugl-Meyer Motor Assessment - Lower Extremity Subscale[37], FAC: Functional Ambulation Categories[43], TIS: Trunk Impairment Scale[38], Mini-BESTest: shortened version of Balance Evaluation Systems Test[39], BBS: Berg Balance Scale[41,42], 10mWT: 10-meter walk test[15,45], 6MWT: 6-minute walk test[15,46], DGI: Dynamic Gait Index[44]

Box 3. SRRR3 recommendations for a core set of assessment tools for measuring lower extremity motor function, balance and mobility post-stroke.

Agreed biomechanical metrics for measuring quality of sitting, standing, and walking.

Box 4 presents the preliminary core set of biomechanical metrics for assessing balance and mobility in stroke recovery and rehabilitation studies within the first six months post-stroke. For measuring quality of sitting, we are unable to provide recommendations on how to measure sitting balance in a biomechanical way due to a lack of validated instruments and robust protocols.

Outcome	Domain	Biomechanical metric	Equipment
Sitting balance		No recommendation	
Steady-state standing balance	Postural sway control	CoP velocities and displacements for individual limbs (e.g., asymmetry index, inter-limb synchronization)	Dual force plate
Proactive and reactive standing balance		No recommendation	
Walking	Spatiotemporal	Walking speed and step length (asymmetry)	GaitRite or high- fidelity systems
	Kinetic	Paretic leg propulsion	Force plate
	Kinematic	GPS/GDI	High-fidelity systems
	Muscle activity	No recommendation	EMG

CoP: centre of pressure, GPS: Gait Profile Score, GDI: Gait Deviation Index, EMG: electromyography

Box 4. SRRR3 recommendations for biomechanical metrics and corresponding technological equipment for measuring balance and mobility post-stroke.

For assessing quality of steady-state standing balance, we prioritized center of pressure (CoP) measurements of each individual limb using a dual force plate. More specific, CoP velocity metrics, expressed as asymmetry indexes[48] and inter-limb synchronization measures[49] are of interest, as descriptors of the relative paretic-leg contribution to postural sway control. The participant should be assessed barefoot in at least two core conditions: eyes open and eyes closed for at least 30 s per condition, in-line with the slightly adjusted assessment protocol of Mansfield and colleagues (2015).[50] An average of three successive trials should be reported to maximize reliability of CoP outcomes.[51] However, we could not reach consensus on a definitive biomechanical core set for steady-state, proactive, and reactive balance outcomes and, therefore, recommend a further roundtable with experts in the field of biomechanical measurements.

The minimal reporting requirement to measure quality of walking are spatiotemporal parameters (i.e., walking speed and step length), followed by, in order of priority: kinetics, kinematics, and muscle activity. Kinetic metrics are prioritized for their insights into propulsion mechanisms. Asymmetry metrics are especially recommended to provide greater insights into compensatory mechanisms and underlying kinematic strategies,[52] together with stride-normalized ground reaction forces to measure the relative contribution of the paretic leg to propulsion generation.[53] Furthermore, we recommend the use of a multivariate kinematic metric, such as the Gait Profile Score54 or Gait Deviation Index,[55] which provides a comprehensive and clinically meaningful interpretation of walking. Lastly, surface electromyography was proposed for measuring muscle activity, yet at this stage, we are unable to recommend a single prioritized metric. Similar to CoP measurements of steady-state balance, we provide global recommendations for the assessment of quality of walking and propose a next separate SRRR-round to provide more specific recommendations. Concerning data acquisition, the task force recommends that participants perform tests of walking quality with and without the use of orthoses, walking aids, and footwear, to allow comparison with and between OMI over time.

Agreed technological equipment for measuring quality of balance and mobility.

Concerning biomechanical assessments of balance and mobility, we recommend using force plates (sampling frequency ≥100 Hz)[51] and high-fidelity optoelectronic measurement systems[18] (e.g., 3D motion capture systems with sampling frequency ≥60 Hz). These high-fidelity systems should be applied by people with expertise and access to these technologies, without limiting to specific brands. However, we recommend, at this point, not to use portable equipment (e.g., gaming devices, pressure plates) or wearable equipment (e.g., inertial devices, gyroscopes, and accelerometers) for measuring balance and mobility in recovery studies due to a lack of validated assessment protocols and reliable biomechanical metrics extracted from this equipment. In contrast, for spatiotemporal parameters, we agreed that the GaitRite is the prioritized, non-optical, measurement tool with sufficient reliability and validity.[56]

Discussion

The current consensus builds on previous SRRR[18,21] and provides recommendations for recovery and rehabilitation studies with respect to definitions of balance and mobility, a minimal core set of baseline characteristics, OMI and biomechanical metrics with standardized assessment protocols, and preferred measurement time points. Unfortunately, different protocols are being used for the same test worldwide, which may prevent comparison of results. Therefore, we included assessment protocols with standardization of, e.g., walkway length, walking speed, instructions, use of aids, as well as differences in scoring when the participant is unable to walk. These OMI are core outcomes for the various proposed constructs. It is therefore recommended to first define the study construct before choosing the appropriate OMI from the core set related to this construct. In contrast, the SRRR3 could only provide global recommendations concerning biomechanical metrics and recommends that further collaborative work is needed on establishing core metrics. Particularly, studies adhering to the recommended timing of assessment post-stroke are needed to investigate the longitudinal associations between the different underlying constructs within participants. Therefore, the current results should be seen as a first step towards defining constructs and standardization of testing protocols as a condition for pooling studies and individual data. Ultimately, the current recommendations could lead to high-quality, participant-specific datasets to aid the progress towards precision medicine in stroke rehabilitation. This step is important, acknowledging that stroke is a heterogeneous disorder. Current stroke rehabilitation approaches are based on the 'one-size-fits-all' principle, which treats patients as an 'average' person and ignores the individual differences. Precision medicine, on the other hand, uses 'big data' from clinical and multimodal MRI to tailor the treatment and prevention strategies to each patient's specific needs.[20,57,58] Ultimately, these big data sets allow us to classify pheno(sub)types at a participant-specific level and to identify those who do and do not respond to an evidence-based intervention.

Strengths and limitations

To develop recommendations for measuring balance and mobility in stroke recovery and rehabilitation studies, we undertook an extensive literature review, consulted experts, and applied decision analytics. The latter was based on the voting-based graph-theory resulting into ranked outcomes instead of the commonly used Delphi-method. The Delphi-method is more time-consuming, requires interpretation of complex language and recommends only one outcome, while the adopted methodology is a time-efficient process creating manageable lists with ordinal preference scores per outcome.[26] There are some limitations to consider. Firstly, ICF-mobility items[2] ‘carrying of objects’ and ‘using transportation’, as well as risk of falls[59] were not included in the SRRR3. The ability to be mobile in the presence of external demands or in challenging environments are seen as important factors in regaining independence during activities of daily living. As there are currently no reliable and valid OMI available to assess daily life abilities, the development of these OMI is a research priority. Secondly, although the optional recommended time points for assessments on weeks 5 and 8 were chosen relatively arbitrary, there is some recent evidence supporting this statement. Recent research of Schröder et al. (2023) suggested that a plateau of recovery around week 8 for the majority of measures assessing lower limb function and standing balance.[60] Only the weight-bearing asymmetry improved until week 12 (month 3). Therefore, we have set these time points as optional, yet recommended. Thirdly, we acknowledge that some of our recommended OMI have significant limitations, such as the FMA-LE which lacks responsiveness, shows ceiling effects, and is confounded by muscle strength requirements.[61] Yet, no better psychometrically sound alternative is currently available for assessing pathological synergistic movements of the lower extremity post-stroke. In the future, this void may be filled by using kinematic and kinetic metrics for assessing quality of movement. Thirdly, we acknowledge that recommended OMI show some overlap in their underlying constructs such as the Mini-BESTest measuring not only aspects of balance but also mobility such as compensatory stepping in different directions, change in walking speed and the 'timed up and go'. In addition, we are aware that applying the whole recommended core set may oblige researchers to make prioritizations to reduce the overall testing time. Fifthly, in contrast with SRRR2,[18] we were unable to recommend performance assays for measuring behavioral restitution at the ICF-level of body functions of the lower extremity, nor a standardized test at the level of daily activities for identification of compensation post-stroke. For this standardized test, we need a large age- and sex-matched normative dataset captured with a high-fidelity 3D-system. Subsequently, although some recommendations were provided as a first step towards global recommendations, further work on biomechanical metrics in a future consensus meeting is required. These recommendations should be based on principles derived from motor control and include the technological equipment and validated assessment protocols for measuring quality of balance and mobility post-stroke. Lastly, the recommended OMI were selected by researchers, although some members of the core and advisory group also had clinical training; the recommended OMI might not represent the preferences and priorities of practicing clinicians and/or patients.

Future Research

First, our recommendation to only assess walking when participants have a FAC score ≥ 3 leads to missing data for those who can walk with some physical assistance from another person for balance control. We acknowledge that this restricts our ability to measure change in individuals with a FAC < 3, resulting in the loss of relevant information. There are several protocols in which physical assistance is allowed during walking, limited to support with one hand.[62,63] We propose that future research should further validate these assessment protocols in which physical assistance is allowed. In addition, we only recommended OMI that are qualified as 'capacity' (i.e., individual can complete in a standardized environment[2]), as opposed to 'performance' (i.e., what a person actually does in their usual environment[2]). Of note, improvements in capacity may not directly translate into improvements in real-world performance, as research has demonstrated changes in capacity without observed performance improvements in individuals post-stroke undergoing walking interventions.[64] Moreover, walking independence which was defined in this study as FAC > 3 might have a different meaning to stroke survivors and could be entangled with measures of endurance or walking speed (for example, the freedom to walk whenever they need to, for whatever distance, in whatever environment). This perceived independence of the subject was not part of the current consensus-based study. Yet, identifying the potential impact of rehabilitation interventions on both capacity and performance, and participants' perceived change through self-report, is a necessity to gain further insights into the effectiveness of rehabilitation interventions and aid appropriate application of interventions into clinical practice. More research on the measurement of real-world performance requires validation of protocols in which portable and wearable instrumentation is applied.

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SUMMARY

Stroke is one of the main causes of serious adult disability in Europe. Approximately 80% of people who have experienced a stroke suffer from motor impairments, typically affecting unilateral motor control of the face, arm, and leg; this condition is referred to as hemiplegia. In turn, these impairments cause poor execution of balance control reactions with a resultant elevated risk of falls, which greatly restricts a patient's ability to participate in society. Therefore, improving balance control while sitting, transferring, standing, and walking is a cornerstone of stroke rehabilitation when aiming to improve a patient's ability to perform activities of daily life and enable home discharge.

As outlined in **chapter 1**, most patients show spontaneous motor recovery in the first 5 to 8 weeks post-stroke, measured with the Fugl-Meyer lower extremity motor subscale (FM-LE), which reflects dissociation from abnormal muscle synergies, and the Motricity Index (MI-LE), which reflects strength increases. Unfortunately, how these unilateral motor improvements contribute to recovery in balance control during complex tasks, such as two-legged standing, has not been thoroughly investigated. To this end, it is crucial to acknowledge that task improvements may be compensatory by relying on the less-affected limb, as typically observed in this population. As such, it remains largely unknown *what* patients actually learn when reacquiring balance soon after stroke and, eventually, *how* they should be trained to optimally reduce disabilities and avoid falls in the long term.

Improving our knowledge of behavioral recovery mechanisms after stroke requires well-designed longitudinal studies with instrumented measurements, e.g., center of pressure (COP) movements may serve as a biomechanical measure of individual limb contributions to standing balance. These measures may overcome limitations of traditional clinical outcomes, such as the Berg Balance Scale, which cannot delineate between the re-emergence of more “normal” movement patterns – a process called behavioral restitution – and the use of alternate, compensatory strategies on the rated tasks. In other words, using kinematics and kinetics in a repeated and standardized manner is the only way to capture the quality of movement (QoM) during tasks, and changes therein due to motor recovery or an intervention.

Floor-mounted force plates are currently considered the “gold standard” for obtaining reliable COP measures. However, these devices are expensive and difficult to transport, making them impractical for clinical trials. Therefore, **chapter 2** describes a validation study involving 19 healthy adults to investigate the psychometric properties of using a pressure plate as a portable alternative to force plates. Above their portable design, these devices can record individual-limb COP movements using a single plate due to a larger number of embedded sensors, to calculate contribution measures as the dynamic control asymmetry (DCA). This advantage may further reduce the need for extensive infrastructure, thus improving the feasibility of performing serial measurements to address changes in QoM post-stroke.

Our results show that the pressure plate yields, despite its sufficient test-retest reliability, center-of-pressure (COP) measures of standing balance that are strongly associated with, but not equivalent to, those obtained by force plates. This concern about the criterion validity of pressure plates as a balance assessment tool strongly suggests using the same instrument to monitor changes within an individual subject. Comparison *between* subjects using *different* plate types must be avoided.

Chapter 3 describes the design of an observational study, the TARGEt-1 trial, which aims to unravel the finer-grained changes in balance performance early post-stroke. We chose a quiet standing task with relatively low functional demands to start our measurements as early as 3 weeks post-stroke and relate subsequent performance changes to ongoing motor recovery (FM-LE and MI-LE) at 5, 8 and 12 weeks post-stroke follow-up. We either used dual force plates or a pressure plate to assess patients independent of our laboratory, if needed. Importantly, building upon the findings of **chapter 2**, the different plate types were not interchanged, such that individual recovery courses are not confounded by this factor.

We hypothesized that time-dependent improvements in FM-LE and MI-LE make a beneficial contribution to standing balance recovery by a partial return toward normal levels of interlimb symmetry, using a group of age-matched healthy participants as a reference group. We therefore expected, similar to recent kinematic studies of upper limb recovery, a time-restricted period soon after stroke onset during which QoM on this task “normalizes”.

The findings of TARGEt-1 are provided in **chapter 4**. In total, 60 first-ever stroke survivors participated, of which 48 were tested at sufficient occasions to be included in the longitudinal analyses. Consistent with the literature, we found a time-dependent course of FM-LE and MI-LE with significant improvements in the first 5 to 8 weeks after stroke. During the same period, patients exhibited improvements in their ability to maintain postural stability while standing. However, when observed *within* subjects, reductions in lower limb motor impairments were not significantly associated with improved postural stability, or with changes in DCA and weight-bearing asymmetry (WBA). In fact, DCA and WBA were quite invariant for change and remained significantly different from normative symmetry scores obtained in the healthy reference group. Hence, against our expectations, QoM did not normalize and behavioral restitution of motor functions in the hemiplegic limb appears to hardly contribute to balance recovery. Together with previous studies reporting unchanged posture and gait asymmetries in most patients throughout the first 3-6 months post-stroke, our results suggest that early improvements in steady-state balance and related activities depend to a large extend on compensatory learning involving the less-affected limb.

The innate ability of the brain to undergo plastic changes raises the question of how to capitalize on an enhanced state of brain plasticity early post-stroke that enables widespread functional reorganization. An extensive body of clinical evidence emphasizes the amount of task practice as a critical factor in enhancing recovery from disabilities. Likewise, a literature review with meta-analyses (15 studies, 915 subjects) described in **chapter 5** found that starting higher training intensities within the first month post-stroke – the critical period for motor recovery – is safe and likely important for promoting walking independence. This may involve the use of therapeutic robots that enable patients with more impairments to exercise, when otherwise not feasible.

Chapter 6 describes a pilot rehabilitation study, the TARGEt-2 study, involving 19 stroke patients. Here, we hypothesized that the restorative effects of additional training with a wearable exoskeleton – a bilateral robotic orthosis that steers the lower limb in symmetric patterns – are enhanced if delivered within the first 5 weeks post-stroke, when compared with a delayed delivery 8 weeks post-stroke. While the intervention was found feasible and safe to be tested in an adequately powered phase II trial, our findings suggest that robotic exercises were generally ineffective in enhancing FM-LE recovery beyond gains attributable to spontaneous recovery alone. Therefore, we were unable to prevent compensation with the less-affected leg, even if robotic gait training targeting symmetry was applied during the critical recovery period with enhanced plasticity.

In this thesis, we suggest that current robotic designs that focus on “correcting” kinematics to mimic trajectories as seen in healthy controls are inadequate for neurorehabilitation purposes. After all, the enforced symmetric gait patterns hardly allow adaptions in which patients learn compensatory movements to optimally cope with existing deficits. This may include an asymmetric weight-bearing to control balance predominantly through the less-affected leg, as reflected by DCA.

Chapter 7 concludes with a discussion of the main findings of this thesis and possible next steps for future research. In addition to the obvious recommendation to confirm our findings on the time course of QoM in larger samples, we advise starting measurements even earlier in those who reacquire balance relatively quickly and include tasks that go beyond quiet standing. This may include tasks that assay reactive balance, which is often impaired post-stroke and may better reflect falling in daily life scenarios. While our results do suggest that even “well-recovered” patients may rely on behavioral compensation to recover balance, this needs further investigation in more difficult balance tasks. Only then can we judge whether a patient’s preferred asymmetry is actually beneficial in reducing disabilities and preventing falls, and whether these adaptions in motor control should be encouraged early on during rehabilitation to enable safe discharge.

In addition, it is deemed important to include ambulatory measurement systems of brain activation (e.g., EEG, fNIRS) in longitudinal studies to associate behavioral restitution or compensation during balance recovery with dynamics of task-related cortical activation. This may elucidate the neuronal mechanisms that direct post-stroke recovery and contribute to the development of novel rehabilitation interventions, including non-invasive brain stimulation protocols.

To facilitate recovery and rehabilitation trials in general, a strong case is made for the development and validation of easy-to-use portable measurement systems with highly standardized protocols. This is seen as a prerequisite for following patients after discharge, regardless of their location of residence, and build toward large-scale epidemiological studies of post-stroke recovery.

NEDERLANDSE SAMENVATTING

Een cerebro-vasculair accident (CVA), ofwel beroerte, is een van de belangrijkste oorzaken van ernstige invaliditeit bij volwassenen in Europa. Een beroerte wordt veroorzaakt hetzij door een blokkade van de bloedtoevoer naar een hersengebied (herseninfarct), hetzij door een bloeding (hersenbloeding). Doorgaans lijdt ongeveer 80% van de overlevende patiënten aan motorische stoornissen, met uitvalverschijnselen in de unilaterale motorische controle van het aangezicht, de arm, en het been, wat een hemiplegie wordt genoemd. Deze stoornissen beïnvloeden op hun beurt de balanscontrole om valincidenten te vermijden, wat een grote impact heeft op het veilig uitvoeren van dagelijkse activiteiten en participatie in de samenleving. Daarom is het verbeteren van balanscontrole bij patiënten met een beroerte een speerpunt in de neurorevalidatie om ontslag naar huis mogelijk te maken.

Zoals beschreven in **hoofdstuk 1**, vertonen de meeste patiënten spontaan motorisch herstel in de eerste 5-8 weken na de beroerte. Dit wordt gemeten met de Fugl-Meyer motorische schaal voor de onderste extremiteit (FM-LE), die de dissociatie van abnormale spiersynergieën weergeeft, en de Motricity Index (MI-LE), die de toename van kracht weergeeft. Helaas is nog nauwelijks onderzocht hoe deze unilaterale verbeteringen in de motorische sturing van de onderste extremiteit exact bijdragen aan het herstel in balanscontrole tijdens complexe taken, zoals recht blijven staan op de twee benen. Hiervoor is het cruciaal om te erkennen dat taakverbeteringen immers compensatoir kunnen zijn door voornamelijk de minder-aangedane zijde in te schakelen, zoals typisch wordt waargenomen in deze populatie. Dus, het blijft onbekend *wat* patiënten daadwerkelijk leren wanneer ze hun evenwicht hervinden na een beroerte en, uiteindelijk, *hoe* ze getraind moeten worden om optimaal te functioneren en valincidenten te vermijden.

Een betere grip krijgen op de gedragsmatige herstelmechanismen na een beroerte vereist longitudinale studies die gebruik maken van geïnstrumenteerde metingen. Een voorbeeld hiervan zijn metingen van het *center of pressure* (COP), een biomechanische maat die de bijdrage van elk individueel lidmaat aan de staande balanscontrole weergeeft. In tegenstelling tot traditionele klinische maten, zoals de Berg Balance Scale, kan op die manier een onderscheid gemaakt worden tussen het opnieuw ontstaan van "normale" bewegingspatronen, een proces dat gedragsmatige restitutie wordt genoemd, en het gebruik van alternatieve taakstrategieën om een blijvend functieverlies te compenseren. Met andere woorden, het herhaaldelijk en gestandaardiseerd gebruik van kinematica en kinetica (beschrijving van de bewegingstrajecten en -krachten) is voorwaardelijk om de kwaliteit van beweging tijdens taken te meten, en veranderingen daarin als gevolg van motorisch herstel of een interventie.

Op de vloer gemonteerde krachtplaten worden momenteel beschouwd als de “gouden standaard” voor het verkrijgen van betrouwbare COP-maten. Deze apparaten zijn echter duur en moeilijk te transporteren, wat ze ongeschikt maakt voor klinisch onderzoek. Daarom beschrijft **hoofdstuk 2** een validatiestudie met 19 gezonde proefpersonen om de psychometrische eigenschappen te onderzoeken van het gebruik van een draagbare drukplaat als alternatief. Draagbare drukplaten zijn niet alleen makkelijker te vervoeren, maar kunnen ook individuele COP-bewegingen registreren van elke zijde met slechts één apparaat door een grotere hoeveelheid ingebouwde sensoren. Dit maakt het mogelijk om symmetrie maatstaven die de bewegingskwaliteit weergeven bij hemiplege patiënten, zoals de dynamische controle asymmetrie (DCA), te bepalen. Het gebruik van dergelijke apparaten kan de behoefte aan uitgebreide infrastructuur verkleinen en daarmee de haalbaarheid van regelmatige metingen in klinische proeven verhogen.

Onze resultaten tonen aan dat de drukplaat, ondanks de voldoende test-hertest betrouwbaarheid, COP-maten van de staande balanscontrole oplevert die sterk associëren met, maar niet gelijkwaardig zijn aan, die van de krachtplaten. Deze bezorgdheid over de criteriumvaliditeit van de drukplaat suggereert sterk om steeds hetzelfde meetinstrument te gebruiken om het herstelverloop van een individueel proefpersoon op te volgen. Vergelijkingen *tussen* proefpersonen, die met *verschillende* platen getest werden, moeten vermeden worden.

Hoofdstuk 3 beschrijft de opzet van een observationele studie, het TARGEt-1 onderzoek, met als doel een beter grip te krijgen op de fijnere veranderingen in de balanscontrole kort na de beroerte. We kozen voor het stil blijven staan als taak met relatief lage functionele eisen, waardoor metingen al 3 weken na de beroerte konden beginnen om, vervolgens, de prestatieveranderingen te relateren aan de voortgang van motorisch herstel (FM-LE en MI-LE) op 5, 8 en 12 weken na de beroerte. Indien nodig gebruikten we krachtplaten of een drukplaat om patiënten buiten ons laboratorium te beoordelen. Belangrijk is dat, voortbouwend op de bevindingen in **hoofdstuk 2**, de verschillende platen niet werden verwisseld om te verzekeren dat het individuele herstelverloop niet beïnvloed werd door deze factor.

We formuleerden de hypothese dat vroege, tijdsafhankelijke verbeteringen in FM-LE en MI-LE scores een gunstige bijdrage leveren door een gedeeltelijke terugkeer naar normale niveaus van symmetrie tijdens het staan. Vergelijkbaar met recente kinematische studies over het herstel van arm- en handfunctie, verwachtten we dat er kort na de beroerte een specifieke periode zou zijn waarin de bewegingskwaliteit van de staande balanscontrole als het ware normaliseert. Om normalisatie te toetsen, rekruteerden we eveneens een groep van gezonde deelnemers van vergelijkbare leeftijd als referentiegroep.

De uiteindelijke bevindingen van TARGEt-1 staan in **hoofdstuk 4**. In totaal namen 60 proefpersonen na een eerste beroerte deel, waarvan er 48 deelnamen aan minstens twee herhaalde metingen. Overeenkomstig met bestaande literatuur vonden we tijdsafhankelijk herstel van FM-LE en MI-LE scores, met name in de eerste 5-8 weken na de beroerte. In dezelfde periode vertoonden patiënten verbeteringen in hun houdingsstabiliteit tijdens het staan. Echter, bij individuele observaties *binnen* de proefpersonen was er geen significante associatie tussen de afname van de motorische stoornissen en een verbeterde houdingsstabiliteit, en met veranderingen in DCA en de asymmetrische gewichtsverdeling. In feite waren de asymmetriematen vrij invariant voor verandering over tijd en bleven significant verschillend ten opzichte van normatieve waardes gedurende het herstel. Tegen onze verwachtingen in lijkt werkelijk herstel van motorische functies in het hemiplegische been nauwelijks bij te dragen aan herstel van de staande balanscontrole. Eerder doen onze bevindingen vermoeden, samen met observaties in de literatuur over onveranderde houdings- en gangasymmetrieën in de subacute herstelfase, dat vroege verbeteringen in balans en gerelateerde activiteiten nauw samenhangen met het leren van compensatoire bewegingsstrategieën.

Het vermogen van de hersenen om plastische veranderingen te ondergaan roept de vraag op hoe we optimaal gebruik kunnen maken van een “neuroplastisch milieu” dat wijdverspreide reorganisatie in de hersenen toelaat kort na de beroerte. Uitgebreid klinisch onderzoek benadrukt dat de hoeveelheid taakoefeningen een belangrijke factor is in het bevorderen van herstel van dagelijkse activiteiten. Eveneens laat een literatuurstudie met meta-analyses (15 onderzoeken, 915 proefpersonen), beschreven in **hoofdstuk 5**, zien dat het starten aan hogere trainingsintensiteiten binnen de eerste maand na de beroerte - de kritieke herstel periode - veilig is en het herstel van onafhankelijk stappen kan bevorderen. De toepassing van therapeutische robots kan hierbij helpen door patiënten met grotere beperkingen in staat te stellen intensiever te trainen, wanneer dit anders niet haalbaar is.

Hoofdstuk 6 gaat over het TARGEt-2 pilootonderzoek met, in totaal, 19 beroerte patiënten. Dit onderzoek richtte zich op de vraag of training met een robotisch exoskelet – een geautomatiseerde orthese die de benen in symmetrische bewegingspatronen aanstuurt – effectiever is wanneer het binnen 5 weken na een beroerte wordt gestart, in vergelijking met een start 8 weken na de beroerte. Hoewel de trainingsinterventie als voldoende veilig werd geacht voor een definitief fase II onderzoek, toonden preliminaire resultaten aan dat oefeningen met het exoskelet niet effectief waren in het verbeteren van FM-LE scores bijkomend op de winst die toe te schrijven is aan spontaan herstel. Vervolgens zijn we er niet in geslaagd om compensaties van het minder-aangedane been tijdens het staan te voorkomen, zelfs als symmetrie training met het exoskelet vroegtijdig werd toegepast.

Dit proefschrift suggereert dat huidige therapeutische robots, die zich louter richten op “correctie” van bewegingstrajecten om stappatronen van gezonde controles na te bootsen, ontoereikend zijn voor de neurorevalidatie. De afgedwongen symmetrische patronen laten namelijk nauwelijks adaptaties toe waarbij patiënten leren omgaan met een bestaand functieverlies, inclusief een asymmetrische gewichtsverdeling om het evenwicht voornamelijk te handhaven door middel van het minder-aangedane been.

Hoofdstuk 7 sluit af met een bespreking van de belangrijkste bevindingen van dit proefschrift en mogelijke stappen voor toekomstig onderzoek. Een primaire aanbeveling is om onze bevindingen over het herstelverloop van bewegingskwaliteit tijdens balanstaken vroeg na de beroerte te bevestigen in grotere steekproeven. Verder adviseren we om nog eerder te starten met deze metingen bij patiënten die de balans relatief snel herwinnen, en taken toe te voegen die verder gaan dan enkel stilstaan. Zo kan bijvoorbeeld reactief evenwicht, dat na een beroerte eveneens verminderd is, een betere indicatie geven van het valrisico in het dagelijks leven. Hoewel onze bevindingen suggereren dat zelfs mensen met milde stoornissen in belangrijke mate afhankelijk kunnen zijn van compensatiestrategieën, is verder onderzoek nodig bij meer complexe balanstaken. Enkel op die manier kan een afweging worden gemaakt of de asymmetrische voorkeursstrategieën van patiënten daadwerkelijk helpen bij het voorkomen van vallen en of deze vroegtijdig getraind moeten worden tijdens revalidatie ter voorbereiding op ziekenhuisontslag.

Daarnaast wordt het belangrijk geacht om ambulante meetsystemen van hersenactivatie (bijv. EEG, fNIRS) op te nemen in longitudinale studies. Dit zou het mogelijk maken om gedragsmatig herstel bij balanstaken te associëren met de dynamiek van taak-gerelateerde corticale activatiepatronen. Dergelijk onderzoek zou waardevolle inzichten bieden in de neuronale mechanismen die herstel na een beroerte sturen en kan bijdragen aan de ontwikkeling van nieuwe interventies, zoals niet-invasieve hersenstimulatie protocollen.

Om herstel- en revalidatieonderzoek te vergemakkelijken, wordt sterk gepleit voor het ontwikkelen en valideren van gebruiksvriendelijke draagbare meetsystemen met gestandaardiseerde protocollen. Dit wordt gezien als een eerste vereiste om patiënten te kunnen opvolgen, ongeacht hun verblijfplaats na ontslag, en om grootschalige epidemiologische studies naar beroerteherstel te faciliteren.

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ABOUT THE AUTHOR

Jonas Schröder was born on February 11th, 1992 in Salzkotten, Germany. He attended secondary school at the Städtisches Gymnasium in Harsewinkel, where he graduated in 2011 with a major in Biology and English.

From 2012 to 2017, Jonas studied Physiotherapy at the University of Antwerp (UA) in Belgium as a Bachelor and Master student. He was immediately drawn to neurorehabilitation and dedicated his Master's studies specifically to the rehabilitation of patients with acquired brain injuries, such as stroke. During his final year, his interest in research was sparked while writing his thesis in the field of balance rehabilitation after stroke under the supervision of prof. dr. Wim Saeys and prof. dr. Steven Truijen. This included postural sway experiments with patients in the M²OCEAN laboratory at the UA. In 2017, Jonas received his Master's degree in rehabilitation sciences and physiotherapy in neurological conditions Magna Cum Laude.

The collaboration with prof. Saeys and prof. Truijen continued and led to a grant proposal in the field of stroke recovery later that year. Jonas subsequently received a 1-year fellowship from the UA to prepare the TARGEt research project, followed by a full 4-year PhD fellowship funded by the Flanders Research Foundation (FWO).

Currently, Jonas is employed as a teaching assistant at the University of Hasselt, Belgium. In this position, he is involved in the education of undergraduate and graduate physiotherapy students, giving practical and theoretical lectures on evidence-based neurorehabilitation and the use of health technologies.

“I was taught that the way of progress is neither swift nor easy.”

- Marie Skłodowska-Curie