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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effect of split-belt treadmill walking on gait in stroke patients: a systematic review

Heidi Nieuwkoop
Gilles Paredis
Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :
Prof. dr. Pieter MEYNS

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THE EFFECT OF SPLIT-BELT TREADMILL WALKING ON GAIT IN STROKE PATIENTS: A SYSTEMATIC REVIEW.

What is the training effect on gait in patients post-stroke, both during and after split-belt treadmill walking intervention?

- Ambulatory function is impaired in patients after stroke. Their ability to walk is limited by both gait pattern asymmetries and increased energy cost of walking.
- To address these limitations in walking performance, novel studies are investigating the effect of a split-belt treadmill walking paradigm.
- Split-belt treadmill walking, with both belts running at different speeds (2:1 speed ratio), appears to significantly address gait both during and after split-belt treadmill walking in post-stroke patients. A significant effect occurred on all included gait parameters and on energy cost of walking, concerning muscle activity, Muscular Utilization Ratio and lactate concentrations. These effects significantly improved walking performance.
- Sufficient studies have been conducted in order to draw a conclusion on gait pattern parameters. However, the sample size of all included studies is not large enough with regard to generalizability and only few studies tested long-term effects. The training effect on the energy cost of walking of stroke patients has not been sufficiently investigated.

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Promotor: Prof. dr. Pieter Meyns
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BACKGROUND

This literature review concerns the effect of split-belt treadmill walking on gait in post-stroke patients. The topic fits within the neurological research domain, i.e. neurological rehabilitation. It provides insight into aspects of the locomotor learning process and associated improvement of functions of neurological patients (e.g. stroke individuals). These new insights regarding split-belt interventions will help physiotherapists, who rehabilitate patients post-stroke, understand more about gait rehabilitation, which might help these patients receive a more optimal gait rehabilitation compared to conventional therapy.

This literature review, as part of a master's thesis commissioned by the UHasselt, is not linked to any ongoing projects.
Research concerning part two of this master's thesis will be conducted at Maastricht University, more specifically in the Human Performance Laboratory. This virtual lab contains the Computer Aided Rehabilitation ENvironment (CAREN System), which is used to train and evaluate locomotor ability in patients (i.e. walking disabilities).

In consultation with our promoter, we opted for a central format. We have drafted our research question based on previously read literature and thereafter presented it to our promoter, who then adjusted and subsequently approved it. This literature study was carefully carried out by both students. The protocol is a continuation of the literature study and therefore drawn up by both students in consultation with each other and subsequently approved again by the promoter. The idea of this protocol is based on our literature study and therefore an ideal protocol following our systematic review. The protocol has not yet been investigated in previous research and probably will not be carried out in the second part of our master's thesis either.

Both students had an equal share in the realization of this literature study. Throughout the entire process, every step has been carefully talked over among both students and was often revised by the promoter. From the drafting of the research question to the determination of the search strategy, we worked together. Afterwards, we both separately assessed the quality of all included studies. We then each separately extracted data from half of the included studies, in order to work as efficiently as possible. One student then wrote the results and discussion to be able to discuss the results together and formulate a conclusion for the literature study. Finally, the other student wrote the protocol, also read and approved by both students.

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PART 1: LITERATURE STUDY

1. Abstract

Background: Gait pattern asymmetries and increased energy cost of walking are common in stroke patients. Recent studies have investigated the effect of split-belt treadmill walking on these parameters. The purpose of this systematic review is to investigate the training effect on gait in post-stroke patients, during and after split-belt treadmill walking.

Method: PubMed and Web of Science were used to search for derivatives of stroke, split-belt, gait pattern and energy cost of walking. Subsequently, title and abstract, and full text of the obtained studies were evaluated. Eligibility criteria were: patients post-stroke; no medical and cognitive conditions, aside from stroke; split-belt treadmill walking, with both belts running at different speeds; and energy cost of walking or gait pattern parameters. Fourteen studies remained on which data extraction was performed.

Results: Gait parameters and energy cost of walking showed improvements in post-stroke patients during and after split-belt treadmill walking.

Discussion: The results were comparable across studies. Sufficient studies were conducted on gait pattern, but not on energy cost of walking. Few studies tested long-term effects and the sample size was insufficient in all studies.

Conclusion: A split-belt treadmill walking intervention has a significant training effect on gait during and after split-belt treadmill walking, in post-stroke patients.

Purpose of investigation: To investigate the training effect of split-belt treadmill walking on the energy cost of walking in stroke patients.

Operationalization of research question: Energy expenditure will be measured at baseline and at the end of each session. Follow up will take place after one week, one month and three months.

Keywords: stroke, split-belt, gait, energy cost

2. Preface

Cerebrovascular accidents, also known as stroke, are the second leading cause of death and the third leading cause of disability worldwide (Global Health Estimates, 2012). Stroke occurs when the blood flow to the brain is lost by blockage or rupture of an artery to the brain, this in turn causes sudden death of some brain cells due to lack of oxygen (Johnson, Onuma, Owolabi & Sachdev, 2016).

A primary concern of individuals experiencing a stroke is the ability to regain ambulatory function (Bohannon & Andrews, 1998), as improved ambulatory function post-stroke is linked to increased community participation, improved cardiovascular fitness and decreased risk of stroke recurrence (Go et al, 2014). As such, gait retraining is a major component of rehabilitation (Jette et al, 2005).

Gait post-stroke is characterized by pronounced asymmetry (Patterson, Gage, Brooks, Black & McIlroy, 2010). Following stroke, individuals are more reliant on the non-paretic lower extremity in static standing as well as during ambulation (Helm & Reisman, 2015). This results in a shortened non-paretic swing phase and increased stance phase on the non-paretic lower extremity (Helm & Reisman, 2015). The resulting spatio-temporal asymmetries (stance time, swing time and step length asymmetries) are well documented in individuals post-stroke (Patterson et al, 2008; Patterson, Gage, Brooks, Black & McIlroy, 2010). Step length asymmetry, in particular, has been proven to influence other gait deviations (Helm & Reisman, 2015). By taking a shorter non-paretic step, the propulsive force of the paretic limb is decreased thereby limiting forward propulsion of the body (Balasubramanian, Bowden, Neptune & Kautz, 2007). Step length asymmetry and its associated gait deviations have been linked to decreased walking speed (Balasubramanian, Bowden, Neptune & Kautz, 2007; Olney, Griffin & McBride, 1994) and efficiency (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015) as well as decreased dynamic balance (Lewek, Bradley, Wutzke & Zinder, 2014) thereby limiting safe functional ambulation (Helm & Reisman, 2015). Various novel rehabilitation interventions have attempted to target these asymmetries to improve safe locomotion. In particular, several studies have applied the principles of motor learning to target specific gait deviations using a split-belt treadmill (Reisman, 2007, 2009, 2013; Tyrell, 2014).

Motor learning has been defined as a set of processes associated with practice or experience leading to relatively permanent changes in skilled behavior (Schmidt, Lee, Winstein, Wulf &

Zelaznik, 2018). Motor adaptation is the process of modifying or adjusting an already well-learned movement or motor skill that occurs over a period of trial-and-error practice when exposing the movement to a novel, perturbing context or environment (Martin, Keating, Goodkin, Bastian & Thach, 1996).

With a split-belt treadmill, locomotor adaptation can be tested (Reisman, 2010a). Two options are described to obtain split-belt treadmill adaptation, i.e. error augmentation and error minimization. Both are based on established motor learning principles (Lewek, 2018), including error-based learning (Kawato, 1990) and variability of practice (Schmidt, 1975). The approach of error augmentation is based on increasing gait asymmetry on the split-belt treadmill (Lewek, 2018) by placing the short step length limb (either paretic or non-paretic) on the fast belt (2:1 speed ratio) (Reisman, 2007). The approach of error minimization is based on minimizing asymmetry during gait (Lewek, 2018). Here, the longer step length (either paretic or non-paretic) is being placed on the slow belt (2:1 speed ratio), in order to improve gait symmetry. It is described that when the legs are forced to walk at two different speeds, both rapid and longer-lasting (adaptive) changes to the gait pattern occur in adult healthy people (Dietz, Zijlstra & Duysens, 1994; Reisman, Block & Bastian, 2005). People with chronic cerebral stroke and hemiparesis were found to adapt similarly to healthy controls, suggesting that unilateral cerebral damage does not affect the ability to acquire a novel locomotor adaptation, despite the presence of significant paresis and somatosensory loss (Reisman, 2010a). Thus, the compromised nervous system of an adult with stroke is still capable of producing a more-normal spatio-temporal walking pattern (Reisman, 2010a).

Improvements in the energy cost of walking are associated with a more-normal gait pattern (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015). This is in particular important for health care, since a higher energy cost of walking post-stroke has been linked to reduced walking performance and reduced participation in the community (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015). Interventions that reduce the energy cost of walking may therefore facilitate better long-distance walking function in people after stroke (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015).

In this systematic review, we would like to investigate to what extent we can expect improvement in gait of a post-stroke patient, both during and after split-belt treadmill walking, an intervention that focuses on trial-and-error learning required for both motor adaptation and motor learning (Martin, Keating, Goodkin, Bastian & Thach, 1996; Schmidt, Lee, Winstein, Wulf & Zelaznik, 2018). In this case, gait consists of both all gait pattern parameters of overground walking and the energy cost of walking.

3. Method

This systematic review is reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (Liberati et al., 2009).

3.1. Research question

What is the training effect on gait in patients post-stroke, both during and after split-belt treadmill walking intervention?

P	Post-stroke patients
I	Split-belt treadmill walking
C	/
O	Spatio-temporal parameters, kinematics, kinetics and energy cost of walking

3.2. Literature search

In order to execute our search strategy, we used two different databases, i.e. PubMed and Web of Science (WoS). Our search strategy, which we lastly executed on the 25th of May 2019, appears as follows:

stroke (**#1**)
AND split-belt (**#2**)
AND gait pattern (**#3**) OR energy cost of walking (**#4**)

It is necessary to refine the keywords (the so-called search terms) used here, in order to obtain an adequate search strategy. That is why we tried to find suitable synonyms for each keyword. All synonyms for both stroke (**#1**), split-belt (**#2**), gait pattern (**#3**) and energy cost of walking (**#4**) can be found in Table 1a and 1b below. Table 1a provides the search strategy for PubMed and Table 1b provides the search strategy for Web of Science. In PubMed we worked with "MeSH Terms" as much as possible. If none were available, we indicated these terms as "Title/Abstract". Web of Science does not work with "MeSH Terms" and so all terms were indicated as "Topic". The number of hits for each keyword, for both PubMed and WoS, can be found in the column behind the keywords. These two tables also show the number of hits, after we have combined the different keywords (starting from **#5**) using the 'AND' or 'OR' Boolean operators. Lastly, we added several filters in order to limit the final number of hits obtained (starting from **#7**). For PubMed, these filters contained article types and species, see Table 1a. For Web of Science, these filters contained document types and WoS Categories, see Table 1b.

Table 1a
Search strategy for PubMed

	Search terms	**Number of hits in PubMed**
#1	((((((((((((((((((((((((((stroke[MeSH Terms]) OR stroke[Title/Abstract]) OR ischemic[Title/Abstract]) OR ischaemic[Title/Abstract]) OR ischemia[MeSH Terms]) OR ischemia[Title/Abstract]) OR ischaemia[Title/Abstract]) OR infarction[MeSH Terms]) OR infarction[Title/Abstract]) OR cerebral infarction[MeSH Terms]) OR brain infarction[MeSH Terms]) OR brain infarction[Title/Abstract]) OR brain hemorrhage[MeSH Terms]) OR intracranial hemorrhage[MeSH Terms]) OR cerebral hemorrhage[MeSH Terms]) OR hemorrhage[MeSH Terms]) OR hemorrhage[Title/Abstract]) OR haemorrhage[Title/Abstract]) OR apoplexy[Title/Abstract]) OR ischemic attack, transient[MeSH Terms]) OR attack[Title/Abstract]) OR cva[Title/Abstract]) OR cerebrovascular disorders[MeSH Terms]) OR cerebrovascular accident[Title/Abstract]) OR cerebrovascular disease[Title/Abstract]) OR brain diseases[MeSH Terms]) OR hypertensive encephalopathy[MeSH Terms]	1.984.530
#2	((split-belt[Title/Abstract]) OR split belt[Title/Abstract]) OR splitbelt[Title/Abstract]	229
#3	(((((((((((((((((((((((((((((step length[Title/Abstract]) OR stride length[Title/Abstract]) OR cadence[Title/Abstract]) OR swing time[Title/Abstract]) OR support time[Title/Abstract]) OR velocity[Title/Abstract]) OR speed[Title/Abstract]) OR symmetry[Title/Abstract]) OR spatio-temporal analysis[MeSH Terms]) OR spatiotemporal[Title/Abstract]) OR spatial[Title/Abstract]) OR coordination[Title/Abstract]) OR mobility[Title/Abstract]) OR locomotor[Title/Abstract]) OR locomotion[MeSH Terms]) OR locomotion[Title/Abstract]) OR adaptation[Title/Abstract]) OR change[Title/Abstract]) OR variance[Title/Abstract]) OR biomechanical phenomena[MeSH Terms]) OR biomechanical phenomena[Title/Abstract]) OR kinematics[Title/Abstract]) OR kinetics[MeSH Terms]) OR kinetics[Title/Abstract]) OR gait[MeSH Terms]) OR gait[Title/Abstract]) OR walking[MeSH Terms]) OR walking[Title/Abstract]) OR electromyography[MeSH Terms]) OR electromyography[Title/Abstract]	2.995.055
#4	((((((((((((((((((metabolic cost[Title/Abstract]) OR energy cost[Title/Abstract]) OR energy metabolism[MeSH Terms]) OR energy metabolism[Title/Abstract]) OR basal metabolism[MeSH Terms]) OR oxygen consumption[Title/Abstract]) OR oxygen consumption[MeSH Terms]) OR saturation[Title/Abstract]) OR sweating[MeSH Terms]) OR sweating[Title/Abstract]) OR heart rate[MeSH Terms]) OR heart rate[Title/Abstract]) OR blood pressure[MeSH Terms]) OR blood pressure[Title/Abstract]) OR muscle activity[Title/Abstract]) OR fatigue[MeSH Terms]) OR fatigue[Title/Abstract]) OR physical exertion[MeSH Terms]) OR physical exertion[Title/Abstract]	1.220.786
#5	**#3 OR #4**	3.972.030
#6	**#1 AND #2 AND (#3 OR #4)**	60

#7	**#1 AND #2 AND (#3 OR #4)** Additional filters: - Article types: Case Reports; Classical Article; Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study; Controlled Clinical Trial; Journal Article; Multicenter Study; Observational Study; Pragmatic Clinical Trial; Randomized Controlled Trial; Validation Studies - Species: Humans	**52**

Table 1b

Search strategy for WoS

	Search terms	**Number of hits in WoS**
#1	(((((((((((((((((((((stroke[Topic]) OR ischemic[Topic]) OR ischaemic[Topic]) OR ischemia[Topic]) OR ischaemia[Topic]) OR infarction[Topic]) OR cerebral infarction[Topic]) OR brain infarction[Topic]) OR brain hemorrhage[Topic]) OR intracranial hemorrhage[Topic]) OR cerebral hemorrhage[Topic]) OR hemorrhage[Topic]) OR haemorrhage[Topic]) OR apoplexy[Topic]) OR ischemic attack[Topic]) OR attack[Topic]) OR cva[Topic]) OR cerebrovascular disorders[Topic]) OR cerebrovascular accident[Topic]) OR cerebrovascular disease[Topic]) OR brain diseases[Topic]) OR hypertensive encephalopathy[Topic]	1.530.651
#2	((split-belt[Topic]) OR split belt[Topic]) OR splitbelt[Topic]	1.057
#3	(((((((((((((((((((((((step length[Topic]) OR stride length[Topic]) OR cadence[Topic]) OR swing time[Topic]) OR support time[Topic]) OR velocity[Topic]) OR speed[Topic]) OR symmetry[Topic]) OR spatio-temporal analysis[Topic]) OR spatiotemporal[Topic]) OR spatial[Topic]) OR coordination[Topic]) OR mobility[Topic]) OR locomotor[Topic]) OR locomotion[Topic]) OR adaptation[Topic]) OR change[Title/Abstract]) OR variance[Topic]) OR biomechanical phenomena[Topic]) OR kinematics[Topic]) OR kinetics[Topic]) OR gait[Topic]) OR walking[Topic]) OR electromyography[Topic]	9.487.546
#4	(((((((((((metabolic cost[Topic]) OR energy cost[Topic]) OR energy metabolism[Topic]) OR basal metabolism[Topic]) OR oxygen consumption[Topic]) OR saturation[Topic]) OR sweating[Topic]) OR heart rate[Topic]) OR blood pressure[Topic]) OR muscle activity[Topic]) OR fatigue[Topic]) OR physical exertion[Topic]	1.499.309
#5	**#3 OR #4**	10.521.897
#6	**#1 AND #2 AND (#3 OR #4)**	112

#7	**#1 AND #2 AND (#3 OR #4)**	**86**

Additional filters:

- Document Types: ARTICLE
- WoS Categories: neurosciences
  OR rehabilitation
  OR sports sciences
  OR clinical neurology
  OR orthopedics
  OR robotics
  OR biophysics
  OR psychology experimental
  OR biology
  OR multidisciplinary sciences

3.3. Selection criteria

The selection criteria were based on the population studied, the intervention performed, the outcome measures investigated, the design set up, the language used and the purpose intended. Table 2 provides a clear overview of all different selection criteria, distinguished in both inclusion and exclusion criteria.

The purpose of this systematic review was to investigate patients after stroke and their ability to improve their gait pattern and to rationalize energy cost of walking after a split-belt treadmill intervention. Consequently, subjects with any neurological disorder other than stroke were excluded. Also, all possible conditions that could affect walking capacity or locomotor ability were removed from the obtained studies. In addition, all articles that performed split-belt treadmill intervention, but did not have both belts running at different speeds, were also excluded. Next, included outcome measures of the gait pattern were: step length, stride length, cadence, swing time, stance time, double support time, velocity, speed, symmetry, spatio-temporal analysis, spatio-temporal parameters, coordination, mobility, locomotor measures, locomotion, adaptation, change, variance, biomechanical phenomena, kinematics, kinetics, gait, walking and electromyography. Furthermore, included outcome measures of the energy cost of walking were: metabolic cost, energy cost, energy metabolism, basal metabolism, oxygen consumption, saturation, sweating, heart rate, blood pressure, muscle activity, fatigue and physical exertion. Lastly, we only included English or Dutch literature.

Table 2
Selection criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Patients post-stroke	Medical and cognitive conditions, aside from stroke, that could affect walking capacity or locomotor ability
Intervention	Split-belt treadmill walking	/
Outcome	Gait pattern: step length, stride length, cadence swing time, stance time, double support time, velocity, speed, symmetry, spatio-temporal analysis, spatio-temporal parameters, coordination, mobility, locomotor measures, locomotion, adaptation, change, variance, biomechanical phenomena, kinematics, kinetics, gait, walking, electromyography Energy cost of walking: metabolic cost, energy cost, energy metabolism, basal metabolism, oxygen consumption, saturation, sweating, heart rate, blood pressure, muscle activity, fatigue, physical exertion	/
Design	RCT, cohort, case control, case series, case report	Practice guideline, cochrane meta-analysis, cochrane systematic review, meta-analysis, systematic review, review, animal, in vitro
Language	English, Dutch	/
Purpose	To investigate the energy cost of walking and the gait pattern in stroke patients that participated in a split-belt treadmill walking intervention.	/

3.4. Quality assessment

We obtained various types of studies. In order to assess the quality of the obtained studies (n = 14) we divided the different types of studies into Randomized Controlled Trials and non-Randomized Controlled Trials. Based on Cochrane (Higgins, 2008) we decided to perform the quality assessment of the Randomized Controlled Trials with the Cochrane Risk of Bias tool (Higgins, 2008), and the quality assessment of the non-Randomized Controlled trials with the ROBINS-I tool (Sterne, 2016). Table 3 attached in the Appendix contains criteria for judging risk of bias in the Cochrane Risk of Bias tool and Table 4 (Appendix) provides an empty version of the ROBINS-I tool.

3.5. Data extraction

Data were extracted from all included studies by two independent investigators, who screened all articles on full text. Afterwards, all obtained data were provided in tables. One table showed study purpose, type of intervention, possible control and study sample of all obtained studies. Outcome measures, and both results and conclusion for all included studies were be described in another table.

Data were sought based on inclusion criteria, described in Table 2 above, in order to answer the research question. The results of studies were combined on the basis of common outcome measures.

4. Results

4.1. Results study selection

With the search strategy described in Table 1 above, all together we obtained 138 articles. Some of these articles were published on both PubMed and WoS. After filtering the duplicates, 100 original articles remained. Figure 1 provides a clear overview of the study selection process.

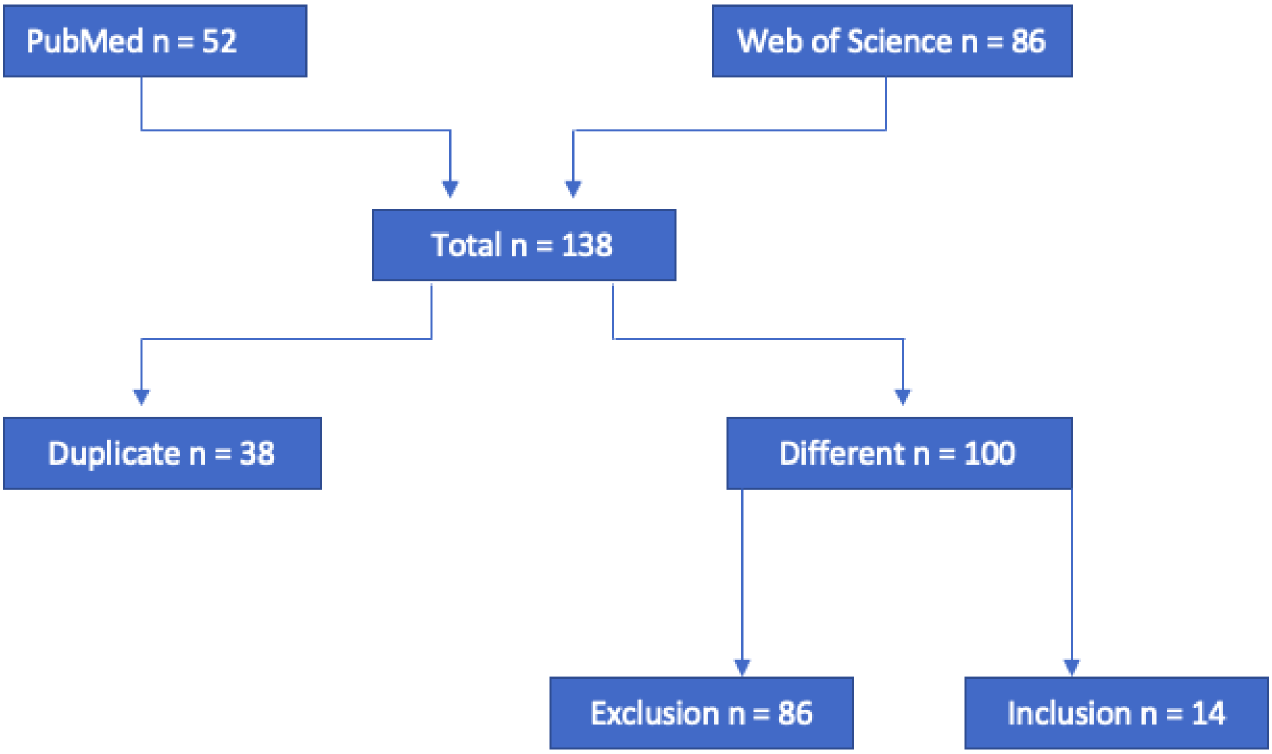

Figure 1. Study Selection Process.

Inefficient articles were excluded based on the exclusion criteria described in Table 2. First, we evaluated the 100 obtained studies on title and abstract, and afterwards, we performed a full text evaluation. In total, we excluded 86 articles based on the preconceived selection criteria. Fourteen studies (Alcântara, 2018; Betschart, 2017, 2018; Charalambous, 2018; Lauzière, 2014, 2016; Lewek, 2018; Malone & Bastian, 2014; Reisman, 2007, 2009, 2010b, 2013; Tyrell, 2014, 2015) were included for data extraction. Table 5 shows all excluded studies (n = 86) together with the reason for exclusion. Table 6 provides an extensive overview of all included studies (n = 14), among which their title, author(s), publication year and journal.

In our title and abstract evaluation, studies were excluded based on population, intervention, outcome, design and purpose. For population, 31 articles were excluded because they did not examine stroke patients. For intervention, 36 articles were excluded as they did not test the effect of a split-belt treadmill walking intervention. For outcome, three studies were excluded following the absence of research into gait outcome measures. For design, one study was removed. It was in fact a review. Lastly, for purpose, three articles were excluded. In these articles, the study purposes did not include the investigation of the effect of split-belt treadmill walking on gait in patients post-stroke.

In our full text evaluation, articles were omitted based on population, intervention, outcome and design. For population, only one study was excluded because of research on simulated stroke subjects. For intervention, eight articles were removed as they did not test the effect of a split-belt treadmill walking intervention. For outcome, two studies were excluded thanks to the absence of research into gait outcome measures. And lastly, for design, one article was thrown out. The design of this study was a review.

Table 5

Overview of the excluded studies (n = 86)

	Reason of exclusion	Number of studies	Reference of studies
Title and abstract evaluation	Population		
	Parkinson's disease	7	Bekkers, E. M. J., et al (2017), Dietz, V., et al (1995), Fasano, A., et al (2016), Mohammadi, F., et al (2015), Nanhoe-Mahabier, W., et al (2013), Roemmich, R. T., et al (2014a), Roemmich, R. T., et al (2014b)
	Cerebral Palsy	3	Bulea, T. C., et al (2017), Damiano, D. L., et al (2017), Levin, I., et al (2017)
	Traumatic Brain Injury	1	Vasudevan, E. V., et al (2014)
	Cerebellar lesion	3	Hoogkamer, W., et al (2015a), Hoogkamer, W., et al (2015b), Morton, S. M., et al (2006)
	Hemispherectomy	1	Choi, J. T., et al (2009)
	Val66Met polymorphism	1	Helm, E. E., et al (2016)
	Healthy subjects	15	Alingh, J. F, et al (2019), Day, K. A., et al (2018), Finley, J. M., et al (2013), Helm, E. E., et al (2017), Hinkel-Lipsker, J. W., et al (2017), Hinkel-Lipsker, J. W., et al (2018), Jansen, K., et al (2013), Kim, S. H., et al (2010), Lauzière, S., et al (2014), Luu, T. P., et al (2017), Roper, J. A., et al (2013), Skidmore, J., et al (2016), Sorrento, G. U., et al (2018), Tesio, L., et al (2018), Yokoyama, H., et al (2018),
	Intervention		
	A modular ankle robot	2	Forrester, L. W., et al (2013), Takahashi, K. Z., et al (2015)
	A motion controlled gait enhancing mobile shoe	1	Handzic, I., et al (2011)
	Body weight shifting on a force platform	1	Chen, H. Y., et al (2012)
	An articulated foot orthosis	9	Blanchette, A. K., et al (2014), Kobayashi, T., et al (2015), Kobayashi, T., et al (2016), Kobayashi, T., et al (2017a), Kobayashi, T., et al (2017b), Kobayashi, T., et al (2018a), Kobayashi, T., et al (2018b), Kobayashi, T., et al (2019), Singer, M. L., et al (2014)
	A novel swing phase perturbation	1	Savin, D. N., et al (2013)
	A split-crank bicycle ergometer	4	Alibiglou, L., et al (2011a), Alibiglou, L., et al (2011b), Straw, A. H., et al (2017), Van der Loos, H. M., et al (2010)
	A treadmill	2	Lauzière, S., et al (2015), Savin, D. N., et al (2014)

An inclined treadmill	2	Phadke, C. P. (2012), Reissman, M. E., et al (2018)
A treadmill against an impeding force	1	Lewek, M. D., et al (2018)
A novel user-driven treadmill control scheme	1	Ray, N. T., et al (2018)
The Integrated Virtual Environment Rehabilitation Treadmill (IVERT) system	1	Feasel, J., et al (2011)
A new Lokomat(®) asymmetrical restraint paradigm	1	Bonnyaud, C., et al (2014)
A robotic Tethered Pelvic Assist Device	1	Bishop, L., et al (2017)
A treadmill with unilaterally applied ankle weight	2	Gama, G. L., et al (2018), Yen, S. C., et al (2015)
Cerebellar transcranial direct current stimulation combined with transcutaneous spinal direct current stimulation	2	Picelli, A., et al (2018, 2019)
Ipsilateral tibial nerve stimulation on contralateral soleus (cSOL)	1	Stubbs, P. W., et al (2009)
Stepping training in variable, challenging contexts at high aerobic intensities	1	Holleran, C. L., et al (2014)
Frontal plane mirror feedback on gait adaptation	1	Stone, A. E., et al (2019)
A practice structure	1	Helm, E. E., et al (2019)
A single session of high-definition transcranial direct current stimulation	1	Kindred, J. H., et al (2019)

	Outcome		
	Sensory perception and its impact on the control of walking	1	Chu, V. W., et al (2015)
	Reactive adaptation and fall-risk	1	Bhatt, T., et al (2019)
	Motor commands	1	Iturralde, P. A, et al (2019)
	Design		
	Review	1	Reisman, D. S., et al (2010)
	Purpose		
	To clearly present the definitions of the gait parameters that are commonly used in split-belt treadmill studies	1	Hoogkamer, W., et al (2014)
	Investigates the development of a gait phase time-based split-belt treadmill measurement system	1	Ando, T., et al (2012)
	To determine the validity and between-day repeatability of spatiotemporal metrics as measured with the APDM Opal IMUs and Mobility Lab system	1	Washabaugh, E. P., et al (2017)
Full text evaluation	Population		
	Simulated stroke	1	Liu, Y. H., et al (2015)
	Intervention		
	Use of an instrumented split-belt treadmill with both belts set to the same speed	7	Balasubramanian, C. K., et al (2010), Beaman, C. B., et al (2010), Finley, J. M., et al (2015), Kautz, S. A., et al (2011), Little, V. L., et al (2018), Raja, B., et al (2012), Walker, E. R., et al (2016)
	Dual-learning condition: 2 distinct motor tasks	1	Cherry-Allen, K. M., et al (2018)
	Outcome		
	Gait asymmetry perception post-stroke	1	Wutzke, C. J., et al (2015)
	Balance	1	Miéville, C., et al (2018)

Design		
Review	1	Helm, E. E., et al (2015)

Table 6

Overview of the included studies (n = 14)

Title	Author(s)	Publication year	Journal
Different error size during locomotor adaptation affects transfer to overground walking post-stroke.	Alcântara, C. C. Charalambous, C.C. Morton, S.M. Russo, T. L. Reisman, D. S.	2018	Neurorehabilitation neural repair.
Changes in lower limb muscle activity after walking on a split-belt treadmill in individuals post-stroke	Betschart, M. Lauzière, S. Mieville, C. McFadyen, B. J. Nadeau, S.	2017	Journal of Electromyography and Kinesiology
Repeated split-belt treadmill walking improved gait ability in individuals with chronic stroke: a pilot study	Betschart, M. McFayden, B.J. Nadeau, S.	2018	Physiotherapy Theory and practice
A single exercise bout and locomotor learning after stroke: physiological, behavioural, and computational outcomes.	Charalambous, C. C. Alcântara, C.C. French, M.A. Li, X. Matt, K. S. Kim, H. E. Reisman, D. S.	2018	The Journal of Physiology
A more symmetrical gait after split-belt treadmill walking increases the effort in paretic plantar flexors in people post-stroke.	Lauzière, S. Mieville, C. Betschart, M. Duclos, C. Aissaoui, R. Nadeau, S.	2016	Journal of Rehabilitation Medicine
Plantarflexion moment is a contributor to step length after-effect following walking on a split-belt treadmill in individuals with stroke and healthy individuals.	Lauzière, S. Mieville, C. Betschart, M. Duclos, C. Aissaoui, R. Nadeau, S.	2014	Journal of Rehabilitation Medicine
The role of movement errors in modifying spatiotemporal gait asymmetry post stroke: a randomized controlled trial	Lewek, M. D. Broun, C. H. Wutzke, C. Giuliani, C.	2018	Clinical rehabilitation

Spatial and temporal asymmetries in gait predict split-belt adaptation behavior in stroke.	Malone, L. A. Bastian, A. J.	2014	Neurorehabilitation and Neural Repair
Split-belt treadmill training post-stroke: a case study	Reisman, D. S. McLean, H. Bastian, A. J.	2010	Journal of Neurologic Physical Therapy
Repeated split-belt treadmill training improves poststroke step length asymmetry.	Reisman, D. S. McLean, H. Keller, J. Danks, K. A. Bastian, A. J.	2013	Neurorehabilitation and Neural Repair
Split-belt treadmill adaptation transfers to overground walking in persons poststroke.	Reisman, D. S. Wityk, R. Silver, K. Bastian, A. J.	2009	Neurorehabilitation and Neural Repair
Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke.	Reisman, D. S. Wityk, R. Silver, K. Bastian, A. J.	2007	Brain
Learning the spatial features of a locomotor task is slowed after stroke.	Tyrell, C. M. Helm, E. Reisman, D. S.	2014	Journal of neurophysiology
Locomotor adaptation is influenced by the interaction between perturbations and baseline asymmetry after stroke.	Tyrell, C. M. Helm, E. Reisman, D. S.	2015	Journal of biomechanics

4.2. Results quality assessment

Two of the included studies (Alcântara, 2018; Lewek, 2018) were RCTs. Both were at an overall low risk of bias and therefore consisted of good quality. The non-RCTs (n = 12) (Betschart, 2017, 2018; Charalambous, 2018; Lauzière, 2014, 2016; Malone & Bastian, 2014; Reisman, 2007, 2009, 2010b, 2013; Tyrell, 2014, 2015) were at overall low risk of bias as well. Only bias due to confounding was at moderate risk for two studies (Betschart, 2017; Reisman, 2010b) and bias due to missing data was at moderate risk for two studies (Reisman, 2007, 2013). Lastly, bias in measurement of outcomes was at moderate risk of bias for no fewer than 11 studies (Betschart, 2017, 2018; Charalambous, 2018; Lauzière, 2014, 2016; Malone & Bastian, 2014; Reisman, 2007, 2009, 2013; Tyrell, 2014, 2015) and even at serious risk of bias for one study (Reisman, 2010b).

Table 7

Quality assessment of Randomized Controlled Trials (n = 2)

COCHRANE TOOL FOR RISK OF BIAS ASSESSMENT		**Alcântara, C. C. et al (2018)**	**Lewek, M. D. et al (2018)**
Selection Bias	**Random sequence generation.**	'Low risk' of bias	'Low risk' of bias
	Allocation concealment.	'Low risk' of bias	'Low risk' of bias
Performance bias	**Blinding of participants and personnel.**	'Unclear risk' of bias	'Unclear risk' of bias
Detection bias	**Blinding of outcome assessment.**	'Unclear risk' of bias	'Low risk' of bias
Attrition bias	**Incomplete outcome data.**	'Low risk' of bias	'Low risk' of bias
Reporting Bias	**Selective reporting.**	'Low risk' of bias	'Low risk' of bias
Other Bias	**Other sources of bias.**	'Low risk' of bias	'Low risk' of bias

Table 8

Quality assessment of non-Randomized Controlled Trials (n = 12)

ROBINS-I TOOL FOR RISK OF BIAS ASSESSMENT		Betschart, M., et al (2017)	Betschart, M., et al (2018)	Charalambous, C. C., et al (2018)	Lauziere, S., et al (2016)	Lauziere, S., et al (2014)	Malone, L.A., et al (2014)	Reisman, D. S., et al (2010)	Reisman, D. S., et al (2013)	Reisman, D. S., et al (2009)	Reisman, D. S., et al (2007)	Tyrell, C. M., et al (2014)	Tyrell, C. M., et al (2015)
Bias due to confounding	1.1	Y	N	N	N	N	N	Y	N	N	N	N	N
	1.2	N	/	/	/	/	/	N	/	/	/	/	/
	1.3	/	/	/	/	/	/	/	/	/	/	/	/
	1.4	Y	/	/	/	/	/	Y	/	/	/	/	/
	1.5	Y	/	/	/	/	/	Ni	/	/	/	/	/
	1.6	N	/	/	/	/	/	Ni	/	/	/	/	/
	1.7	Y	/	/	/	/	/	/	/	/	/	/	/
	1.8	Y	/	/	/	/	/	/	/	/	/	/	/
		Mo	Low	Low	Low	Low	Low	Mo	Low	Low	Low	Low	Low
Bias in selection of participants into the study	2.1	N	N	N	N	N	N	N	N	N	N	N	N
	2.2	/	/	/	/	/	/	/	/	/	/	/	/
	2.3	/	/	/	/	/	/	/	/	/	/	/	/
	2.4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	2.5	/	/	/	/	/	/	/	/	/	/	/	/
		Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias in classification of interventions	3.1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	3.2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	3.2	N	N	N	N	N	N	N	N	N	N	N	N
		Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias due to deviations from intended interventions	4.1	N	N	N	N	N	N	N	N	N	N	N	N
	4.2	/	/	/	/	/	/	/	/	/	/	/	/
	4.3	/	/	/	/	Y	/	/	/	Y	Y	Y	Y
	4.4	Y	/	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	4.5	Y	/	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	4.6	/	/	/	/	/	/	/	/	/	/	/	/
		Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias due to missing data	5.1	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y
	5.2	N	N	N	N	N	N	N	N	N	N	N	N
	5.3	N	N	N	N	N	N	N	N	N	N	N	N
	5.4	/	/	/	/	/	/	/	Y	/	Y	/	/
	5.5	/	/	/	/	/	/	/	Y	/	N	/	/
		Low	Low	Low	Low	Low	Low	Low	Mo	Low	Mo	Low	Low
Bias in measurement of outcomes	6.1	N	N	N	N	N	N	Y	N	N	N	N	N
	6.2	Ni	Ni	Ni	Ni	Ni	Ni	Ni	Ni	Ni	Ni	Ni	Ni
	6.3	/	/	/	/	Y	/	/	/	Y	Y	Y	Y
	6.4	N	N	N	N	N	N	N	N	N	N	N	Y
		Mo	Mo	Mo	Mo	Mo	Mo	Ser	Mo	Mo	Mo	Mo	Mo
Bias in selection of the reported result	7.1	N	N	N	N	N	N	N	N	N	N	N	N
	7.2	N	N	N	N	N	N	N	N	N	N	N	N
	7.3	N	N	N	N	N	N	N	N	N	N	N	N
		Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Overall bias		/	/	/	/	/	/	/	/	/	/	/	/

4.3. Results data extraction

Study purpose, type of intervention, possible control and the study sample for each included study can be found in Table 9 below. Outcome measures, and both results and conclusion for all included studies are provided in Table 10 below.

Type of intervention

All interventions (n = 14) consisted of a different intervention structure, duration and frequency. Nevertheless they all started with baseline treadmill walking, with both belts running at the same speed, in order to get used to walking on the treadmill. After baseline treadmill walking, a split-belt treadmill adaptation period, with both belts running at different speeds (2:1 speed ratio), followed for all included interventions. Five of our included studies (Betschart, 2017; Lauzière, 2014; Lewek 2018; Reisman, 2007; Tyrell, 2015) investigated two conditions and thus placed both non-paretic and paretic leg on the fast belt. Three articles investigated only the non-paretic leg on the fast belt (Alcântara, 2018; Lauzière, 2016; Malone & Bastian, 2014). Six studies examined the leg with the shortest step length on the fast belt in order to augment step length asymmetry (Betschart, 2018; Charalambous, 2018; Reisman 2009, 2010b, 2013; Tyrell, 2014), this could be either the paretic or the non-paretic leg.

The interventions ended with a treadmill post-adaptation period, again with both belts running at the same speed, or ended with post-overground walking, in order to transfer and retain the newly learned walking pattern to overground walking (Alcântara, 2018).

Table 9

Population, study purpose, intervention and control (n = 14)

Article	Population	Study purpose	Intervention	Control
Alcântara, C. C., et al (2018) Neurorehabilitation neural repair	26 individuals post- stroke	To determine whether introducing gradual perturbations, during locomotor learning using a split-belt treadmill influences learning the novel walking pattern or transfer to overground walking post-stroke.	Walking testing paradigm: - Baseline overground walking - Baseline treadmill walking - Split-belt treadmill/adaptation period: belts moving at different speeds, the paretic leg to the slow belt - Catch trial (belts at same speed) - Post overground walking Subjects were randomly assigned to the gradual (gradual changes in belt speed during adaptation; n=13) or abrupt (a single, large, abrupt change in during adaptation group; n=13).	/
Betschart, M., et al (2017) Journal of electromyography	16 individuals post- stroke	To analyze lower limb muscle activity in individuals post-stroke related to 'split-belt treadmill'-induced changes in step length.	Participants were exposed to two split-belt treadmill walking conditions: 1. Baseline period: 3 min walking at comfortable speed (tied-belts) Adaptation period: 6 min walking with belt speed doubled (2:1 speed ratio), here the non-paretic leg walked on the fast belt during adaptation (NP-fast condition) Post-adaptation period: 3 min walking at comfortable speed (tied-belts) 2. Baseline period: 3 min walking at comfortable speed (tied-belts) Adaptation period: 6 min walking with belt speed doubled (2:1 speed ratio), here the paretic leg walked on the fast belt during adaptation (P-fast condition) Post-adaptation period: 3 min walking at comfortable speed (tied-belts)	/

Betschart, M., et al (2018) Physiotherapy Theory and practice	12 individuals post- stroke	To provide a protocol which leads to clinically relevant and durable reduction in step length asymmetry after a short period of training as well as to investigate its effect on additional gait parameters (speed, endurance, and functional mobility).	Six sessions of split-belt treadmill walking over a period of 2-3 weeks based on error augmentation strategy: • Comfortable speed determined on the treadmill at equal belt speeds prior to training at each session • 20 min on a split-belt configuration with a 2:1 ratio (the leg with the shorter step length walked on the fast belt). The participants' comfortable speed determined the speed of the slower belt. • After the training on the split-belt configuration, participants walked for 3 min on the tied-belt configuration	/
Charalambous, C. C., et al (2018) The Journal of Physiology	37 people post- stroke	First purpose: to investigate whether an acute high-intensity exercise bout would influence locomotor learning in people post-stroke. Second purpose: to determine whether the timing of the exercise influenced locomotor learning in people post-stroke.	Two high-intensity exercise groups, two sessions 24 h apart: **Treadmill walking (TMW)** Session 1: 1.) 5 min high intensity treadmill walking (70-85% of age-predicted HR max and 13-15 on the 6-20 'rate of perceived exertion' scale 2.) 15 min split-belt walking adaptation (2:1 speed ratio)* Session 2: 15 min split-belt walking adaptation (2:1 speed ratio)* to test for retention **Total body exercise on a cycle ergometer (TBE)** Session 1: 1.) 15 min split-belt walking adaptation (2:1 speed ratio)* 2.) 5 min high intensity total body exercise (70-85% of age-predicted HR max and 13-15 on the 6-20 'rate of perceived exertion' scale Session 2: 15 min split-belt walking adaptation (2:1 speed ratio)* to test for retention	One low-intensity exercise group, two sessions 24 h apart: **Active control (CON)** Session 1: 1.) 5 min low intensity treadmill walking (25% of their fast-comfortable walking speed) 2.) 15 min split-belt walking adaptation (2:1 speed ratio)* Session 2: 15 min split-belt walking adaptation (2:1 speed ratio)* to test for retention *The leg with the longer step length was placed on the slow belt.

Lauzière, S., et al (2016) Journal of Rehabilitation Medicine	20 individuals post- stroke	To determine if the level of effort in paretic plantar flexors during gait could be a factor in explaining locomotor asymmetry.	Participants walked on a split-belt treadmill for 3 periods: • Baseline: with both belts running at self-selected speed for 3 min • Adaptation: with the belt speed doubled (2:1 speed ratio) on the non-paretic side for 6 min • Post-adaptation: both belts at self-selected speed for 3 min	/
Lauzière, S., et al (2014) Journal of Rehabilitation Medicine	20 individuals post-stroke 10 healthy individuals	To assess plantarflexion moment and hip joint moment after-effects following walking on a split- belt treadmill in healthy individuals and individuals post-stroke.	Split-belt treadmill walking: • Baseline: comfortable treadmill gait speed for 3 min • Adaptation: 6 min with the fast belt speed set at twice the speed of the slow belt (protocol was performed twice to allow both the paretic and non-paretic side on the fast belt) • Post-adaptation: both belts at baseline speed (tied-belts) for 3 min	Healthy participants: • Baseline: 3 min with the speed of the belts set 30% slower than their comfortable speed (tied-belt) • Adaptation: 6 min with the belt under the dominant side at twice the speed of the belt under the non-dominant side • Post-adaptation: both belts at baseline speed (tied-belts) for 3 min
Lewek, M. D., et al (2018) Clinical rehabilitation	48 individuals with chronic hemiparesis post-stroke and spatio-temporal gait asymmetry	To determine which of the motor learning strategies (error augmentation or error minimization) best improves overground spatiotemporal gait symmetry.	**Asymmetry augmentation (n=16)** <u>18 sessions:</u> • 2 min of control walking with both belts moving at the same speed • Asymmetry augmentation: 2:1 speed ratio with paretic limb on the fast belt for up to 18 min • 10-15 min of overground training to encourage carryover of training to overground surfaces	**Conventional treadmill training (n=14)** <u>18 sessions:</u> • 2 min of control walking with both belts moving at the same speed • Training phase (control) for up to 18 min • 10-15 min of overground training to encourage carryover of training to overground surfaces

			Asymmetry minimization (n=18) 18 sessions: • 2 min of control walking with both belts moving at the same speed • Asymmetry minimization: 2:1 speed ratio with non-paretic limb on the fast belt for up to 18 min • 10-15 min of overground training to encourage carryover of training to overground surfaces	
Malone, L. A., et al (2014) Neurorehabilitation and Neural Repair	22 individuals post-stroke (>6m) 7 healthy age-matched controls	To investigate whether baseline gait asymmetries affected how patients adapt and store new walking patterns.	Split-belt treadmill training: • Three baseline periods during which the belts were tied at 0.5, 1.0 and 0.5 m/s • Three 5 minute periods of belts split at 0.5 and 1.0 m/s (slow belt on the hemiparetic limb) • A 5 min de-adaptation period, where the belts were again tied at 0.5 m/s	Healthy participants: • Three baseline periods during which the belts were tied at 0.5, 1.0 and 0.5 m/s • Three 5 minute periods of belts split at 0.5 and 1.0 m/s (slow belt on the dominant limb) • A 5 min de-adaptation period, where the belts were again tied at 0.5 m/s
Reisman, D. S., et al (2010b) Journal of Neurologic Physical Therapy	A 36-year-old woman who was 1.6 years post-stroke	To provide repetitive split-belt treadmill training in a person with stroke to determine whether longer-term changes in step length asymmetry and gait function could be achieved.	Split-belt treadmill walking: • a warm-up on the treadmill • six 5-minute bouts, for a total of 30 minutes • followed by overground walking practice for 5 minutes with verbal cueing • 3 d/wk for 4 weeks • with the paretic leg on the slow belt, to exaggerate baseline step length asymmetry	/

Reisman, D. S., et al (2013) Neurorehabilitation and Neural Repair	13 persons with chronic stroke (>6m)	To determine whether longer-term improvements in step length asymmetry could be achieved with repeated split-belt treadmill walking practice using an error augmentation strategy.	Split-belt treadmill training: • 3d/wk for 4 weeks (12 sessions) • a warm-up on the treadmill • six 5-minute bouts, for a total of 30 minutes • followed by overground walking practice for 5 minutes with verbal cueing • belt speeds were set to augment step length asymmetry	/
Reisman, D. S., et al (2009) Neurorehabilitation and Neural Repair	11 people post-stroke 11 age- and gender-matched healthy control subjects	To examine whether aftereffects following split-belt treadmill adaptation transfer to overground walking in healthy persons and those post-stroke.	Post-stroke patients: • Overground baseline period: at their self-selected gait speed for 5 to 10 trials • Treadmill baseline period: with the belts tied at their slow speed for 2 minutes • Adaptation period: with belts split for 15 min (and with a 1 min 'Catch Trial' after 10 min), leg with the shortest step length on the fast belt • Overground post-adaptation period: walking overground for 10 trials	Matched controls: • Overground baseline period: at their self-selected gait speed for 5 to 10 trials • Treadmill baseline period: with the belts tied at their slow speed for 2 minutes • Adaptation period: with belts split for 15 min (and with a 1 min 'Catch Trial' after 10 min), either right or left leg on the fast belt (random) • Overground post-adaptation period: walking overground for 10 trials
Reisman, D. S., et al (2007) Brain	13 individuals post-stroke (>6m) 13 age- and gender-matched healthy control subjects	<u>First purpose:</u> to understand the role of cerebral structures in reactive modifications and/or adaptation of the locomotor pattern. <u>Second purpose:</u> to investigate whether after-effects following split-belt treadmill walking lead to improvements in gait symmetry in subjects following stroke.	Stroke subjects participated in two testing sessions: 1. The leg assigned to the fast belt during the split-belt period was randomly determined as either the paretic or non-paretic leg • Baseline period: the belts were tied and moved first at the slow speed 2 min, then at the fast speed 2 min, and then again at the slow speed 2 min	Matched controls participated in only one testing session: 1. Randomly assigned to either right or left leg on the fast belt • Baseline period: the belts were tied and moved first at the slow speed 2 min, then at the fast speed 2 min, and then again at the slow speed 2 min • Adaptation period: the treadmill belts were split for 15 min

			• Adaptation period: the treadmill belts were split for 15 min • Post-adaptation period: the belts were returned to the tied slow configuration, 6 min 2. The contralateral leg was tested on the fast belt during split-belt walking • Baseline period • Adaptation period • Post-adaptation period	• Post-adaptation period: the belts were returned to the tied slow configuration, 6 min
Tyrell, C. M., et al (2014) Journal of neurophysiology	16 people post-stroke (>6m) 16 age- and gender-matched neuro-logically intact participants	To characterize learning of a novel locomotor task in stroke survivors.	Post-stroke participants: • before the first split-belt session, baseline data were collected with participants walking with the belts travelling at the same speeds • walked on the split-belt treadmill for 15 min in a 2:1 speed ratio for 5 consecutive days • one final 15 minute split-belt treadmill exposure was completed after 2 days without exposure, to evaluate retention • leg assignment was chosen in order to induce exaggeration of baseline asymmetries	Neurologically intact participant: • walked on the split-belt treadmill for 15 min in a 2:1 speed ratio for 5 consecutive days • leg assignment was randomized
Tyrell, C. M., et al (2015) Journal of biomechanics	17 individuals post-stroke 17 age- and gender-matched neuro-logically intact participants	<u>First purpose:</u> to compare the rate and magnitude of adaptation and de-adaptation in subjects who have had a stroke to those who are neurologically intact. <u>Second purpose:</u> to examine the effect of exaggerating or reducing a stroke survivor's asymmetry on the rate and magnitude of adaptation and de-adaptation.	The participants with stroke: • Two separate days of split-belt walking, with at least one week separating the two data collections • Baseline: first, belts at slow speed for 2 min and afterwards, belts at fast speed for 2 min • Adaptation: 10 min of split-belt treadmill walking (2:1 speed ratio) • De-adaptation: five minutes of tied-belt walking One data collection was completed with the paretic leg on the fast belt (HemiFast), and the other with the paretic leg on the slow belt (HemiSlow)	Neurologically intact participants: • walked at the same speeds as their stroke participant counterparts • the limb that was placed on the fast belt was randomized.

Outcome measures

For gait pattern, the outcome measures that we obtained after data extraction from all included studies (n = 14) were: step length (asymmetry), stride length, stance time, double support time, moments at the ankle and hip joints, interlimb phasing, surface EMG activity of lower limb muscles, gait speed, functional mobility, adaptation and de-adaptation behavior, locomotor learning measures, and transfer of learning to overground walking.

For energy cost of walking, the outcome measures that we obtained after data extraction from all included studies (n = 14) were: endurance, perceived exertion, muscular utilization ratio, and changes in lactate and BDNF concentrations.

Table 10 provides an overview of which outcome measures were extracted from which included studies.

Gait parameters

Step length (asymmetry) was found in all included studies except one (Alcântara, 2018; Betschart, 2017, 2018; Charalambous, 2018; Lauzière, 2014, 2016; Lewek, 2018; Malone & Bastian, 2014; Reisman, 2007, 2009, 2010b, 2013; Tyrell, 2014). Split-belt treadmill walking to augment step length asymmetry, effectively improved step length asymmetry afterwards, and maintained or even improved after one month of follow-up. At the end of day one each group returned to its baseline asymmetry. Both Abrupt and Gradual perturbation had a similar after-effect magnitude on the treadmill and learned a similar amount.

During both conditions of split-belt treadmill walking, significant bilateral increase of step length occurred. During the paretic fast condition, step length ratios did not differ from the baseline ratio. Both non-paretic fast condition and paretic fast condition, caused significant lower step length asymmetry afterwards and at follow-up, and led to a significant decrease of slow step length after split-belt walking. Fast step length remained significantly increased during the non-paretic fast condition and showed tendency to remain increased during paretic fast condition.

Stride length was found in one study (Reisman, 2007) and stance time was found in four studies (Lewek, 2018; Reisman, 2007, 2010b, 2013). During both conditions of split-belt treadmill walking, all stride lengths rapidly changed (fast stride was longer and slow stride was shorter), and stance time on the fast leg quickly decreased and quickly increased on the slow leg. Both stride length and stance time of both legs rapidly returned to baseline levels afterwards.

Double support time was found in five studies (Lauzière, 2016; Reisman, 2007, 2009, 2010b, 2013). During split-belt interventions that augmented error, no changes in double support time occurred. Afterwards, a change was found, indicating a transfer of the after-effect to overground walking, but significantly washed out (gradually adjusted back to baseline levels).
After split-belt interventions that placed the non-paretic leg on the fast belt, double support time symmetry significantly improved.

Ankle and hip moments were found in two studies (Lauzière, 2014, 2016). After split-belt treadmill walking with the non-paretic leg on the fast belt, mean paretic plantar flexion ankle moment and peak non-paretic hip extension moment significantly increased. The non-paretic mean plantar flexion ankle moment significantly decreased, and no differences were found for paretic hip extension and hip flexion moments.
After split-belt treadmill walking with the paretic leg on the fast belt, paretic plantar flexion ankle moment, non-paretic plantar flexion ankle moment and peak non-paretic hip extension moment showed reverse effects of split-belt treadmill walking with the non-paretic leg on the fast belt (cf. supra). Significant decrease in peak paretic hip flexion moment and significant increase in peak paretic hip extension moment was found.

Interlimb phasing was found in four studies (Malone & Bastian, 2014; Reisman, 2007; Tyrell, 2014, 2015). Across subjects, phasing of the hemiparetic limb was distributed between leading and lagging legs, meaning individuals may have the same step asymmetry, but opposite hemiparetic leg phase deficits (one leg leads, one leg lags). During both conditions of split-belt treadmill walking, phasing changed significantly, but adapted back toward its baseline (a)symmetry afterwards. Magnitude of early limb phase asymmetry is largest after one split-belt treadmill walking intervention and reduced with repeated exposure.

Muscle activity was found in one study (Betschart, 2017). During both conditions of split-belt treadmill walking, a significant increase in some slow and fast muscles occurred and some muscles presented insignificant changes. Afterwards, some of both the slow and fast muscles significantly increased and then gradually returned to baseline activity.

Gait speed was found in three studies (Betschart, 2018; Lewek 2018; Reisman, 2010b) and functional mobility was found in one study (Betschart, 2018). After both conditions of split-belt treadmill walking, (comfortable and maximal) gait speeds significantly increased over time and continued to improve at one month after training. Functional mobility increased after split-belt treadmill walking (with the shortest step length on the fast belt) and persisted until one month of follow-up.

Adaptation and de-adaptation were found in two studies (Malone & Bastian, 2014; Tyrell, 2015). Patients with the paretic leg on the fast belt showed a significant (either improving or worsening) difference between baseline asymmetry and late adaptation. After both error minimizing or error augmenting during split-belt treadmill walking (non-paretic leg on the fast belt), stroke patients adapted toward their baseline asymmetry. However, error minimizing and error augmenting showed different results in de-adaptation. Both paretic and non-paretic leg on the fast belt show a similar rate of de-adaptation.

Locomotor learning measures were found in two studies (Charalambous, 2018; Tyrell, 2014). Participants with stroke (regardless of their level of sensorimotor impairment) retained the newly learned locomotor task, even after two days without split-belt treadmill walking (error augmentation). Nevertheless, practice does not increase retention or re-adaptation rate of stroke individuals, despite intensity and timing.

Transfer to overground walking was found in two studies (Alcântara, 2018; Reisman, 2009). Split-belt treadmill interventions to augment asymmetry, caused transfer of the after-effect to overground walking. Nevertheless, this overground walking after-effect was typically a bit smaller than the catch trial period (tied belts). Also, the magnitude of transfer to overground walking was significantly greater after introduction of gradual (small error) compared to abrupt (larger error) perturbations.

Energy cost of walking

Both endurance and perceived exertion were found in one study (Betschart, 2018), the muscular utilization ratio (MUR) was found in one study (Lauzière, 2016), and changes in both lactate and BDNF concentrations were found in one study (Charalambous, 2018). After split-belt treadmill walking augmented asymmetry, there was no improvement in endurance, insignificant decrease in perceived exertion, significant effect on lactate change and no significant main effect on BDNF change.

During split-belt treadmill walking with the non-paretic leg on the fast belt, paretic plantar flexion MUR values increased significantly and no effect was found between periods for non-paretic plantar flexion MUR and bilateral hip flexion MUR.

Table 10

Outcome measures, results and conclusion (n = 14)

Article	Outcome measures	Results and conclusion
Alcântara, C. C., et al (2018) Neurorehabilitation neural repair	• Step length asymmetry adaptation response on the treadmill • Transfer of learning to overground walking • No long-term follow-up period	• Step length asymmetry during the catch trial was the same between groups (P=.195) confirming that both groups learned a similar amount. The magnitude of transfer to overground walking was greater in the Gradual than in the Abrupt group (P=.041). • The introduction of gradual perturbations (small errors), compared with abrupt (larger errors), during a locomotor adaptation task seems to improve transfer of the newly learned walking pattern to overground walking post-stroke. However, given the limited magnitude of transfer, future studies should examine other factors that could impact locomotor learning and transfer post-stroke.
Betschart, M., et al (2017) Journal of electromyography	• Step length • Surface EMG activity of six lower limb muscles • No long-term follow-up period	• During adaptation, significant increases in EMG activity were mainly found in proximal muscles (p≤0.023), whereas after-effects were observed particularly in the distal muscles. The plantar flexor EMG increased after walking on the slow belt (p≤0.023) and the dorsiflexors predominantly after walking on the fast belt (p≤0.017) for both, non-paretic and paretic-fast conditions. Correlation analysis revealed that after-effects in step length were mainly associated with changes in distal paretic muscle activity (0.522≤r≤0.663) but not with functional deficits. • Based on our results, SBT walking could be relevant for training individuals post-stroke who present shorter paretic step length combined with dorsiflexor weakness, or individuals with shorter non-paretic step length and plantar flexor weakness.

Betschart, M., et al (2018) Physiotherapy Theory and practice	• Step length asymmetry • Gait speed • Endurance • Perceived exertion • Functional mobility • Follow-up period of four weeks post-training	• After only six sessions of training, all participants reduced their SL asymmetry from an average ratio of 1.39 to 1.17 (p=0.002) and increased walking speed (p=0.043). Improvements in symmetry and speed were retained over 1 month (p≤0.008). No effect was observed in participants' endurance, assessed with the 6-min walk test. Perceived exertion ranged from 3 to 7 during the first session and from 2 to 5 during the last session (p>0.05). • These findings suggest that the present SBT protocol has potential to be an efficient intervention to improve not only SL symmetry but also gait speed, in individuals post-stroke.
Charalambous, C. C., et al (2018) The Journal of Physiology	• Changes in lactate and BDNF concentrations in response to exercise priming • Step length symmetry index • Locomotor learning measures • A 24 hour long-term retention, no longer-term follow-up period	• There was a significant effect of exercise on lactate change in both high-intensity exercise groups and no significant main effect of exercise on BDNF change. • Behavioral data showed that neither high-intensity group showed greater 24 h retention compared to CON, and computational data showed that 24 h retention was attributable to a slow learning process for sensorimotor adaptation. • Our findings demonstrated that acute exercise coupled with a locomotor adaptation task, regardless of its intensity and timing, does not improve retention of the novel locomotor task after stroke. We postulate that exercise effects on motor learning may be context specific (e.g. type of motor learning and/or task) and interact with the presence of genetic variant (BDNF Val66Met).
Lauzière, S., et al (2016) Journal of Rehabilitation Medicine	• Maximal voluntary contraction (MVC) of plantar flexors and hip flexors to calculate the muscular utilization ratio (MUR; level of effort of a muscle group) • Walking moments at the ankle and hip joints • Step length • Double support time • No long-term follow-up period	• Baseline level of effort in plantar flexors was negatively related to changes in paretic plantar flexion moments ($r = –0.70$; $p = 0.001$) and changes in non-paretic step length ($r = –0.65$; $p = 0.003$). A more symmetrical spatiotemporal gait increased the paretic plantar flexor effort from 73.7% to 86.6% ($p = 0.007$). • The mean step length symmetry ratios and the double support time symmetry ratios decreased significantly from baseline to post-adaptation periods. • A more symmetrical gait increases paretic plantar flexor efforts. Individuals post-stroke presenting high plantar flexor efforts when walking have limited muscle capacity to increase non-paretic step after split-belt walking.
Lauzière, S., et al (2014) Journal of Rehabilitation Medicine	• Step length • Joint (ankle and hip) net moment • Symmetry • No long-term follow-up period	• Post-hoc testing in each group showed significant differences between the ratio at baseline and at post-adaptation with respect to step length symmetry values. • In both groups, the fast plantarflexion moment was reduced and the slow plantarflexion moment was increased from midstance to toe-off in the post-adaptation period. Significant relationships were found between the plantarflexion moment and contralateral step length.

		• Split-belt treadmills could be useful for restoring step length symmetry in individuals post-stroke who present with a longer paretic step length because the use of this type of intervention increases paretic plantarflexion moments. This intervention might be less recommended for individuals post-stroke with a shorter paretic step length because it reduces the paretic plantarflexion moment.
Lewek, M. D., et al (2018) Clinical rehabilitation	• Overground spatiotemporal asymmetries: step length asymmetry and stance time asymmetry • Gait speeds • Follow-up period of one week and of four weeks post-training	• Step length asymmetry reduced after training, but stance time did not. There was no group × time interaction. Gait speed improved after training, but was not affected by type of asymmetry, or group. Of those who trained to modify step length asymmetry, there was a moderately strong linear relationship between the change in step length asymmetry and the change in gait speed. • Augmenting errors was not superior to minimizing errors or providing only verbal feedback during conventional treadmill walking. Therefore, the use of verbal feedback to target spatiotemporal asymmetry, which was common to all participants, appears to be sufficient to reduce step length asymmetry. Alterations in stance time asymmetry were not elicited in any group.
Malone, L. A., et al (2014) Neurorehabilitation and Neural Repair	• Step length symmetry • Phasing • Adaptation and de-adaptation behavior • No long-term follow-up period	• Those with stroke adapted more slowly ($P<.0001$), though just as much as healthy older adults. During split-belt walking, the participants with stroke adapted toward their baseline asymmetry (e.g. $F=14.02$, $P<.01$ for step symmetry), regardless of whether the subsequent after-effects improved or worsened their baseline step asymmetries. No correlation was found between baseline spatial and temporal measures of asymmetry ($P = .38$). Last, the initial spatial and temporal asymmetries predicted after-effects independently of one another. The after-effects in the spatial domain (i.e. center of oscillation difference) are only predicted by center of oscillation difference baseline ($F=15.3$, $P=.001$), while all other parameters were nonsignificant (all $P>.17$). Temporal coordination (i.e. phasing) after-effects showed a significant effect only from phasing baseline ($F=26.92$, $P<.001$, all others $P>.33$). • This work demonstrates that stroke patients adapt toward their baseline temporal and spatial asymmetries of walking independently of one another. We define how a given split-belt training session would affect asymmetries in these domains, which must be considered when developing rehabilitation interventions for stroke patients.

Reisman, D. S., et al (2010b) Journal of Neurologic Physical Therapy	• Step length asymmetry • Stance time • Double support time • Walking speeds • Follow-up period of one week and of four weeks post-training	• With training, step length asymmetry decreased from 21% to 9% and decreased further to 7% asymmetry 1 month after training. Self-selected walking speed increased from 0.71 m/s to 0.81 m/s after training and 0.86 m/s 1 month later. Percent recovery, measured by the Stroke Impact Scale (SIS), increased from 40% to 50% post-training and to 60% 1 month later. • Stance and double support time asymmetries remained essentially unchanged • Improvements in step length symmetry were observed following training and these improvements were maintained 1 month later. Concomitant changes in clinical measures were also observed, although these improvements were modest. The outcomes for this participant are encouraging given the relatively small dose of training. They suggest that after stroke, short-term adaptation can be capitalized on through repetitive practice and can lead to longer-term improvements stroke.
Reisman, D. S., et al (2013) Neurorehabilitation and Neural Repair	• Step length asymmetry • Stance time • Double support time • Follow-up period of one month and of three months post-training	• For the group and for the responders (7 individuals), step length asymmetry improved from baseline to post-testing (P<.05) through an increased step length on both legs but a relatively larger change on the shorter step side (P<.05). Other parameters that were not targeted (e.g. stance time asymmetry) did not change over the intervention. • This study demonstrates that short-term adaptations can be capitalized on through repetitive practice and can lead to longer-term improvements in gait deficits post-stroke. The error augmentation strategy, which promotes stride-by-stride adjustment to reduce asymmetry and results in improved asymmetry during overground walking practice, appears to be critical for obtaining the improvements observed.
Reisman, D. S., et al (2009) Neurorehabilitation and Neural Repair	• Step length • Double support time • No long-term follow-up period	• Both groups demonstrated partial transfer of the aftereffects observed on the treadmill (P<.001) to overground walking (P<.05), but the transfer was more robust in the subjects post-stroke (P<.05). The subjects with baseline asymmetry after stroke improved in asymmetry of step length and double limb support (P=.06). • The partial transfer of aftereffects to overground walking suggests that some shared neural circuits that control locomotion for different environmental contexts are adapted during split-belt treadmill walking. The larger adaptation transfer from the treadmill to overground walking in the stroke survivors may be due to difficulty adjusting their walking pattern to changing environmental demands. Such difficulties with context switching have been considered detrimental to function post-stroke. However, we propose that the persistence of improved symmetry when changing context to overground walking could be used to advantage in post-stroke rehabilitation.

Reisman, D. S., et al (2007) Brain	• Stride length • Stance time • Step length • Double support time • Interlimb phasing • No long-term follow-up period	• Results showed that stroke involving cerebral structures did not impair either reactive or adaptive abilities and did not disrupt storage of new interlimb relationships (i.e. after-effects).This suggests that cerebellar interactions with brainstem, rather than cerebral structures, comprise the critical circuit for this type of interlimb control. Furthermore, the after-effects from a 15-min adaptation session could temporarily induce symmetry in subjects who demonstrated baseline asymmetry of spatiotemporal gait parameters. In order to re-establish symmetric walking, the choice of which leg is on the fast belt during split-belt walking must be based on the subject's initial asymmetry. These findings demonstrate that cerebral stroke survivors are indeed able to adapt interlimb coordination. This raises the possibility that asymmetric walking patterns post-stroke could be remediated utilizing the split-belt treadmill as a long-term rehabilitation strategy.
Tyrell, C. M., et al (2014) Journal of neurophysiology	• Step length • Limb phase • A 2 day follow-up to test for retention, no longer-term follow-up period	• For both step length and limb phase, magnitude of early symmetry is largest on day 1, followed by a reduction with repeated exposure • Learning the spatial pattern of split-belt treadmill walking was slowed after stroke when compared to neurologically intact subjects, whereas there were no differences between these two groups in learning the temporal pattern. During the retention test, participants post-stroke demonstrated equal retention of the split-belt treadmill walking pattern compared to those who were neurologically intact. The results suggest that, although stroke survivors are slower to learn a new spatial pattern of gait, if given sufficient time, they are able to do so to the same extent as those who are neurologically intact.
Tyrell, C. M., et al (2015) Journal of biomechanics	• Rate and magnitude of locomotor (de)adaptation • No long-term follow-up period	• There were no differences between the groups with the exception of the reduced step length asymmetry configuration, in which case there was a significantly reduced magnitude ($p<0.000$) and rate ($p=0.011$) of adaptation when compared to controls. There was a similar trend observed during post-adaptation for the exaggerated asymmetry group. The rate and magnitude of locomotor (de)adaptation is similar between chronic stroke survivors and neurologically intact controls, except when the adaptation or de-adaptation response would take the stroke survivors away from asymmetric step length pattern. This suggests that there may be some benefit to symmetry that is recognized by the system.

5. Discussion

5.1. Reflection on quality studies

Overall risk of bias ranged from low to moderate. The moderate risk of bias due to confounding (Betschart, 2017; Reisman, 2010b) was ascribable to the possibility of unknown disruptive variables, which could have led to an incorrect interpretation of the results. This could mean that the outcomes were not related to split-belt walking, but to the unknown confounding variable. The moderate risk of bias due to missing data (Reisman, 2007, 2013) could be attributed to unreliable data, such as foot scuffing during walking, quitting intervention because of medical reasons, equipment failure or not completing follow-up evaluation. Both studies took this into account by excluding the incomplete data in the discussion in order to keep the results as accurate as possible. A moderate risk of bias in measurement of outcomes was attributed to 11 studies (Betschart, 2017, 2018; Charalambous, 2018; Lauzière, 2014, 2016; Malone & Bastian, 2014; Reisman, 2007, 2009, 2013; Tyrell, 2014, 2015) because none of these studies mentioned whether the outcome assessors were aware of the intervention received. If this was the case, their assessment of the intervention could have been subjective in favor of split-belt treadmill intervention, which could have had an influence on the results. In Reisman (2010b), there was a serious risk of bias in measurement of outcomes because the participant was aware of the intervention received. This could have had an influence on the patient's motivation, which in turn could have altered the outcomes.

Both included RCTs (Alcântara, 2018; Lewek, 2018) had an unclear risk of bias for performance, because it was not described how or if blinding of participants and personnel was done. A lack of blinding of participants could have influenced motivation, and a lack of blinding of assessors could have led to a subjective evaluation of the intervention. Both biases could have resulted in an inaccurate representation of the results. Lastly, Alcântara (2018) had an unclear risk of bias for detection because no blinding of outcome assessment was mentioned in this study. Outcomes could have been assessed differently if the assessors knew which intervention was received by which participant, resulting in inaccurate or incorrect conclusions.

5.2. Reflection on findings in function of the research question

Gait parameters

With reference to the type of error caused while walking on a split-belt treadmill, i.e. error augmentation versus error minimization, we concluded that both conditions had a significant effect on gait parameters. Although the majority of the included studies compared both conditions of split-belt treadmill walking, none of them made a clear statement about which of the two is recommended for optimal gait training in stroke patients. The study of Lewek (2018) concluded that error augmenting was not superior to error minimization while the study of Malone & Bastions suggested that the approach of error augmentation, was the best option for gait rehabilitation in stroke patients. Lastly, the study of Tyrell (2015) showed no differences between both error augmenting and error minimization in rate of adaptation, magnitude of initial after-effect, and magnitude and rate of de-adaptation.

As hypothesized in the preface of this systematic review, stroke patients were as capable of adapting gait to a more-normal spatio-temporal walking pattern as healthy subjects (Dietz, Zijlstra & Duysens, 1994; Reisman, Block & Bastian, 2005; Reisman, 2010a), both during and after split-belt treadmill intervention.

Outcome measures with 1b level of evidence

All included studies investigating step length asymmetry (Alcântara, 2018; Betschart, 2017, 2018; Charalambous, 2018; Lauzière, 2014, 2016; Lewek, 2018; Malone & Bastian, 2014; Reisman, 2007, 2009, 2010b, 2013; Tyrell, 2014) found matching results, concluding that step length asymmetry improved in stroke patients during and after both conditions of split-belt treadmill walking.

No inconsistencies were found between the four studies in the results of stance time (Lewek, 2018; Reisman, 2007, 2010b, 2013). Because of this, we concluded that during both conditions of split-belt treadmill walking in stroke patients, stance time asymmetry improved and returned to baseline afterwards.

The results over all three included studies concerning gait speed (Betschart, 2018; Lewek 2018; Reisman, 2010b) were consistent. After both conditions of split-belt treadmill walking (comfortable and maximal) gait speeds significantly increased over time and continued to improve one month post-training.

No inconsistencies were found between both of the included studies in the results of transfer to overground walking (Alcântara, 2018; Reisman, 2009). Because of this, we concluded that both conditions of split-belt treadmill walking caused transfer of the after-effect to overground walking.

Based on the results of these studies concerning step length asymmetry, stance time, gait speed and transfer to overground walking, following hypothesis can be confirmed with a high level of evidence: split-belt treadmill walking intervention has a significant training effect on gait in post-stroke patients, both during and after split-belt treadmill walking.

Outcome measures with 2b level of evidence

The results concerning double support time (Lauzière, 2016; Reisman, 2007, 2009, 2010b, 2013) were consistent across all five studies. After split-belt treadmill walking with either non-paretic leg or leg with the shortest step length on the fast belt, double support time asymmetry significantly improved but gradually adjusted back to baseline levels in post-stroke patients.

Both studies investigating ankle and hip moment (Lauzière, 2014, 2016) found consistent results, concluding that after both split-belt treadmill walking conditions ankle and hip moments significantly changed in post-stroke patients.

No inconsistencies were found between the four included studies in the results of interlimb phasing (Malone & Bastian, 2014; Reisman, 2007; Tyrell, 2014, 2015). During both conditions of split-belt treadmill walking phasing changed significantly and then adapted back toward its baseline (a)symmetry.

The results of both included studies concerning locomotor learning measures (Charalambous, 2018; Tyrell, 2014) were consistent, concluding that the newly locomotor task retained although practice did not increase retention rate.

The gait parameters stride length (Reisman, 2007), muscle activity (Betschart, 2017) and functional mobility (Betschart, 2018) could not be compared as they were each examined in only one study. Each of the three studies were of good quality and the only limitation regarding external validity was the limited sample size used in each study. Conclusions were that during both conditions of split-belt treadmill walking, stride length asymmetry improved and a significant increase in some slow and fast muscles occurred. Afterwards, stride length and muscle activity returned to baseline, and functional mobility increased and persisted until one month of follow-up.

Based on the results of these studies concerning double support time, interlimb phasing, stride length, muscle activity and functional mobility, following hypothesis can be confirmed with a moderate level of evidence: split-belt treadmill walking intervention has a significant training effect on gait in post-stroke patients, both during and after split-belt treadmill walking.

Outcome measures with 3b level of evidence

No inconsistencies were found between both included studies investigating the results of adaptation and de-adaptation (Malone & Bastian, 2014; Tyrell, 2015). Because of this, we concluded a significant (either improving or worsening) difference during split-belt treadmill walking with the paretic leg on the fast belt, and similar rate of de-adaptation back to baseline asymmetry between both conditions of split-belt treadmill walking.

For the study of Malone & Bastian (2014), the investigators tried to solve the problem of 3b level of evidence by assembling a control group consisting of age-matched controls. For the study of Tyrell (2015), this was solved by gathering age- and gender-matched controls.

Energy cost of walking

Endurance and perceived exertion (Betschart, 2018), muscular utilization ratio (MUR) (Lauzière, 2016), and changes in both lactate and BDNF concentrations (Charalambous, 2018) were each found in only one study and could therefore not be compared . The level of evidence of each of these three included studies was 2b.

From this, we concluded that few articles investigated the training effect on the energy cost of walking in stroke patients, both during and after split-belt treadmill walking. The available results however, showed significant effects in reducing Muscular Utilization Ratio and lactate concentrations. This reduce appeared to significantly improve walking performance in individuals after stroke, as was already proven in healthy subjects (Roper, Stegemöller, Tillman & Hass, 2013).

The hypothesis, in the preface of this systematic review, regarding the relationship between reduced energy cost of walking and better long-distance walking function in people after stroke (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015) could not be confirmed nor denied. None of the included studies incorporated long-distance walking after a split-belt treadmill intervention as an outcome measure.

5.3. Reflection on strengths and limitations of the literature study

One of the strengths of this literature study is the detailed search strategy concerning the keywords stroke, split-belt, gait and energy cost. It enabled us, in our study selection process, to choose from a variety of interesting articles. The detailed search strategy and thorough study selection process enabled us to obtain 14 articles on which we based this literature review. Lastly, almost all of the included studies are up-to-date. The reason for this is the relatively new concept of a split-belt treadmill to rehabilitate a post-stroke patient.

One of our limitations is the small amount of useful articles concerning energy usage from patients post-stroke and split-belt treadmill walking. The secondary purpose was to research this, but because we found no articles regarding this topic we must conclude as of yet no studies were done. This topic is a recommendation to research in future studies. More of the limitations in this study are small sample sizes in nearly all of the included articles, the contradictory ways to evaluate split-belt walking in each study and the lack of long-term follow-up periods in most studies.

We also provided an extensive overview of the strength-weakness analysis of the included studies (Alcântara, 2018; Betschart, 2017, 2018; Charalambous, 2018; Lauzière, 2014, 2016; Lewek, 2018; Malone & Bastian, 2014; Reisman, 2007, 2009, 2010b, 2013; Tyrell, 2014, 2015). This can be found in Table 12 in the Appendix.

5.4. Recommendations for future studies

Gait outcome measures on split-belt treadmill walking post-stroke should be re-examined in the long-term. Each study should be repeated with an adequate number of test subjects and with a Randomized Controlled Trial design, resulting in higher level of evidence.

This literature review also showed the limited number of studies (n = 4) concerning one or more energy cost of walking outcome measures in people with stroke after split-belt treadmill walking. Therefore, additional research into this matter should be conducted.

Last but not least, none of the included studies subdivided post-stroke patients based on their degree of stroke impairment (mild, moderate and severe). Therefore, it is not known whether patients with, for example, severe stroke impairments benefit more from split-belt treadmill walking than patients with mild stroke impairments. As a result, future studies should investigate the effect of split-belt treadmill walking on gait in subgroups of stroke patients with different functional levels.

6. Conclusion

A split-belt treadmill walking intervention has a significant training effect on gait, in post-stroke patients, both during and after split-belt treadmill walking.

For most gait parameters in stroke patients, a significant change in favor of a more symmetrical gait pattern occurred during split-belt treadmill walking, and retained or returned to baseline asymmetry after split-belt treadmill walking. Patients with stroke were therefore just as suitable as healthy subjects in adapting the gait pattern to a more-normal spatio-temporal gait, both during and after split-belt treadmill intervention.

The training effect on the energy cost of walking of stroke patients has not been sufficiently investigated. Only few studies, with a small sample size and short-term follow-up periods, can be found. These studies confirm a significant reduce in energy cost of walking regarding Muscular Utilization Ratio and lactate concentrations, which significantly improves walking performance.

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PART 2: RESEARCH PROTOCOL

1. Preface

In our literature study we investigated the training effect of a split-belt treadmill walking intervention on gait in post-stroke patients. Here, gait consisted of all gait pattern parameters of overground walking and the energy cost of walking.

Stroke is the leading cause of adult neurologic disability that impairs different aspects of life involving mobility, activities of daily living, communication, and cognition (Patterson, 2008). One of the most important motor activities that are limited after stroke is locomotion. It is linked to reduced community participation, reduced cardiovascular fitness and increased risk of stroke recurrence (Go et al, 2014), and therefore considerable effort is spent on re-learning to walk during rehabilitation (Charalambous, 2018).

Gait post-stroke is characterized by explicit asymmetry (Patterson, Gage, Brooks, Black & Mcllroy, 2010) leading to a reduction in the efficacy of walking (Roper, Stegemöller, Tillman & Hass, 2013). Several innovative studies have attempted to address these asymmetries to improve secure locomotion, by targeting specific gait deviations using a split-belt treadmill (Reisman, 2007, 2009, 2013; Tyrell, 2014).

While using a split-belt treadmill, the speed of both belts can be controlled independently (Reisman, 2010a). This forces the legs to walk at two different speeds which induces both rapid and longer-duration changes in gait pattern in healthy adults (Dietz, Zijlstra & Duysens, 1994; Reisman, Block & Bastian, 2005). The intervention has also shown evidence of improving gait deficits in individuals with neurologic impairment such as Parkinson’s disease and stroke (Roper, Stegemöller, Tillman & Hass, 2013). Thus, the damaged nervous system of an individual following stroke is still capable of producing a more-normal spatio-temporal walking pattern following split-belt treadmill training (Reisman, 2010a).

Previous studies have established that individuals with neurologic disorders such as stroke and Parkinson’s disease show an increased metabolic demand during gait and during the execution of daily activities (Roper, Stegemöller, Tillman & Hass, 2013). People suffering from the consequences of a stroke are limited in their peak aerobic capacity and experience a higher perceived effort during performance of daily activities (Gjellesvik, Brurok, Tjønna, Tørhaug, Askim, 2017). In normal healthy adults, the energy cost of walking depends on the speed of walking. It is lowest at a speed of approximately 1.1 m/s and is greater at higher or lower speeds. On the other hand, patients with gait impairments generally choose lower walking speeds which shows a greater energy cost but probably yields better stability (Zamparo, Francescato, De Luca, Lovati, di Prampero, 1995). The metabolic demand is an important factor for health care, since a higher energy cost of walking post-stroke has been proven to reduce walking performance and therefore reduce participation in the community (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015). Based on these results we can theorize that interventions to reduce the energy cost of walking can facilitate long-distance walking in people post-stroke (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015). These interventions should focus on improving the gait pattern, which is accompanied by an improvement in energy cost of walking (Awad, Palmer, Pohlig, Binder-Macleod & Reisman, 2015).

Some research concerning energy cost has been performed on stroke patients (Jung, Ozaki, Lai, & Vrongistinos, 2013) and sufficient research concerning this topic has been performed on healthy subjects using a split-belt treadmill. (Roper, Stegemöller, Tillman & Hass, 2013). However, so far no research is available on the effect of a split-belt treadmill training on energy cost in post-stroke patients.

2. Purpose of investigation

The purpose of this research study is to investigate the training effect during and after a split-belt treadmill walking intervention, on the energy cost of walking in subjects post-stroke. We will describe energy cost as oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory exchange ratio (RER), heart rate and perceived effort (Jung, Ozaki, Lai, & Vrongistinos, 2013; Roper, Stegemöller, Tillman & Hass, 2013; Sanchez, Finley, 2018).

Hypothesis:

- H1: The energy cost of walking will increase during an intervention on a split-belt treadmill, with the emphasis on increasing asymmetry by placing the short step length limb on the fast belt. After the intervention, the energy cost of walking will be lower because a more symmetric gait pattern has arisen as a result of the split-belt intervention.

- H2: The energy cost of walking will decrease during an intervention on a split-belt treadmill, with the emphasis on decreasing asymmetry by placing the short step length limb on the slow belt. After intervention, the energy cost of walking will be lower because a more symmetric gait pattern has arisen as a result of the split-belt intervention.

3. Method

3.1 Research question

What is the training effect on the energy cost of walking in post-stroke patients, both during and after a split-belt treadmill walking intervention?

P	Post-stroke patients
I	Split-belt treadmill walking
C	/
O	Energy cost of walking (oxygen consumption, carbon dioxide production, oxygen cost, heart rate and perceived effort)

3.2 Research design

This study will take place at the University of Maastricht, in the Human Performance Laboratory. This virtual laboratory contains the Computer Aided Rehabilitation ENvironment (CAREN System), which can be used to train and evaluate locomotor capacity of patients. Participants will be recruited after an intake interview with Prof. dr. Meyns. When the patients meet the inclusion criteria and have read and signed the informed consent, socio-demographic information will be collected. The participants will then be randomly divided into two groups (group 1 or group 2) by using a randomization program.

3.3 Participants

This study will focus on post-stroke patients.

3.3.1 Inclusion criteria

Following criteria must be met by all patients to participate in this study:

- Age 21-70 years
- Unilateral chronic stroke (>6 months post-stroke)
- Able to walk for a minimum of 10 minutes at self-selected walking speed without assistance from another person (assistive devices are allowed)

3.3.2 Exclusion criteria

Patients with the following criteria will be excluded from this study:

- Medical and cognitive conditions, aside from stroke, that could affect walking capacity or locomotor ability

3.3.3 Recruitment

To calculate the sample size, effect size 0.7 and standard deviation 1.16 (da Cunha Jr, 2002) were used with significance level 0.05 and a power of 80%. A formula specifically for calculating the sample size in clinical trials (Cheran & Biswas, 2013) resulted in a sample size of 86 participants per group. Two interventions will be evaluated, which means at least 172 participants will be included in this study. Recruitment will take place in the vicinity of Maastricht in order to prevent loss to follow-up due to distance.

3.4 Medical ethics

Before participation in this study, all participants will have to read and sign an informed consent during their first consultation with Prof. Meyns. With this they give permission that their data will be collected and applied to scientific research. Through this informed consent participants will be informed about the purpose and intervention of the study.

3.5 Intervention

The split-belt intervention will consist of eight sessions spread over four weeks, followed by a follow-up at one week, one month and three months post-intervention.

Intervention in group one will consist of augmenting error by putting the leg with the short step length on the fast belt whilst intervention in group two will minimize error by putting the leg with the short step length on the slow belt.

At the beginning of each session, baseline measurements will be done to evaluate each participants energy expenditure. Baseline testing will be done by walking for five minutes on the split-belt with both belts at the same speed at self-selected comfortable walking speed. This speed will also be used as the speed of the slow belt and will be doubled for the fast belt (2:1 ratio).

Following baseline testing, participants will have to walk for fifteen minutes (rest breaks permitted) with the split-belt at a 2:1 belt speed ratio, after which they are going to end with a five minute cool-down again at tied belt speed.

Measurements for energy expenditure will always be done in the last 30 seconds of each period (baseline 4:30-5:00 and testing 14:30-15:00).

No restrictions will be imposed concerning performing other activities. Participants will be free to perform their hobbies, work, sports or daily activities.

3.6 Outcomes

3.6.1 Primary outcomes

The primary outcome we are going to assess will be energy expenditure. This outcome will be measured using a portable VO_2 device and the 15-point Borg scale.

- A portable VO_2 device measures oxygen consumption, carbon dioxide production and heart rate. Using these measurements, oxygen cost can be calculated.
- The 15-point Borg scale evaluates the perceived exertion, which is an individual’s rating of exercise intensity. The scale starts with “no sense of effort” with a score of 6 and ends with “extremely hard”, which rates 20. It is also used to estimate the heart rate by multiplying the Borg score by ten.

3.6.2 Secondary outcomes

The secondary outcome we are going to evaluate will be the retention of increased or decreased energy expenditure. Retention will be evaluated in the same way as energy expenditure will be measured.

4. Time planning

Recruitment of participants into our study will start as soon as we get the approval of the medical ethics committee and will be done in the vicinity of Maastricht. We will keep recruiting participants until we include a minimum of 86 subjects per group (cf. supra) into our study. Because of this we cannot determine an end date for the recruitment period. The measurements are scheduled to start mid-November 2019 and will be performed until all patients are evaluated. Measurements will be performed by Prof. Meyns, who will be assisted by two students and will take place at the University of Maastricht, in the Human Performance Laboratory where we will be able to utilize the CAREN system.

The data extraction, which is crucial to answer the research question, starts in early December 2019 and we expect that we will process the data analysis by March 2020. After this we will focus on writing the second part of our thesis, in which we will use the acquired data to provide us with an answer to the stated research question.

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APPENDIX

Table 3

Criteria for judging risk of bias in the Cochrane Risk of Bias assessment tool

RANDOM SEQUENCE GENERATION

Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.

Criteria for a judgement of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

ALLOCATION CONCEALMENT

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.

Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

BLINDING OF PARTICIPANTS AND PERSONNEL

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.

BLINDING OF OUTCOME ASSESSMENT

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome.

INCOMPLETE OUTCOME DATA

Attrition bias due to amount, nature or handling of incomplete outcome data.

Criteria for a judgement of 'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.

SELECTIVE REPORTING

Reporting bias due to selective outcome reporting.

Criteria for a judgement of 'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgement of 'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.

OTHER BIAS

Bias due to problems not covered elsewhere in the table.

Criteria for a judgement of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.

Table 4

Empty template of the ROBINS-I tool for assessing risk of bias

Signalling questions	**Description**	**Response options**
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered		Y / PY / PN / N
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.		NA / Y / PY / PN / N / NI
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		NA / Y / PY / PN / N / NI
Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?		NA / Y / PY / PN / N / NI
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?		NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?		NA / Y / PY / PN / N / NI
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?		NA / Y / PY / PN / N / NI
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.	Low / Moderate / Serious / Critical / NI

Optional: What is the predicted direction of bias due to confounding?		Favours experimental / Favours comparator / Unpredictable

Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4		Y / PY / PN / N / NI
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention? 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI NA / Y / PY / PN / N / NI
2.4. Do start of follow-up and start of intervention coincide for most participants?		Y / PY / PN / N / NI
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NA / Y / PY / PN / N / NI
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.	Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of participants into the study?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in classification of interventions		
3.1 Were intervention groups clearly defined?		Y / PY / PN / N / NI
3.2 Was the information used to define intervention groups recorded at the start of the intervention?		Y / PY / PN / N / NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		Y / PY / PN / N / NI
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias,	Low / Moderate / Serious / Critical / NI

	and responses in red are potential markers for a risk of bias.	
Optional: What is the predicted direction of bias due to classification of interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?		Y / PY / PN / N / NI
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?		NA / Y / PY / PN / N / NI
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?		Y / PY / PN / N / NI
4.4. Was the intervention implemented successfully for most participants?		Y / PY / PN / N / NI
4.5. Did study participants adhere to the assigned intervention regimen?		Y / PY / PN / N / NI
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.	Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?		Y / PY / PN / N / NI
5.2 Were participants excluded due to missing data on intervention status?		Y / PY / PN / N / NI

5.3 Were participants excluded due to missing data on other variables needed for the analysis?		Y / PY / PN / N / NI
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?		NA / Y / PY / PN / N / NI
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?		NA / Y / PY / PN / N / NI
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.	Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to missing data?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in measurement of outcomes

6.1 Could the outcome measure have been influenced by knowledge of the intervention received?		Y / PY / PN / N / NI
6.2 Were outcome assessors aware of the intervention received by study participants?		Y / PY / PN / N / NI
6.3 Were the methods of outcome assessment comparable across intervention groups?		Y / PY / PN / N / NI
6.4 Were any systematic errors in measurement of the outcome related to intervention received?		Y / PY / PN / N / NI
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.	Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to measurement of outcomes?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Bias in selection of the reported result

Is the reported effect estimate likely to be selected, on the basis of the results, from...

7.1. ... multiple outcome *measurements* within the outcome domain?		Y / PY / PN / N / NI
7.2 ... multiple *analyses* of the intervention-outcome relationship?		Y / PY / PN / N / NI
7.3 ... different *subgroups*?		Y / PY / PN / N / NI
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.	Low / Moderate / Serious / Critical / NI
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall bias		
Risk of bias judgement	Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.	Low / Moderate / Serious / Critical / NI
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Table 12

Strength-weakness analysis of the included studies (n = 14)

Article	Strengths	Weaknesses
Alcântara, C. C., et al (2018) Neurorehabilitation neural repair	• Subjects were recruited from a variety of sources • Random allocation to groups (gradual group vs. abrupt group) • Clearly defined walking testing paradigm • Clear description of the purpose of the study • The inclusion of a "washout period" to test for washout of the treadmill after-effect due to overground walking • Subjects were transported in a wheelchair between tests to guarantee that no walking other than that collected by the motion capture system would occur	• The exclusion of subjects who had evidence of cerebellar stroke, because of the role of the cerebellum in learning. Hereby, the generalization to all stroke patients is less applicable • Subjects were allowed to take rest breaks but these are not described in the text • Overground walking assessment consisted of several trials instead of a long-distance walk • There was no comparison of groups with different functional levels
Betschart, M., et al (2017) Journal of electromyography	• Clear and complete description of how data were collected • Clearly defined walking testing paradigm • Repeated-measures ANOVA was used to test the effect of period, condition and side comparisons with a significance level at p=0.5 which was adjusted by using a Bonferroni correction for post hoc multiple comparisons	• Low number of participants (n=16) • It is not specified from where the participants were recruited • The post-adaptation consisted of 3 minutes of tied-belt walking which is rather short to completely wash out after-effects • There is no subgroup analysis of individuals with shorter paretic step or non-paretic step length. This could be helpful to analyze the changes in muscle activity regarding step length asymmetry
Betschart, M., et al (2018) Physiotherapy Theory and practice	• They clearly define the reason and objective for this study • Objective assessment tools were used to evaluate physical impairment, gait deficits and spasticity • Participants were instructed not to participate in other gait-related training during the course of the training and assessment period • Complete outcome assessment on 3 occasions: 1 week prior to training, 1-2 days post-training and 1 month after discharge from training • Clearly defined training protocol • For nonparametric statistics, alpha level was adjusted by the	• Low number of participants (n=12) of which ten subjects were male and only two were female • There were too few training sessions to improve endurance • Patients were permitted to use breaks if their heart rate exceeded 80% of the age-related maximum. This could cause de-adaptation (patients who had to use a break were not permitted to walk to minimize de-adaptation during the 20 minutes) • Two participants completed the entire 20 minutes without breaks and the others required one to three breaks • ¼ of the participants did not achieve the 2:1 split-belt speed ratio which was the goal • There was no double baseline for step length symmetry conducted

	number of comparisons (n=3) requiring a p> 0.017	
Charalambous, C. C., et al (2018) The Journal of Physiology	- Moderate number of participants (n=37) - The inclusion of a control group - They explicitly explain the objective and the purpose of the study - They quantified intensity depending on whether the subject was taking beta-blocker medications or not - They quantified the within session 1 walking pattern to determine whether all groups experienced the same perturbation at the beginning of split-belt walking	- It is not stated from where they acquire the subjects who participated in the study - They excluded subjects who had evidence of a cerebellar stroke, this makes the generalization to all stroke patients less applicable - It is not clearly stated whether allocation to one of the groups was randomized or not - Exercise duration of the high intensity exercise was shorter than in previous studies of neurologically intact subjects which could have influenced their findings - There is a potential effect of interference due to the use of the legs in both the exercise and learning tasks. In this study, the total body exercise group pedaled an ergometer with both arms and legs after the motor task and the treadmill walking groups walked on the treadmill before practice of the motor task
Lauzière, S., et al (2016) Journal of Rehabilitation Medicine	- Clear description of why they conduct the study and what they try to find - Objective measurements of what they want to investigate - They used a control group of healthy subjects	- Low number of participants (n=20) - There is no information given about patient characteristics - There is a restricted number of individuals with step length asymmetry with shorter non-paretic step length. A larger number of participants with a wider range of asymmetry would have made it more likely to find a correlation between initial step length asymmetry and change in paretic and non- paretic step length
Lauzière, S., et al (2014) Journal of Rehabilitation Medicine	- Clear description of the purpose and execution of the study - They used healthy subjects to compare against the post-stroke participants - Clearly defined inclusion and exclusion criteria were used for both healthy and post-stroke subjects - Objective measurements of functionality to evaluate a baseline - Walking speed was comparable between healthy and post-stroke subjects	- Low number of participants (healthy controls n=10, post-stroke n=20) - Interpretation of the joint moment after-effects in the post-adaptation period could be misinterpreted because individuals post-stroke had to hold on to the handrail during the adaptation period for safety purposes - There was no inclusion of dorsiflexion moment, knee joint moment or joint powers in the data analyses, which might have contributed to step length adaptation

Lewek, M. D., et al (2018) Clinical rehabilitation	• High number of participants (n=47) • Participants were randomized in the different groups • Complete description of the reason and purpose of the study, as well as how the intervention was done • It is described from where the participants were recruited, which inclusion or exclusion criteria they used and how assessors were blinded	• The assessment for the last four participants was not blinded • There was a large number of dropouts because the participants had to go to the lab for 18 training sessions. 77% of the participants completed the full training • Additional information about lesion location could have helped them with the interpretation of data
Malone, L. A., et al (2014) Neurorehabilitation and Neural Repair	• Thorough illustration of the purpose and how the study was conducted • Baseline asymmetries were not subtracted out. this allowed them to assess the effects of split-belt training on individual subject asymmetries • All subjects were able to complete the walking task • Intervention was specific to each patient's baseline asymmetries	• Low number of participants and uneven distribution subjects post-stroke vs healthy controls (individuals post-stroke n=22, healthy controls n=7) • More studies of long-term training are needed to understand if error augmenting split-belt training can lead to more symmetric walking patterns
Reisman, D. S., et al (2010b) Journal of Neurologic Physical Therapy	• Clear description of the purpose of the study and how the study was conducted • Thorough explanation of the patient characteristics and baseline examination in which objective measurements were used • Intervention sessions were given by one physical therapist and evaluations were done by another physical therapist • Intervention period was clearly defined and long enough	• Extremely low number of participants (n=1) • In the study they used step length data collected from 3 persons post-stroke during overground walking with the motion capture system but these 3 subjects were not evaluated further • Their goal was to evaluate longer-term changes in step length asymmetry and gait function but they only did a follow-up at 1 month. This is not enough time to evaluate longer-term changes • The physical therapist performing the evaluations was not blinded to the intervention • Gains in step length asymmetry could be due to the overground walking training
Reisman, D. S., et al (2013) Neurorehabilitation and Neural Repair	• It is made clear why and how the study was conducted • It is clearly described how patients were evaluated at baseline, how the testing paradigm looked, how training was done and for how long • In this study participants trained 3 d/wk for 4 weeks. there was a follow-up at 1 month and at 3 months which is long enough to evaluate for longer-term improvements	• Low number of participants (n=13) • Data were not available for all participants • There was a significant loss to follow-up. Data are presented from 12/13 participants because walking data from one participant could not be reliably calculated because of foot scuffing during walking. Two participants did not complete the 3 month evaluation, one subject had a new diagnosis of cancer after 1 month evaluation and one person was unavailable. gait data from 1

	• They made subgroups via changes in step length asymmetry after training. (responder or non- responder) • They evaluated participant's perceived exertion scores	participant at 1 month follow-up were unavailable because of equipment malfunction
Reisman, D. S., et al (2009) Neurorehabilitation and Neural Repair	• The control group (healthy subjects) is equivalent in age and gender to the post-stroke group • Clear description of the aim of the study and a thorough explanation of findings regarding the subject resulting from previous studies • Equal distribution of lesion location between hemispheres among post-stroke subjects (6 left and 5 right) • Clinical examination was done using objective measurements. • Extensive illumination of the testing paradigm • There was a blinding of participants. they knew the 2 belts would move at different speeds at some point but they were not told when • Participants were instructed not to look down at the belts to minimize the effect of visual information about belt speeds	• Low number of participants (post-stroke subjects n=11, healthy subjects n=11) • One of the factors contributing to only a partial transfer might be that transfer of the adapted pattern is greatest when subjects walk in contexts that are most similar to that experienced during training. Here subjects were tested with eyes open and holding onto the handrail during treadmill walking. which explained a modest 30% transfer in control subjects. Future studies should take this into account • Post-stroke participants were beyond the level of household ambulation according to Perry's classification of walking disability. Because of this generalisation to all stroke survivors is difficult
Reisman, D. S., et al (2007) Brain	• The participant characteristics of the healthy control group are similar to that of the post-stroke group in age and gender • Thorough illustration of the purpose and goal of the study • Complete description of testing paradigm and intervention • Participants had were given no practice on the split-belt, they were told that the two belts would move at two different speeds at some point but they were not told when this would happen and they were instructed not to look down so that they were not able to use visual feedback to determine the speed of the belts • Subjects had a wide range of damage to different structures which resulted in a wide range of sensory and motor impairments. this makes generalisation applicable	• Low number of participants (post-stroke subjects n=13, healthy controls n=13) • Testing consisted of only two testing sessions. future studies should investigate the effects of long-term training and how these effects transfer to real- world tasks like walking overground

Tyrell, C. M., et al (2014) Journal of neurophysiology	• Thorough explanation and description of the reason and purpose of the study • Comprehensive evaluation of previous studies regarding the split- belt subject • Clear description of patient characteristics, patient recruitment, testing paradigm and intervention protocol	• Low number of participants (post-stroke subjects n=16, healthy controls n=16) • Intervention duration was rather short to evaluate longer-term retention. • It is not described if they had a loss to follow-up • They did not do a follow-up to evaluate further for retention
Tyrell, C. M., et al (2015) Journal of biomechanics	• Thorough description of the purpose of the study and of previous studies regarding the subject • Split-belt walking protocol was completed twice on separate days once with the paretic leg on the slow belt and once with the non- paretic leg on the slow belt, the order of which was randomized • Normality of the data distribution was confirmed using the Kolmogorov-Smirnov test for normality and all statistical testing was completed using SPSS v19 • Clear and full evaluation of data and results	• Low number of participants (post-stroke subjects n=17, healthy controls n=17) • It is not clear from where participants were recruited • Healthy subjects walked at speeds that matched their stroke subject counterparts. This resulted in control subjects that walked at speeds slower than their typical self-selected speed, and could therefore result in a perturbation too small to induce locomotor adaptation or de-adaptation

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
12/11/'18	• In orde maken en laten ondertekenen van het wetenschappelijke stagecontract. • Kennismaking met de promotor.	Promotor: Copromotor/begeleider: Student(e): Student(e):
17/12/'18	• Bespreking van verschillende vragen en onduidelijkheden omtrent onderwerp. • Overleg onderzoeksvraag.	Promotor: Copromotor/begeleider: Student(e): Student(e):
08/01/'19	• Overleg onderzoeksvraag • Voorstellen van de split-belt. • Praktische afspraken	Promotor: Copromotor/begeleider: Student(e): Student(e):
11/03/'19	• Bespreking in- en exclusiecriteria na goedkeuring zoekstrategie	Promotor: Copromotor/begeleider: Student(e): Student(e):
13/04/'19	• Bespreking checklist voor kwaliteitsbeoordeling van de bekomen artikels	Promotor: Copromotor/begeleider: Student(e): Student(e):
16/05/'19	• Laten lezen van de inleiding • Bespreking opstelling onderzoeksprotocol.	Promotor: Copromotor/begeleider: Student(e): Student(e):
03/06/'19	• Verbetering eerste versie thesis.	Promotor: Copromotor/begeleider: Student(e): Student(e):
12/06/'19	• Goedkeuring presentering masterproef	Promotor: Copromotor/begeleider: Student(e): Student(e):
		Promotor: Copromotor/begeleider: Student(e): Student(e):
	Niet-bindend advies: De promotor verleent hierbij het advies om de masterproef WEL/~~NIET~~ te verdedigen.	Promotor: Copromotor/begeleider: Student(e): Student(e):