Lower limb muscle synergies during walking after stroke : a systematic review

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Muscle synergies after stroke

Original article: systematic review

Abstract

Purpose: The aim of this systematic review was to determine the number of muscle synergies and the distribution of muscle weightings in stroke patients during gait.

Material and Methods: This review is registered on PROSPERO (number: CRD42018088701) and is written following the PRISMA guidelines. A systematic search was conducted using following databases: PubMed, Web of Science, Naric, Cochrane and PEDro. Methodological quality was assessed by the Newcastle-Ottawa Scale and data extraction (subject characteristics, outcome measures and walking protocols) was performed by two independent researchers. The amount and structure of the muscle synergies were the two main outcome measures.

Results: In total, ten studies were included in this review. While four synergies are common in healthy controls, stroke patients often showed less synergies during gait. Synergies were determined by the number of muscles measured which varied greatly between studies. Only Tibialis Anterior, Soleus, Gastrocnemius and Rectus Femoris were assessed in all studies.

Conclusions: A consensus regarding the amount and composition of muscle synergies in stroke patients is difficult. The majority observed three to four muscle synergies. The decrease in amount of synergies can be explained by merging of synergies, often seen in hip/knee extensors with plantar flexors and hip/knee extensors with knee flexors.

Keywords: stroke, cerebrovascular disorder, gait, locomotion, muscle synergies, EMG and muscle coordination

Introduction

Only 60 to 70 percent of stroke survivors are able to walk again independently after rehabilitation, while others remain disabled (1, 2). Stroke survivors who regain the ability of walking, develop different muscular motor behaviors such as delayed onset time, decreased muscle strength, changed on and off times during muscle contractions and diminished synchronization (3-5). These changes present themselves at the individual level of a muscle and recruitment of muscles to perform coordinated movements is interrupted. At early stages of recovery, cortical plasticity may influence the recruitment pattern of muscles needed to perform voluntary movements (6).

Muscle activity during walking is recorded by electromyography and by using different matrix factorization methods, muscle activation profiles can be detected (7). A muscle synergy or muscle module is a group of muscles contracting together as part of a functional unit (8). In a healthy population, four or five muscle synergies are activated during specific parts of the gait cycle (9). These modules consist out of a large quantity of muscles and are present in all functions and transitions of the human body in various compositions, from locomotion to postural tasks (9). Muscle synergies are the lowest level of the motor control hierarchy, recruited by a good amount of different neural pathways for rhythmic, reactive and voluntary motor behaviors (10). They make a bridge between task-level goals and much more complex patterns of muscle activation, representing abstract motor variables, including the cortex, superior colliculus and spinal cord (10). Thus, muscle synergies form a modular group of actions that is specific to any given task but recruited by a variety of neural pathways governing different motor behavior. In other words, muscles synergies are dependable on the performed task, some synergies may occur when walking but will not be observed during other motor tasks (11). Since muscle activations change on an individual level after stroke, groups of muscles working together as a synergy, will probably change as well. Muscle synergies are not necessarily relearnt after stroke, instead recovery is driven by augmentation of existing abnormal synergies (12). These initial abnormal synergies are not suppressed but progressively altered during stroke recovery (12).

Although several studies investigated the presence of synergies in the upper limb after stroke, little is known regarding muscles synergies during walking (13, 14). Upper limb muscle synergies may serve as a physiological marker to classify stroke patients and for identifying the optimal rehabilitation setting and methods (13, 14). The increased number of muscle synergies after upper limb rehabilitation suggests improved motor control for patients with low motor-function (13). Therefore, muscles synergies might be a clinically useful tool in predicting the success rate of rehabilitation protocols and help us with clinically evaluating stroke patients. In addition, recovery of gait is a primary goal in stroke rehabilitation (15). Although approximately 70 percent of stroke patients achieve an independent gait, only 41 percent were able to independently walk outdoors and 54 percent were able

to independently climb stairs (16). During walking, coordinated lower limb muscle activity is necessary to remain balanced and generate forward propulsion. A better understanding of the coordinated activation patterns of the lower limbs, also known as muscle synergies, might help us improve assessment, goal setting and treatment plans. Therefore, a better understanding concerning the number of muscle synergies and the distribution of muscle weightings which are present during gait after stroke is necessary. The amount of muscle synergies and muscle weighting might be a successful tool for assessing gait performance.

Thus, the aim of this systematic review is to specify the amount and composition of muscle synergies during walking after stroke.

Materials and Methods

Protocol and registration

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Statement (PRISMA) and was registered in the PROSPERO database (no: CRD42018088701).

Eligibility criteria

The search strategy was put together by following inclusion criteria: 1) Adults diagnosed with an ischemic or hemorrhagic stroke; 2) Analysis had to be performed during walking; 3) The number or distribution of muscle synergies and the distribution of muscle weightings (composition synergy) had to be described; 4) Studies had to be written in English, Dutch, German or French. Studies were excluded when the population included other neurological disorders or when the intervention was not adequately specified or did not include walking. Study designs such as reviews and case reports were also excluded. There were no limitations applied regarding time post-stroke, length of intervention and follow-up.

Information sources

A systematic search strategy was conducted using the electronic databases of PubMed, Web of Science, Naric, Cochrane and the Physiotherapy Evidence Database (PEDro). A combination of the following free text words and Medical Subject Headings were used: stroke, cerebrovascular disorder, gait, locomotion, muscle synergies, EMG and muscle coordination. The final search strategy for PubMed can be found as supplementary Table S1. The final search strategy was performed in March 2018.

Study collection

The screening procedure was performed by two independent researchers (K.W. and J.V.). To collect potentially relevant studies, eligibility was screened based on title and abstract. Full texts were retrieved and evaluated based on the a-priori provided inclusion and exclusion criteria. Reference lists of the included studies were manually screened to identify additional relevant studies. If there were any discrepancies, this was cleared up by an independent person (T.V.C). Afterwards full texts were gathered and evaluated on the previously set inclusion criteria. Reference lists were manually screened to identify additional relevant studies.

Risk of bias

The risk of bias was assessed by two independent reviewers (J.V. and K.W.) by using the Newcastle-Ottawa Quality Assessment Scale (NOS). In case of uncertainty at any point during the scoring process, consensus was sought by a third reviewer (T.V.C.). According to the design of the study, the checklist for case-control or cohort, or adapted version for cross-sectional studies by Herzog et al. (17) was employed. The NOS is an instrument that assesses the risk of bias by awarding a star for each answer that meets the criteria, a maximum of nine stars can be obtained: four stars for selection, two stars for comparability and three stars for outcome. Each star given, projects a low risk of bias for this criterion. As criterion for quality, the Agency of Healthcare Research standards were used (18, 19). Included studies were of good quality when they scored three or four stars in the selection domain, one or two in comparability domain and two or three in outcome/exposure domain. Fair quality was considered when studies scored two stars in the selection domain, one or two in the comparability domain and two or three in the outcome/exposure domain. At last, poor quality was considered when studies received zero or one star in selection domain, zero stars in comparability domain and zero or one star in the outcome/exposure domain. The developers of the NOS have established the face and criterion validity, and inter-rater reliability (18, 19).

Data extraction and analysis

Extracted data consisted of subject characteristics (age, time post-stroke and type of hemiparesis), outcome measures (muscle activity) and walking protocols defined by their surface (treadmill/split belt treadmill/over ground), length, time and speed. The amount and composition of synergies were described and compared between healthy adults and stroke survivors. In addition, if studies examined the hemiplegic and non-hemiplegic side separately, a comparison of both sides were made. Time post-stroke or intervention strategies were not included in the analysis.

Results

Study selection

The final search strategy resulted in 879 studies obtained from five databases. There were 118 duplicates, which left 761 studies for screening. Manual reference list screening did not result in any additional studies. The studies were first screened on title and abstract, excluding on different parameters like population, intervention and outcome. Following this screening, 95 full texts were retrieved and evaluated on those same parameters. Eventually, ten studies met all the inclusion- and exclusion criteria and were included. See flowchart for a more detailed overview (Figure 1).

[INSERT Figure 1: Flowchart]

Risk of bias

Methodological quality was assessed using the NOS. Results are shown in Tables 1 and 2. There were eight case-control studies and two cross-sectional studies included. The average score for both the case-control and cross-sectional studies was seven. Two studies were of good quality, seven of fair quality and one of poor quality. The highest score was eight and the lowest four.

[INSERT TABLE 1]

[INSERT TABLE 2]

Study characteristics

Study characteristics are shown in Table 3. The included population consisted of a post-stroke group and a healthy control group in eight out of ten studies (20-27). Other studies did not compare the stroke group to healthy subjects (28, 29), or refer to previous studies for data of post-stroke patients (20). In total, there are 218 post-stroke patients and 102 healthy control subjects included in this study. The time post-stroke varies within a range from 10 weeks to 5.1 years post-stroke. Two studies do not mention the time post-stroke (21, 22). Healthy patients are aged matched with the stroke survivors. The mean age of the healthy control subjects is 57.4 ± 9.7 years for the studies that mention it (20, 21, 23, 25). The mean age of the post-stroke patients is 56.6 ± 5.0 years for 6 out of 10 studies (20, 21, 23, 25, 28, 29). Other studies only mentioned that the healthy population is age matched or did not mention age (22, 24, 26, 27). Among the post-stroke patients, there are 101 left sided hemiparesis and 76 right sided hemiparesis. Two studies do not consider the side of hemiparesis (26, 29).

All studies assessed muscle synergies as a single measurement during walking, but there was a variation in protocol. Parameters were measured on a time basis of 30 seconds of walking (20, 21, 23) or on a fixed distance of 6m, 10m, 11m (25, 28, 29). In four studies timing or distance protocols were not mentioned (22, 24, 26, 27). In eight studies patients were asked to walk at their self-selected speed (21, 23-29). In one study, they were asked to walk at a set speed of 0.5, 0.7, 0.9 and 1.1 km/h (22) and

in one study they were also asked to walk at their fastest comfortable speed (23). In three studies patients walked on a split-belt treadmill (20, 21, 23), in six studies patients walked over ground (23-25, 27-29) and in two studies patients walk on a normal treadmill (22, 26). Two studies allowed the use of a walking aid (cane) (27, 29). All other studies either did not mention it or prohibited the use of walking aids (21-23).

The main outcome measure in all studies was assessed by EMG. Nine out 10 studies used non-negative matrix factorization as an algorithm to extract the number of synergies out of the EMG data (20-26, 28, 29). One study did not mention the statistical method (27). Non-negative matrix factorization takes a matrix as an input and generates a set of topics that represent weighted sets of co-occurring terms. By combining attributes non-negative matrix factorization can display patterns, topics, or themes which can be clustered as a unit (30).

All studies used EMG to assess muscle activity, but the number of muscles measured varied greatly. The following muscles were measured: Tibialis Anterior, Soleus, Gastrocnemius, Vastus medialis, Vastus lateralis, Rectus femoris, Medial hamstrings, Lateral hamstrings, Gluteus Medius, Gluteus maximus, Semimembranosus, Biceps femoris, Peroneus longus, Semitendinosus, Adductor longus, Tensor fascia latae, Rectus Abdominus, Erector spinae. Tibialis Anterior, Soleus, Gastrocnemius and Rectus Femoris are the only muscles that are assessed in all ten studies.

[INSERT TABLE 3]

Amount of muscle synergies

Healthy

Six out of eight studies concluded that they found four synergies in healthy subjects when assessing on average ten muscles (Table 4) (20, 22-26). In another study, approximately 55 percent of the subjects showed four synergies during walking, yet there was no clear consensus since the other half had varying results in the amount of muscle synergies recorded (21). Only one study obtained different results, two synergies were described when assessing five muscles (27).

Paretic side post-stroke

A great amount of variation existed in adults post-stroke since the majority of studies had difficulties to give a fixed number of muscle synergies. Three studies detected four synergies (22, 23, 25), while three studies suggested the presence of three or four synergies (20, 24, 28). Furthermore, three studies observed two, three or four synergies (21, 26) and one study observed additionally a fifth synergy (29)

(Table 5). On average studies describing four synergies examined eight to twelve muscles to obtain their results. However, three studies gave results of a number lower than four in 81% (21), 69% (29) and 59% (26) of the cases. These studies favored two or three synergies (21, 26, 29). These studies found less muscle synergies, but there were still seven to eight muscles measured. One study did not succeed at profiling the synergies as they were so indistinct (27). A more detailed presentation regarding the amount of synergies can be found as supplementary Table S2.

Non-paretic side post-stroke

Only three studies measured muscles at the non-paretic side in adults suffering from a stroke (Tables 4 and 5) (21, 25, 28). These results were similar to those healthy adults, as they indicate that 45%, 58% and 80.7% of the synergy-number was four. One of those studies specified a percentage of 22% for three synergies and 33% for five synergies (28).

Composition of muscle synergies

Healthy

A clear structural description of the muscle synergies were found in seven of the included studies (Table 4) (20-22, 24-27). Four studies found M. Gluteus Medius to be included in synergy 1 (S1) (20, 21, 24, 26) which was mostly activated together with the M. Quadriceps during early and mid-stance, more specifically M. Rectus Femoris and M. Vastus Medialis/Lateralis. In one study where 12 muscles were examined, additional hip and knee extensors such as M. Gluteus Maximus, Tensor Fascia Latae and M. Biceps Femoris were included in S1 (22). The combination of hip abductors and hip/knee extensors as seen in S2 are activated during early stance. Synergy 2 (S2) was found in all studies which was a combination of M. Soleus and M. Gastrocnemius during late stance (20-22, 24-27). Synergy 3 (S3) which consisted of M. Tibialis Anterior as found in five studies, while five studies found combined activation with the M. Rectus Femoris (21, 24-27). One study found a synergy which consisted solely of M. Tibialis Anterior (20). Activation of the dorsal flexors in combination with knee extensor activity was seen during early swing. At last, in the majority of cases synergy 4 (S4) was formed by the Hamstrings during swing into early stance (20, 21, 24-26).

Paretic side post-stroke

Seven studies described the composition of the muscle synergies in stroke survivors (Table 5) (20-22, 24-27). Muscle synergies of the paretic side in stroke survivors did not always differ from those observed in healthy controls (21, 22, 24-26).

When four synergies were found, the composition was mostly similar to healthy adults. In stroke patients, M. Gluteus Medius in combination with M. Quadriceps, known as S1, was found in two studies during early stance (21, 24). S2 was composed of M. Soleus and Gastrocnemius during late stance in four studies (21, 22, 24, 26). The synergy including M. Tibialis Anterior was also found as S3, solely (24, 25) or in combination with M. Rectus Femoris (21, 26). At last, S4 was characterized by the Hamstrings in four studies (21, 24, 26, 28).

When less than four synergies were observed, merging of synergies often occurred in stroke survivors (20, 21, 26). Merged synergy 1 (MS1) consisted of S1 and S2 which merged the M. Soleus and M. Gastrocnemius with the M. Gluteus Medius and M. Quadriceps during pre-swing (20, 21, 26). Merged synergy 2 (MS2) included S1 and S4 of the healthy adults, the Hamstrings merged with M. Gluteus Medius and M. Quadriceps during late swing (20, 21, 26). The synergy including M. Tibialis Anterior was now found as merged synergy 3a (MS3a), solely (20) or in combination with M. Rectus Femoris as seen in healthy adults (21). A different combination merging S2 and S4 was found by integrating the Hamstrings with M. Soleus and M. Gastrocnemius which we called merged synergy 3b (MS3b) (26). Some other, not so distinctive, synergies were observed, which can be found as supplementary Table S2.

Non-paretic side post-stroke

Only two studies discussed the muscle synergies of the non-paretic side of the adult stroke participants (21, 25). Both the amount of muscles synergies and composition were comparable to healthy adults (21, 25).

[INSERT TABLE 4]

[INSERT TABLE 5]

[INSERT TABLE 6]

Discussion

In order to fully understand the changed motor behaviors after stroke, we tried to give an overview of the number of muscle synergies, their functions and the distribution of muscle weightings which are present during gait after stroke. The results of this review are of clinical importance to gain knowledge about the different contributions and merges of muscles which are crucial for understanding the gait pattern and its biomechanical factors. To our knowledge this is the first study examining similarities, combinations and patterns of muscle synergies during walking. It is not only the merging of muscles or the amount of synergies that is crucial to look at, an added value to this study should be identifying

the structure, composition and function of the synergies. Overall, the included studies had a good to fair methodologic quality.

In seventy percent of the healthy adults included, the complexity of muscle activity during walking could be explained by four distinctive muscle synergies in accordance with previous studies (5, 30-32) (Table 6): **S1)** Hip abductors and hip/knee extensors which are responsible for body weight support during weight acceptance and early stance braking; **S2)** Plantar flexors which are necessary for body support, late stance forward propulsion and swing initiation; **S3)** Dorsal flexors with or without knee extensors which is used for foot clearance during swing; and **S4)** Hamstrings acting as knee flexors for decelerating the leg at the end of swing and propelling the body during early stance. Studies that reported less synergies also assessed less muscles, suggesting that these results can be explained based on the methodology rather than by a physiological phenomenon. It is therefore important to standardize and clearly report both the number of muscles and which muscles are measured since this clearly influences the results. The majority of studies included eight muscles, the following muscles are recommended to incorporate in the non-negative matrix factorization: M. Tibialis Anterior, M. Soleus, M. Gastrocnemius, M. Rectus Femoris, M. Vastus Lateralis, medial and lateral Hamstrings and M. Gluteus Medius.

Stroke survivors had either the same or a reduced number of synergies in the paretic limb during walking. A similar composition as healthy adults was found when the same amount of synergies was present, suggesting that the neural structures required for the activation of synergies were still intact. When less synergies were described, merging occurred as muscles of different synergies were included in one synergy. It is plausible that they form, as it were, their own synergy due to co-contractions of several muscles. This might suggest, that the composition of synergies were still intact but that stroke survivors have difficulties with the individual recruitment of them. Evidence was found for merging of synergies which is typically seen in adults with low-motor function who have difficulties with complex tasks (13). Since there is no real consensus between studies, it is difficult to define the exact combination of muscle synergies of a stroke patient. Yet, we were able to describe the four most observed muscle synergies (Table 6): **MS1)** M. Soleus, M. Gastrocnemius, M. Gluteus Medius and M. Quadriceps. MS1 was described as merging of synergy 1 and 2 which might have contradicting functions e.g. braking (S1) and propulsion (S2). We hypothesize that prolonged activity of S1 and early activity of S2 results in reduced forward propulsion by increased braking and impaired propulsion capacity (20-22, 26). As a consequence, paretic swing was altered. Activation of M. Quadriceps and M. Soleus and M. Gastrocnemius during late stance into swing can cause insufficient clearance during swing which might lead to compensations such as hip hiking or circumduction to prevent tripping. Clinically this resembles an extension synergy pattern; **MS2)** Hamstrings, M. Gluteus Medius and

Quadriceps results from merging of S1 and S4. We hypothesize that prolonged activity of the hamstrings into stance impedes body support since activation might result in knee flexion instead of hip extension (20-22). Moreover, hamstrings accelerates the leg in swing, yet decelerates the leg in in preparation for foot contact. Therefore, prolonged activity also interferes with propulsion generation (26). Increased co-contractions surrounding the knee might also be a compensatory mechanism to ensure sufficient stability which cannot be provided by the ankle muscles (33). Moreover, this increased co-activation limits knee flexion during swing resulting in a clinical gait pattern known as stiff knee gait (33)**;** and **MS3a**) M. Tibialis Anterior and M. Rectus Femoris (S3). When both muscles are activated, the muscle activity pattern resembles S3 of healthy adults (20, 21). However, increased activation during stance from M. Tibialis Anterior is seen as a compensatory mechanism (34). We hypothesize that increased co-contraction during stance surrounding the ankle complex can be due to muscle weakness of the plantar flexors resulting in decreased efficiency of propulsion and instability (33, 34). A Less frequent synergy, yet still observed is **MS3b)** M. Tibialis Anterior and Hamstrings indicating merging of S2 and S4 which might result in increased step length and propulsion asymmetry, slower walking speed and decreased pre-swing angle (26).

The results of this review indicate that the synergies are altered during hemiplegic gait and that merging of synergies occurs. However, it is still unclear if these synergies are pathological or learned behavior. Although we found several reoccurring and distinctive synergies, no clear consensus can be reached concerning the amount and composition of synergies between studies. It might be that muscle synergies are dependent on the severity of the lesion and if the neural structures required for the activation of the synergies are affected. It is important to further investigate the underlying mechanisms responsible for the merging of synergies since they are an important predictor for poor motor outcome (13, 20, 27). In general, a higher number of synergies was associated with intact motor function. Moreover, less synergies was related to poor improvements in muscle strength and gait kinematics (27). Studies showed that although stroke survivors showed similar synergy strength and muscle weightings, observed changes in muscle synergies were mostly the cause of reduced muscle participation of individual muscles to a muscle synergy, impaired activation timing of a certain synergy or the ability to differentially activate the synergies (21, 24, 26). It is also important to consider that different muscle synergies are observed between the paretic and non-paretic side. Although, some studies concluded that the non-paretic side had a similar synergy amount as healthy individuals, a small shift in composition was observed (21, 22, 25). It is possible that, although contralesional efferent neurons are still intact, impairments of the paretic side influence the non-paretic side. Therefore, we recommend investigating both the paretic and non-paretic side since clear differences were found between both limbs.

However, not all studies concluded that the observed differences were due to merging of synergies. First of all, the number of synergies seems to be dependent on walking speed (21, 35). Although the composition seems to be similar across walking speeds, the activity of individual muscles change depending on walking speed (35). For example, in healthy adults the increase of walking speed coincides with decreased weightings of the M. Gluteus Medius (35). The observed changes in muscle synergies seemed to be related to changes in kinematic and kinetic output depending on the walking speed (35). Second, variations were observed concerning the walking surface: over ground walking, treadmill walking and split-belt treadmill walking. Further research is necessary comparing different walking surfaces since some studies conclude that although, temporal gait parameters and kinematic parameters are quite similar when walking on a treadmill, muscle activation used to achieve movement patterns are often different compared to over ground walking (36-38). On a treadmill, there is for example a constraint space and less power generation during push off due to the continuous motion generated by the treadmill which leads to compensation, implicating that there is a manifestation of increased or decreased muscle activation. Third, the amount of muscles included in the analysis seems to be a crucial factor for investigating muscle synergies. When a low amount of muscles are being investigated, there is less merging of synergies. At last, some study-related practicalities of the EMG signal might be the cause for a lack of merging. Both the normalization technique of the EMG signal and electrode placing varied between studies or was not mentioned. Since subcutaneous fat reduces the transmitted signal (39), it is very important to use a standardized protocol for electrode placing such as the SENIAM guidelines (40).

Muscle synergy analyses can be a powerful tool for assessing and classifying neurological deficits compared to healthy adults. However, more standardized research is necessary to implement this in clinical practice. The influence of age was ignored since muscle synergies are not dependable on age (41). This confirms that muscle synergies are motor primitives, which means they are hard wired into the motor neuronal network. Yet, spinal activities on the other hand, are impressionable by age (41). The age independence of muscle synergies gives synergies an advantage for assessments in longitudinal studies and longitudinal treatment-observations. However, more research should be conducted to examine if these synergies, which are not dependable on age, differ between sub-acute and chronic stroke patients. Since we assume that in healthy adults synergies do not change over time, new questions can be raised: Does neural plasticity have an influence on these mechanisms? Will synergies change depending on the recovery phase of a patient? Is there a sensitive period when intensive rehabilitation can lead to the regaining of synergies and therefore normal motor behavior, and to these changes persist? Since only two studies examined sub-acute stroke patients (25, 29) and no studies conducted repeated measurement to investigate a recovery process during the period when most recovery gains in body functions and activities are observed, it is impossible to take conclusions

regarding the effect of time post stroke on muscle synergies and the functional impact of altered synergies on walking behavior.

Study Limitations

There are some limitations to consider. Due to the limited amount of research, studies with different protocols were compared to each other. As already mentioned, different walking protocols, walking speeds, time post stroke and normalization methods were compared. Therefore, differences in results are not unlikely. In addition, stroke leads to a very broad range of impairments. Some patients have clear sensory problems while others solely have muscle weakness, spasticity or a combination. Examining all these different impairments as one might be the cause of the great diversity seen in the amount and composition of muscle synergies. These limitation should be taken into considerations.

Conclusion

The purpose of this study was to identify the number of muscle synergies and the distribution of muscle weightings during walking in healthy subjects and post-stroke patients. We were able to abstract a number of four synergies in over 70% of the included healthy population, to a lesser extent five synergies were present. In stroke survivors, the amount and composition of muscle synergies in the non-paretic limb was comparable to those of healthy adults. Concerning the paretic limb, a smaller amount of muscle synergies was observed with the majority of patients having three or four synergies. Evidence was found for the merging of synergies, often seen in hip/knee extensors with plantar flexors and hip/knee extensors with knee flexors. A larger number of synergies was associated with intact motor function.

Acknowledgments

Conflict of interest:

The authors have no conflicts of interest to declare.

Declaration of Sources of Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

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Figure legends

Figure 1. Flow Chart

Table legends (#6)

1. Table 1: Newcastle – Ottowa Quality Assesment Scale – Case-control studies
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Reference	Selection (Max. 4 stars)				Comparability (Max. 2 stars)		Exposure (Max. 3 stars)			Total score	AHRS score
	S1	S2	S3	S4	C1	C2	E1	E2	E3		
Allen et al., 2013 (20)	*			*	*		*	*	*	6/9	Fair
Barroso et al., 2017 (28)	*			*	*	*	*	*	*	7/9	Fair
Clark et al., 2009 (21)	*			*	*		*	*	*	6/9	Fair
Coscia et al., 2015 (22)	*	*		*	*	*	*	*	*	8/9	Good
Gizzi et al., 2011 (25)	*			*	*	*	*	*	*	7/9	Fair
Kautz et al., 2011 (23)	*			*	*		*	*	*	6/9	Fair
Routson et al., 2013 (26)	*	*		*	*		*	*	*	7/9	Good
Srivastava et al., 2016 (24)	*			*	*	*	*	*	*	7/9	Fair

S1: Case definition; S2: Representativeness of cases; S3: Selection of controls; S4: Definition of controls; C1/C2: Comparability of cases and controls/confounding; E1: Ascertainment of exposure; E2: Method of ascertainment for cases and controls; E3: Non-response rate; AHRS: Agency of Healthcare Research standards

Table 1: Newcastle – Ottawa Quality Assessment Scale – Case-Control Studies

Reference	Selection (Max. 4 stars)				Comparability (Max. 2 stars)		Outcome (Max. 3 stars)		Total score	AHRS score
	S1	S2	S3	S4	C1	C2	O1	O2		
Hashiguchi et al., 2016 (29)	*	*	*		*		**	*	7/9	Fair
Shiavi et al., 1987 (27)	*				*		**		4/9	Poor

S1Representativeness of sample; S2: Sample size; S3: Non-respondents; S4: Ascertainment of exposure; C1/C2: Comparability of cases and controls/confounding; O1: Assessment of outcome; O2: Statistical test; NOS: Newcastle-Ottawa Scale; AHRS: Agency of Healthcare Research standards

Table 2: Newcastle – Ottawa Quality Assessment Scale – Adapted for cross sectional studies

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Reference	Design	Sample		Walking protocol	EMG
		Stroke	Healthy		
Allen et al., 2013 (20)	Case-control	M: 7 / F:4 R: 6 / L: 5 Age: 62.2 ± 11.7 TPS: 3.5 ± 2.7 y	M: 2 / F: 12 Age: 63.1 ± 9.1 y	Split-belt TM: 30 s	• Ag/AgCL surface electrodes • NNMF: high-pass filtering at 40 Hz, demeaning, rectification and low-pass filtered at 4 Hz (4th order Butterworth filter)
Barroso et al., 2017 (28)	Case-control	M: 6 / F: 3 R: 4 / L: 5 Age: 53 y TPS: 75.56 m		OG at SS: 10 x 11 m	• NNMF: high-pass filtering at 20 Hz, demeaning, rectification and low-pass filtering at 5 Hz
Clark et al., 2009 (21)	Case-control	M: 35 / F: 20 R: 21 / L: 34 Age: 59.5 ± 11.7 y	M: 4 / F: 16 Age: 59.5 ± 11.7 y	Split-belt TM: 30 s (3 x SS and 2 x FC)	• NNMF: high-pass filtering at 40 Hz, demeaning, rectification and low-pass filtering at 4 Hz (4th order Butterworth filter)
Coscia et al., 2015 (22)	Case-control	M: 9 / F: 3 R: 5 / L: 7	N = 10 (gender- and age-matched)	TM: 0.5, 0.7, 0.9 and 1.1 km/h	• Ag/AgCL surface electrodes • NNMF: Full wave rectification, lowpass filtering (4th order Butterworth filter) at 10Hz
Gizzi et al., 2011 (25)	Case-control	M: 8 / F: 2 R: 8 / L: 2 Age: 45.9 ± 16.5 TPS: 12 ± 5 w	M: 7 / F: 3 Age: 42.2 ± 14.5 y	OG at SS: 5 x 6 m	• Ag/AgCL surface electrodes • NNMF: bandpass filtering (8 order Bessel filter, bandwidth 10-750Hz), sampled at 2048Hz, and analog-to-digitally converted on 12Bits
Hashiguchi et al., 2016 (29)	Cross-sectional	M: 10 / F: 3 Age: 58 ± 13.2 y TPS: 66.8 ± 24.2 days		OG at SS: 2 x 10 m (with or without cane)	• NNMF: bandpass-filtering 20-250 Hz, rectification and low-pass filtering at 10 Hz
Kautz et al., 2011 (23)	Case-control	M: 36 / F: 20 R: 20 / L: 36 Age: 61.0 ± 12.3 y TPS: 5.1 ± 5.6 y	M: 2 / F: 15 Age: 65.1 ± 10.4 y	Split-belt TM at SS: 3 x 30 s OG at SS (3x)/ FC (2x): 4.8 m	• Ag/AgCL surface electrodes • NNMF: high-pass filtering at 40 Hz, debiasing, rectification and smoothing at 4 Hz (4th order Butterworth filter)
Routson et al., 2013 (26)	Case-control	N = 28 TPS: 6 m – 5 y	N= 19 (age-matched)	TM at SS	• 16-channel EMG system at 2000z bilaterally • NNMF: high-pass filtering at 40 Hz, de-meaned, low pass filtering at 10 Hz (4th order Butterworth filter)
Shiavi et al., 1987 (27)	Cross-sectional	N = 12 R: 7 / L: 5 TPS measurement 1: 1-10 w TPS measurement 2: 6-24 m		OG at SS (with cane)	• Bandpass-filtering at 40 Hz (4th order Butterworth filter) and lowpass filtering at 400 Hz (2nd order Butterworth filter)
Srivastava et al., 2016 (24)	Case-control	M: 9 / F: 3 R: 5 / L: 7 TPS: >3 m	Gender- and age-matched	OG at SS	• NNMF: high-ass filtering at 20 Hz, rectification and low-pass filtering at 6 Hz (2nd order Butterworth filter)

M: male; F: female; R: right; L: left; y: years; m: months; w: weeks; n: amount; TPS: time post stroke; SS: self-selected speed; FC: fastest comfortable speed; TM: treadmill; OG: over ground; m: meter; s: seconds; EMG: electromyography; NNMF: nonnegative matrix factorization; Hz: hertz; Ag/AgCl: Silver/Silver-Chloride

Table 3: Study characteristics

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Reference	Muscles															Muscles measured
	TA	SOL	GAS	RF	VM	VL	BF	MH	LH	Gmed	Gmax	PL	AL	TFL	ES	
Allen et al., 2013 (20)	S3	S2	S2	S1		S1		S4	S4	S1						8
Clark et al., 2009 (21)	S3	S2	S2	S1 S3	S1			S4	S4	S1						8
Coscia et al., 2015 (22)	S3	S2	S2	S1 S3	S1 S3		S1 S3		S1 S3	S1	S1	X	S3	S1		12
Gizzi et al., 2011 (25)	S3	S2	S2	S3		S3	S4				S1				X	8
Kautz et al., 2011 (23)	X	X	X	X	X			X	X	X						8
Routson et al., 2013 (26)	S3	S2	S2	S1 S3	S1			S4 S1	S4 S1	S1						8
Shiavi et al., 1987 (27)	S2	S1	S1	S2				S2								5
Srivastava et al., 2016 (24)	S2	S1	S1	S2 S3	S3	S3	S4	S4		S3						9

TA: tibialis anterior; SOL: soleus; GAS: gastrocnemius; VM: vastus medialis; VL: vastus lateralis; RF: rectus femoris; MH: medial hamstrings; LH: lateral hamstrings; Gmed: gluteus medius; Gmax: gluteus maximus; BF: biceps femoris; PL: peroneus longus; ST: semitendinosus; AL: adductor longus; TFL: tensor fascia latae; ES: erector spinae;

S1-S4: synergy 1-4 as mentioned in the studies; X = muscle measured

Consensus synergies review:

1) Blue: synergy 1 = GM + RF + VL
2) Orange: synergy 2 = SOL + GAS
3) Yellow: synergy 3 = TA (+RF)
4) Green: synergy 4 = Hamstrings
5) No colours: no distribution of synergies mentioned in the studies

Table 4: Amount and distribution of muscle synergies in healthy adults

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Reference	Muscles															Muscles measured
	TA	SOL	GAS	RF	VM	VL	BF	MH	LH	Gmed	Gmax	PL	AL	TFL	ES	
Allen et al., 2013 (20)	S3	S1	S1	S1 S2		S1 S2		S2	S2	S1 S2						8
Barroso et al., 2017 (28)	X	X	X	X		X	X			X	X		X	X	X	11
Clark et al., 2009 (21)	S2	S1	S1	S1 S2 S3	S1 S3			S3	S3	S3						8
Coscia et al., 2015 (22)	S3	S2	S2	S1 S3	S1 S3		S1 S3		S1 S3	S1	S1	X	S3	S1		12
Gizzi et al., 2011 (25)	S4	S2 S3	S2	S3		S2 S3	S2 S1				S1				X	8
Hashiguchi et al., 2016 (29)	X	X	X	X	X		X		X							7
Kautz et al., 2011 (23)	X	X	X	X	X			X	X	X						8
Routson et al., 2013 (26)	S4	S2 S3	S2 S3	S1 S2	S1 S2			S1 S3	S1 S3	S1 S2						8
Shiavi et al., 1987 (27)	S1	S2	S2	S1				S1								5
Srivastava et al., 2016 (24)	S2	S1	S1	S2 S3	S3	S3	S4	S4		S3						9

TA: tibialis anterior; SOL: soleus; GAS: gastrocnemius; VM: vastus medialis; VL: vastus lateralis; RF: rectus femoris; MH: medial hamstrings; LH: lateral hamstrings; Gmed: gluteus medius; Gmax: gluteus maximus; BF: biceps femoris; PL: peroneus longus; ST: semitendinosus; AL: adductor longus; TFL: tensor fascia latae; ES: erector spinae;

S1-S4: synergy 1-4 as mentioned in the studies; X = muscle measured

Consensus merged synergies review:

1) *Orange: merged synergy 1 = SOL + GAS + Gmed + Quadriceps*
2) *Green: merged synergy 2 = Hamstrings + Gmed + Quadriceps*
3) *Yellow: synergy 3a = TA (+RF)*
4) *Blue: synergy 3b = SOL + GAS + Hamstrings*
5) *No colours: no distribution of synergies mentioned in the studies*

Table 5: Amount and distribution of paretic muscle in stroke survivors

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Synergy	Muscle group	Muscles	Time gait cycle	Function
S1	Hip abductors and hip/knee extensors	M. Gluteus medius M. Rectus femoris M. Vastus Lateralis (M. Gluteus maximus)	Early stance	• Early stance breaking • Body support during weight acceptance • Controlling contralateral leg swing
S2	Plantar flexors	M. Soleus M. Gastrocnemius	Late stance	• Body support • Forward propulsion • Swing initiation
S3	Dorsal flexors (knee extensors)	M. Tibialis Anterior M. Rectus femoris	Early swing	• Ground clearance of foot
S4	Hamstrings	M. Semimembranosus (medial head) M. Semitendinosus (lateral head) M. Biceps femoris	Late swing into early stance	• Deceleration of the leg at end of swing (controlling leg in swing) • Controlling forward propulsion of body during early stance
Synergy	Muscle group	Muscles	Time gait cycle	Impairments
MS1	Hip abductors, hip/knee extensors and plantar flexors (S1 + S2)	M. Gluteus medius M. Rectus femoris M. Vastus Lateralis (M. Gluteus maximus) M. Soleus M. Gastrocnemius	Stance	• Reduction of forward propulsion generation • Breaking due to prolonged activity S1 and too early activity S2 • Altered paretic leg swing • Extensor synergy
MS2	Hip abductors, hip/knee extensors and Hamstrings (S1 + S4)	M. Gluteus medius M. Rectus femoris M. Vastus Lateralis (M. Gluteus maximus) M. Semimembranosus (medial head) M. Semitendinosus (lateral head) M. Biceps femoris	Swing into late stance	• Forward propulsion, body support and ipsilateral swing leg affected • Impedes body support: flexion of the knee instead of extension of hip • M. Gluteus Medius decelerates the leg swing while knee extensors act to accelerate. Hamstrings potential to decelerate prior to heel strike was reduced. • Stiff knee gait
MS3a	Dorsal flexors with/without knee extensors (S3)	M. Tibialis Anterior M. Rectus femoris	TA: during stance TA+RF: swing	• Decreased forward propulsion
MS3b	Plantar flexors and Hamstrings (S2+S4)	M. Soleus M. Gastrocnemius M. Semimembranosus (medial head) M. Semitendinosus (lateral head) M. Biceps femoris		• Increased step length • Propulsion asymmetry • Slower walking speed • Decreased pre-swing angle
S: synergy, MS: merged synergies, M: musculus, TA: Tibialis Anterior, RF: Rectus Femoris,				

Table 6: Composition and function of muscle synergies in healthy adults and merged synergies in stroke patients