Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in
Biomedical Engineering

Are muscle synergies useful for stroke rehabilitation?

Yoon No Gregory Hong[1], Anjan Nagesh Ballekere[1], Benjamin J. Fregly[2] and Jinsook Roh[1]

Abstract
Modular organization of human movement has been studied for several decades using muscle synergy analysis. Whether the reduction in control dimensionality calculated by muscle synergy analysis is of neural origin or only a mathematical construct remains controversial. Nonetheless, sufficient empirical evidence exists to support the potential utility of muscle synergy analysis for assessing and treating motor impairment. This article reviews recent advances in the use of muscle synergy analysis to assess poststroke motor impairment, assess stroke rehabilitation effectiveness, and design stroke rehabilitation approaches. Synergy-based rehabilitation strategies that attempt to correct impaired neuromuscular coordination have emerged only recently. Expansion of this promising area will likely require integration of muscle synergy concepts, patient-specific neuromusculoskeletal models, and rehabilitation robotics to identify optimal synergy changes and implement effective poststroke training protocols that induce them.

Addresses
[1] Department of Biomedical Engineering, Cullen College of Engineering, University of Houston, Houston, TX, USA
[2] Department of Mechanical Engineering, Rice University, Houston, TX, USA

Corresponding author: Roh, Jinsook (jroh@uh.edu)

Current Opinion in Biomedical Engineering 2021, **19:**100315

This review comes from a themed issue on **Novel Biomedical Technologies; Advances in diagnostic and theranostic systems for disease treatment**

Edited by **Nicholas Peppas** and **Marissa Wechsler**

For complete overview of the section, please refer the article collection - Novel Biomedical Technologies; Advances in diagnostic and theranostic systems for disease treatment

Received 14 November 2020, revised 20 April 2021, accepted 15 June 2021

https://doi.org/10.1016/j.cobme.2021.100315

2468-4511/

Keywords
Muscle synergies, Stroke rehabilitation, Rehabilitation robotics, Neuromusculoskeletal models, Motor coordination.

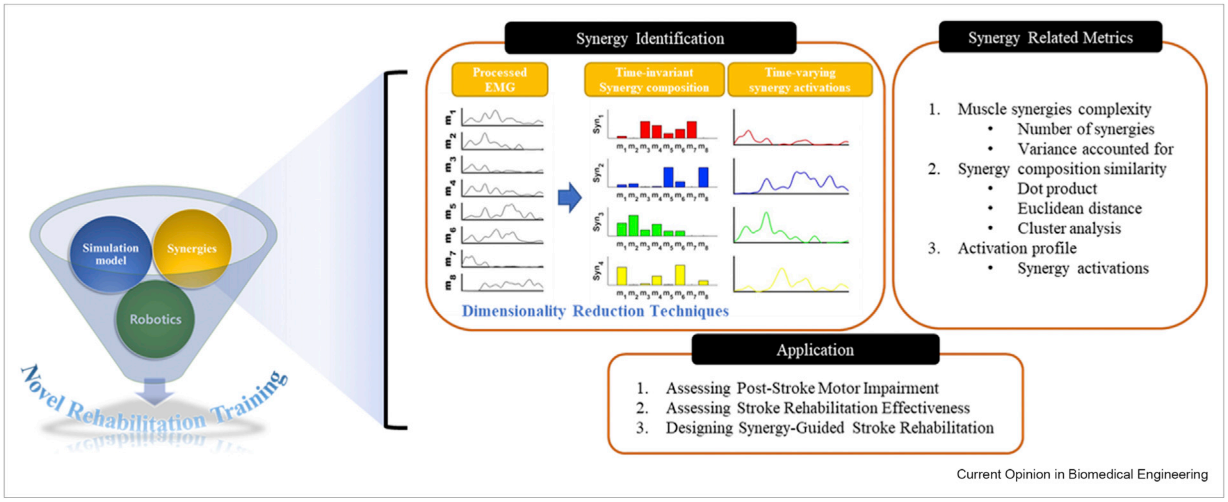
Introduction

Muscle synergy analysis has been used to investigate how the central nervous system coordinates movement in healthy individuals and in individuals after stroke [1–4]. The analysis involves a dimensionality reduction technique, where the most common method decomposes a large number of measured muscle excitations into a smaller number of time-invariant muscle synergy vectors (or motor modules) and corresponding time-varying synergy activations (or activation profiles) that define how each synergy activation contributes to all muscle excitations (Figure 1). Conceptually, muscle synergies can be viewed as coactivation patterns of groups of muscles that can be combined to produce a variety of motor behaviors. Whether muscle synergies possess a neural origin or are only mathematical constructs remains controversial, as decades of studies have yet to either verify or nullify the neural origin hypothesis [5]. Regardless of this ongoing controversy, the concept of modular organization has been proven useful for studying human motor control [6–8] and may also be useful for stroke rehabilitation research [9].

The goal of stroke rehabilitation is to induce favorable neuroplasticity to improve patient movement function. At least two approaches can be followed to achieve this goal. The first approach focuses on changing the patient's kinematic coordination with the hope that beneficial changes in the patient's neuromuscular coordination will result [10,11]. The second approach is the reverse, focusing on changing the patient's neuromuscular coordination with the hope that beneficial changes in the patient's kinematic coordination will result [12,13]. A good example of the first approach is the commonly used 'task-specific training' paradigm, which focuses on achieving desired kinematic trajectories. The vast majority of stroke rehabilitation research has followed the first approach, with little research being performed to date using the second. However, the second approach is more consistent with the assumption that if a patient's neuromuscular coordination (i.e., the cause) can be 'fixed,' then the patient's kinematic coordination (i.e., the consequence) will be fixed as well. Muscle synergies may provide a novel avenue for implementing this alternative focus.

This study reviews how muscle synergy analysis has been applied to stroke rehabilitation with the goal of assessing whether muscle synergy concepts may be helpful for assessing poststroke impairment or stroke rehabilitation effectiveness, as well as for designing stroke rehabilitation approaches that target changes in neuromuscular coordination. A literature search was conducted using PubMed databases for articles published from 2015 to 2020 containing combinations of selected keywords, including 'muscle synergy', 'muscle coordination', 'EMG (electromyogram) controlled', 'EMG', 'assessment', 'rehabilitation', 'training', 'stroke',

Figure 1



Stroke rehabilitation may benefit from the integration of muscle synergy concepts, patient-specific neuromusculoskeletal models, and rehabilitation robotics to identify optimal synergy changes and implement effective poststroke training protocols.

and 'motor module.' A few articles outside of this period and database were also included in the review to avoid omitting noteworthy articles that are relevant to this review. Our review suggests that combining muscle synergy concepts, personalized neuromusculoskeletal modeling, and rehabilitation robotics could be a promising direction for stroke rehabilitation research. The combination could potentially allow researchers to train the specific aspects of neuromuscular coordination that would produce the greatest improvements in movement function.

Synergies for assessing poststroke motor impairment

Muscle synergy analysis has been used to assess motor impairment after stroke. In the present review, most studies reported that impaired upper or lower limb function after stroke is related to changes in time-invariant synergy properties (Figure 1), such as the number of synergies underlying investigated motor function [2,4,14–17], the muscular composition of the synergies [2,18–24], and a specified level of variance accounted for by a certain number of synergies (VAF) achieved by a fixed number of synergies [15,25] (Table 1). Several studies, however, also reported that time-varying synergy activations also changed after stroke [2,4,14,18,19,21,23,24].

Interestingly, recent cross-sectional studies have reported that stroke alters the number of muscle synergies mainly in the lower extremity (LE) but less frequently in the upper extremity (UE) (Table 1). For example, fewer muscle synergies were identified during walking [4] and cycling [14] in the paretic than in the nonparetic lower limb of chronic and subacute stroke survivors, respectively. These results reflected an overall reduction in control complexity and poorer walking performance. In the upper limb, one of the first studies in poststroke muscle synergy quantification also found a change in the number of synergies due to merging or fractionation of normal muscle synergies during arm movement, especially in severely impaired stroke survivors [2]. Relatively, recent UE studies in subacute and chronic stroke survivors, however, reported alterations in muscle synergy composition [2,18–22] and/or synergy activations [2,18,19,21], instead of the number of synergies, as markers of motor impairment during reaching or isometric force generation. Differences in which aspects of muscle synergies are altered after stroke may reflect differences in the neuromuscular control capabilities in the upper and lower limbs.

Recent cross-sectional studies have also reported that merging of two or more normal muscle synergies can contribute to a reduced number of muscle synergies after stroke. Synergy merging in the LE tends to be associated with decreased biomechanical functions such as reduced walking speed and symmetry [17], impaired function of the plantar flexors in generating propulsion [15], or altered preferred walking speed [4]. Synergy merging could be attributed to altered synergy activations viewed as descending commands [26], reflecting reduced independent neural control rather than changes in the muscular composition of normal synergies.

Regardless of which synergy-related parameters are altered after stroke, in the present review, recent studies have consistently argued that the poststroke alterations in muscle synergies correlate to impairment in biomechanical performance and/or clinical assessments. In the

Table 1

Assessment of poststroke motor impairment.

Article	Body part	Group (number of subjects)	Time after stroke onset	Severity of motor impairment	Task	Altered muscle synergy after stroke[a]	Association with motor function/ clinical assessment
Israely et al., 2018	UE	H (12) S (13)	Subacute	Mild	Reaching	SC, SAP	N/A
Pan et al., 2018	UE	H (25) S (35)	Subacute	Moderate to severe	Reaching	SC	Yes
Cheung et al., 2012	UE	S (31)	Subacute + chronic	Mild to severe	Reaching	Num, SAP	Yes
Li et al., 2017	UE	H (9) S (10)	Subacute + chronic	Moderate to severe	Reaching	SC, SAP	Yes
Roh et al., 2015	UE	H (6) S (24)	Chronic	Severe	Isometric force generation	SC, SAP	Yes
Wang et al., 2020	UE	H (15) S (15)	N/A	Mild to moderate	Reaching and grasping	SC	Yes
Ambrosini et al., 2016	LE	H (12) S (16)	Subacute	Mild to moderate	Walking and cycling	Num, SAP	Yes
Ji et al., 2018	LE	H (20) S (22)	Subacute + chronic	N/A	Walking	Num, VAF	Yes
Allen et al., 2019	LE	H (8) S (9)	Chronic	Moderate to severe	Walking and balancing	Number of shared synergies	Yes
Barroso et al., 2017	LE	S (9)	Chronic	Mild to moderate	Walking	VAF	Yes
Clark et al., 2010	LE	H (20) S (55)	Chronic	Mild to severe	Walking	Num, SAP	Yes
de Kam et al., 2018	LE	H (9) S (10)	Chronic	Mild to moderate	Balancing	SC, SAP	Yes
Brough et al., 2019	LE	H (17) S (56)	N/A	N/A	Walking	Num	Yes
Yang et al., 2019	LE	H (12) S (33)	N/A	Mild to severe	Sit to stand	SC, SAP	Yes

UE, upper extremity; LE, lower extremity; S, stroke; H, healthy; Num, number of muscle synergies; SAP, synergy activation profile; SC, synergy composition; VAF, variance accounted for by a certain number of synergies; N/A, not available.
[a] Altered muscle synergies after stroke can induce either positive or negative effects on motor functionality.

upper limb, alterations in muscle synergies after stroke were correlated with peak velocity/duration of reaching, as well as the UE Fugl−Meyer Assessment (FMA) score [2,19,21] or Brunnstrom stage [20]. In the lower limb, alterations in muscle synergies tended to relate to impairments of walking speed [16], step length or time symmetry [16], and step width [16], as well as direction-specific postural instability [17,23]. Furthermore, recent studies proposed combining muscle synergy-related parameters with biomechanical parameters or machine learning principles to quantify motor functions after stroke [22,24,25]. Overall, these studies have provided experimental evidence that the results of muscle synergy analysis exhibit significant correlations with various aspects of motor function and neuromechanical quantities in a variety of motor tasks in the UE and LE after stroke.

Although the current literature supports the correlation between alterations in poststroke muscle synergies and standardized clinical assessment scores (e.g., FMA), whether muscle synergy analysis is more useful than conventional clinical metrics for assessing stroke severity remains unclear. One may argue that the outcomes of muscle synergy analysis could have the potential to objectively guide a new therapeutic intervention by providing a novel rehabilitation target through visualizing which aspects of intermuscular coordination are affected by stroke or improved by the intervention. As a previous review noted, a limited number of studies have focused on how to use muscle synergies in a task space [27], which suggests that the usability of muscle synergy analysis still provides potentially important unexplored research questions.

Synergies for assessing stroke rehabilitation effectiveness

Recent studies have reported that a variety of rehabilitation interventions have the potential to improve motor function and induce alterations in synergy-related parameters (Table 2). Characteristics of the synergy-related parameters were not the same between studies because of the differences in tasks, interventions, and synergy analysis methods used. However, an improvement in synergy complexity — such as an increase in the number of synergies underlying motor performance or the decrease in the VAF achieved by a single synergy — was observed as a general trend after applying an intervention. For example, the number of synergies tended to increase after regular rehabilitation, robot-assisted therapy, Wii-based movement therapy, high-intensity exercise, or locomotor training [10,11,28–32] in both UE and LE, respectively, in subacute or chronic stroke survivors. However, some subjects did not show an increase in the number of synergies in these studies. At baseline, the majority of poststroke subjects tended to have a number of muscle synergies comparable with those of healthy controls and had relatively higher motor function within the same group [30]. In addition, the total number of muscle synergies did not change consistently after intervention because of merging and fractionation of muscle synergies, which would decrease and increase the number of synergies, respectively [32]. The VAF for a fixed number of synergies also tended to decrease over the recovery period and become closer to that of control subjects [11,29]. Alternatively, even without a change in the number of synergies, the portion of the total variance of poststroke muscle excitations, accounted for by fitting normal muscle synergies, significantly increased from pre-training to post-training, suggesting that muscle synergies became more normalized after the intervention [33]. In addition, the most compromised muscle synergies pre-training [33] often changed the most toward healthy muscle synergies after the intervention. Furthermore, a Wii-based movement therapy induced more diversity in muscle synergy composition [30].

Changes in synergy-related parameters due to an intervention have been associated with alterations in biomechanical function and/or clinical assessment. In the UE, as the number of muscle synergies increased, movements became smoother and faster after a robot-assisted therapy [28] or the phases of movement became more distinct after Wii-based movement therapy [30]. In the LE, significant improvements in gait measures were positively associated with an increase in the number of muscle synergies [10,11,31,32] and the similarity of muscle synergies to normal ones [10,30,31,33]. More specifically, previous studies have reported that while a compromised muscle synergy composition would likely change after intervention toward that of healthy controls, a muscle synergy composition at baseline similar to that of healthy controls tended to be preserved [30,33]. Another study

Table 2

Assessment of rehabilitation effectiveness.

Article	Body part	Group (number of subjects)	Time after stroke onset	Impairment severity before intervention	Intervention	Intervention duration [weeks]	Motor function improvement	Affected muscle synergies by intervention[a]	Direct association with motor function/ clinical score improvement
Alnajjar et al., 2019	UE	H (9) S (10)	Subacute	Moderate	Regular rehabilitation program	11	Yes	Num, VAF	N/D
Pierella et al., 2020	UE	H (6) S (6)	Subacute	Mild to severe	Conventional therapy + robot-assisted therapy	4	Yes	Num, SC	Yes
Hesam-Shariati et al., 2017	UE	S (30)	Chronic	Mild to moderate	Wii-based movement therapy	10	Yes	Num, SC	Yes
Tan et al., 2018	LE	S (8)	Acute	Severe	Robot-assisted walking training	3	Yes	Num, SC	Yes
Ambrosini et al., 2020	LE	H (12) S (9)	Subacute	Mild to moderate	FES cycling	3	Yes	VAF, SC	Yes
Hashiguchi et al., 2016	LE	S (13)	Subacute	Mild to moderate	Inpatient rehabilitation program	4	Yes	Num, SC	Yes
Ardestani et al., 2019	LE	S (15)	Subacute + chronic	–	High-intensity stepping training	8–10	Yes	Num, VAF	No
Routson et al., 2013	LE	H (19) S (27)	Chronic	Moderate to severe	Locomotor training program	12	Yes	Num, SC, SAP	Yes

UE, upper extremity; LE, lower extremity; S, stroke; H, healthy; Num, number of muscle synergies; VAF, variance accounted for by a certain number of synergies; SC, synergy composition; SAP, synergy activation profile; N/D, not determined.

[a] Muscle synergies affected by intervention in this table can induce positive effects on motor functionality.

reported that for subjects who had the same number of muscle synergies before intervention compared with healthy controls, synergy activation profiles became similar after intervention to those of healthy controls. However, subjects who had a smaller number of muscle synergies before intervention showed that, although their number of muscle synergies increased, they still exhibited synergy activation after intervention [10]. Overall, these findings indicate that a variety of rehabilitation interventions have the potential to influence the modular organization of neuromuscular coordination based on various mechanisms, which can induce improvements in UE and LE motor performance.

Few studies involving subacute and chronic stroke survivors have shown that intersubject variability in synergy-related parameters changes due to a rehabilitation intervention [30,32]. Intersubject variabilities in these longitudinal studies may be attributed to the between-patient differences in pretraining neurophysiological conditions (e.g., lesion type, location, or size), severity of motor impairment, and time after stroke onset. In this case, the results of muscle synergy analysis, identified as a group effect of rehabilitation intervention, might not be experienced by certain individuals after stroke. Thus, to optimize rehabilitation effects for individuals after stroke, future synergy-guided studies may want to consider developing more tailored, personalized rehabilitation interventions.

A multimodal approach (e.g., involving simultaneous recording of brain, muscular, and kinematic data) became more widely used not only for the quantification of poststroke motor impairment in cross-sectional studies [22,24] but also for the development of more comprehensive, complete patient quantification in longitudinal studies [28]. Considering that precision of current clinical scales has been challenged because of inter-rater and intra-rater reliability [34,35], merging of neuromusculoskeletal data and analyses will be more prevalent as a future research direction for more complete quantification of rehabilitation effectiveness.

Synergies for designing stroke rehabilitation approaches

The two previous sections support the idea that poststroke motor impairments in the UE and LE are associated with quantifiable changes in an individual's muscle synergies. In addition, these synergy-related parameters are altered and could affect motor function during any intervention although their direct relationship after therapy has not yet been proven. Considering that muscle synergies could reflect neuromuscular control impairment after stroke and the extent to which motor recovery is induced by a therapeutic intervention, synergy-based rehabilitation strategies have emerged relatively recently. To our knowledge, in the past five years, only a few studies have tested stroke rehabilitative interventions guided by muscle synergies as a training target [36,37]. Both studies applied synergy-based control strategies to therapeutic functional electrical stimulation (FES) to formulate FES patterns. Although different limbs (upper and lower limbs) were targeted in the studies, the results indicated that synergy-based FES rehabilitation training has the ability to revert the composition of muscle synergies toward normal and enhance motor function after the training.

Besides FES, previous studies have introduced rehabilitation training approaches, such as serious games and virtual reality, to encourage a subject's synergies to become more like those of healthy controls [12,38]. Because the interventions did not directly stimulate muscle activations, these studies have focused on developing effective ways to use muscle synergies as a training target or a control input signal for intervention systems that seek to modify them. The previous study reported that, when the participants were trained to control a visual cursor by projecting the EMG activations of the nondominant arm onto the space formed by two targeted dominant arm muscle synergies and tried to match the targeted locations on that space, the muscle synergy activations but not the pre-existing muscle synergies were modified [12]. Another study introduced a synergy-based virtual reality (VR) interface based on the same research group's previous studies [38]. In their previous works, they demonstrated the feasibility of muscle synergy control (muscle-synergy-to-force mapping) to move a cursor when performing isometric reaching tasks in the VR interface [39]. In addition, when altering the EMG-to-force mapping in the VR interface, adaptations were faster if the composition of muscle synergies remained the same but the synergy activations were modified [40]. They also observed changes of muscle synergies in incompatible conditions [40]. The results of these studies have provided evidence that muscle synergies and/or synergy activations can be changed in response to an intervention [12,40]. However, if the task goal can be achieved by using pre-existing muscle synergies, then alteration of synergy activations would be preferred.

All previous studies used synergies from neurologically intact controls or synergies from the same patient's contralateral limb as a training target who had a stroke (Table 3) [12,36,37]. Previous studies demonstrated that the similarity of muscle synergies after stroke to those of healthy subjects increased as motor function impairment decreased. Furthermore, muscle synergies after stroke tended to become more similar to those of healthy controls or the contralateral limb as a result of training [28,33]. Thus, the 'healthy' or 'healthier' synergies would potentially be promising training targets for stroke rehabilitation. In addition, a previous study showed that subjects who trained using a small number of hand posture synergies performed a new hand posture more accurately than did subjects who trained using a larger number of hand postures [13]. Thus, if the most impaired synergy shared among different biomechanical conditions were targeted for stroke rehabilitation training, the training benefits could potentially extend to a wide range of motor behaviors.

Whether muscle synergies from healthy controls or the nonparetic limb would be optimal targets for effective stroke rehabilitation remains unclear, given that the goal is to maximize improvement in motor function. Owing to the principle of motor abundance [41] and considering the neural damage produced by a stroke, it is possible that abnormal muscle synergies could maximize improvement in motor function even better than could healthy or nonparetic limb muscle synergies. In addition, both muscle synergies and synergy activations could be targeted in a synergy-based intervention because both may be affected by stroke [2,4,14,15,18–25] and both may be changeable through an appropriate intervention [10–12,28–33,36,37]. However, there is currently no way to know which aspects of a particular individual's synergies should be changed, and how, to maximize recovery of lost function.

While an experimental approach to identifying optimal synergy changes for an individual patient would be challenging due to limitations in time, resources, and patient stamina, a computational approach could circumvent these problems. Specifically, patient-specific neuromusculoskeletal models can predict how an individual's muscle synergies should be changed to maximize the recovery of motor function after stroke [41]. Such models can simulate direct cause-and-effect relationships between changes to an individual's muscle synergies and the resultant changes to the individual's movement function. This exciting possibility has come online only in the last few years with improvements in the neuromusculoskeletal model personalization and movement prediction processes [42].

Given these new computational capabilities, patient-specific neuromusculoskeletal models could facilitate an entirely new stroke rehabilitation approach called 'synergy-specific training' as an alternative to 'task-specific training.' Rather than targeting a specific task, this new approach would target a specific synergy, where the target would be defined on an individual patient basis. A movement optimization problem could be formulated to identify an individual patient's 'weakest link' synergy or the synergy that, if changed, would produce the largest improvement in movement function. The optimization problem could be formulated to predict changes in a single synergy activation, a single muscle synergy, or both together. Then, by inputting only the 'fixed' weakest link synergy into the patient's neuromusculoskeletal model and setting all other synergy activations to zero, one could predict the motion produced by the 'fixed' synergy and use that motion to target training of the weakest link synergy. Attempting to train a single synergy could be nonintuitive because it would require performing a coordinated multijoint movement. Nonetheless, the idea is consistent with a recent study reporting that human subjects are capable of voluntarily activating a single muscle synergy under isometric conditions [43].

Rehabilitation robots could be an ideal delivery mechanism for synergy-based stroke rehabilitation prescriptions designed using patient-specific neuromusculoskeletal models. Because of a limited range of motion, decrease in muscle strength, and/or reduction in

Table 3

Development of synergy-guided rehabilitation approaches.

Article	Body part	Group (number of subjects)	Time after stroke onset	Training (intervention system)	Assessment task	Target synergy	Musculoskeletal model-based design
Niu et al., 2019	UE	S (6)	Subacute + chronic	FES	Reaching	Healthy control synergy	No
Berger et al., 2013	UE	H (16)	–	VR interface	Isometric reaching	Adapt different EMG-force mapping	No
Ghassemi et al., 2019	UE	H (20)	–	Human–machine interface	Moving cursor using free arm movement	Contralateral side synergy	No
Patel et al., 2017	UE	H (16)	–	Synergy repetition training	7 basis postural synergies vs 45 hand postures	Basis synergy	No
Ferrante et al., 2016	LE	S (2)	Chronic	FES	Walking	Healthy control synergy	No

UE, upper extremity; LE, lower extremity; S, stroke; H, healthy; FES, functional electrical stimulation; VR, virtual reality.

sensory feedback, stroke survivors typically cannot perform training tasks as desired. However, robotic exoskeletons excel at controlling coordinated multijoint movements and delivering large numbers of training repetitions. They can also fill the gap in the subject's functional capability by providing 'assist-as-needed' control to the individual robot joints, which possess a one-to-one correspondence with the subject's joints. 'Assist-as-needed' control torques would be gradually withdrawn as the subject learns to achieve the desired synergy-specific motion. Previous studies have demonstrated that synergy-based robotic exoskeleton control is feasible for multi-degree-of-freedom motions [44,45] and can produce changes in muscle synergies for both the upper and lower extremities [46–48]. However, no studies have used synergy-based control of a robotic exoskeleton for stroke rehabilitation training. Thus, model-guided synergy-based training is a promising although unexplored area for stroke rehabilitation.

Conclusion

Previous studies have used muscle synergies as a tool to assess poststroke impairment severity and stroke rehabilitation effectiveness and to design novel stroke rehabilitation approaches. Taken as a whole, the reviewed studies suggest that muscle synergies have potential clinical utility, regardless of whether or not they possess a neural origin. If future studies explore the novel concept of synergy-specific training of a weakest link synergy, it will be essential to identify objectively the synergy to be targeted for training, as well as how it should be changed, which will likely require the use of patient-specific neuromusculoskeletal models. By using robotic exoskeletons as a training delivery mechanism, researchers may be able to perform model-guided synergy-based training that can improve targeted aspects of a stroke survivor's neuromuscular coordination.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yoon No Gregory Hong: Data curation, Visualization, Writing – original draft, Writing – review & editing. **Anjan Nagesh Ballekere:** Data curation, Visualization. **Benjamin J. Fregly:** Conceptualization, Writing – review & editing. **Jinsook Roh:** Conceptualization, Supervision, Writing – review & editing.

Acknowledgements

This study was supported by the American Heart Association Scientist Development Grant (#17SDG33670561).

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Bizzi E, Cheung VCK: **The neural origin of muscle synergies**. *Front Comput Neurosci* 2013. https://doi.org/10.3389/fncom.2013.00051.

2. Cheung VCK, Turolla A, Agostini M, Silvoni S, Bennis C, Kasi P, Paganoni S, Bonato P, Bizzi E: **Muscle synergy patterns as physiological markers of motor cortical damage**. *Proc Natl Acad Sci USA* 2012. https://doi.org/10.1073/pnas.1212056109.

3. Torres-Oviedo G, Ting LH: **Muscle synergies characterizing human postural responses**. *J Neurophysiol* 2007. https://doi.org/10.1152/jn.01360.2006.

4. Clark DJ, Ting LH, Zajac FE, Neptune RR, Kautz SA: **Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke**. *J Neurophysiol* 2010. https://doi.org/10.1152/jn.00825.2009.

5. Tresch MC, Jarc A: **The case for and against muscle synergies**. *Curr Opin Neurobiol* 2009. https://doi.org/10.1016/j.conb.2009.09.002.

6. Ivanenko YP, Poppele RE, Lacquaniti F: **Motor control programs and walking**. *Neuroscientist* 2006. https://doi.org/10.1177/1073858406287987.

7. D'Avella A, Giese M, Ivanenko YP, Schack T, Flash T: **Editorial: modularity in motor control: from muscle synergies to cognitive action representation**. *Front Comput Neurosci* 2015. https://doi.org/10.3389/fncom.2015.00126.

8. D'Avella A, Portone A, Fernandez L, Lacquaniti F: **Control of fast-reaching movements by muscle synergy combinations**. *J Neurosci* 2006. https://doi.org/10.1523/JNEUROSCI.0830-06.2006.

9. Ting LH, Chiel HJ, Trumbower RD, Allen JL, McKay JL, Hackney ME, Kesar TM: **Neuromechanical principles underlying movement modularity and their implications for rehabilitation**. *Neuron* 2015. https://doi.org/10.1016/j.neuron.2015.02.042.

10. Routson RL, Clark DJ, Bowden MG, Kautz SA, Neptune RR: **The influence of locomotor rehabilitation on module quality and post-stroke hemiparetic walking performance**. *Gait Posture* 2013. https://doi.org/10.1016/j.gaitpost.2013.01.020.

11. Ardestani MM, Kinnaird CR, Henderson CE, Hornby TG: **Compensation or recovery? Altered kinetics and neuromuscular synergies following high-intensity stepping training poststroke**. *Neurorehabilitation Neural Repair* 2019, **33**:47–58. https://doi.org/10.1177/1545968318817825.

12. * Ghassemi M, Triandafilou K, Barry A, Stoykov ME, Roth E, Mussa-Ivaldi FA, Kamper DG, Ranganathan R: **Development of an EMG-controlled serious game for rehabilitation**. *IEEE Trans Neural Syst Rehabil Eng Publ – IEEE Eng Med Biol Soc* 2019, **27**:283–292. https://doi.org/10.1109/TNSRE.2019.2894102.

This study showed that a synergy-based visual guide could change synergy activation profiles and subsequently induce better motor task performance. Even though only neurologically intact participants were evaluated, it provides feasibility of synergy-guided rehabilitation training without electrical stimulations.

13. ** Patel V, Craig J, Schumacher M, Burns MK, Florescu I, Vinjamuri R: **Synergy repetition training versus task repetition training in acquiring new skill**. *Front Bioeng Biotechnol* 2017. https://doi.org/10.3389/fbioe.2017.00009.

This study showed that when shared muscle synergies in various motions were trained, its motor skills could be transferred to execute new motions more compared to when simple task repetitions were trained. The results provide the potential of muscle synergy-based training for facilitating motor learning in neurologically healthy and impaired individuals.

14. Ambrosini E, De Marchis C, Pedrocchi A, Ferrigno G, Monticone M, Schmid M, D'Alessio T, Conforto S, Ferrante S: **Neuro-mechanics of recumbent leg cycling in post-acute stroke patients**. *Ann Biomed Eng* 2016, **44**:3238–3251. https://doi.org/10.1007/s10439-016-1660-0.

15. Ji Q, Wang F, Zhou R, Li J, Wang J, Ye X: **Assessment of ankle muscle activation by muscle synergies in healthy and post-stroke gait**. *Physiol Meas* 2018, **39**:45003. https://doi.org/10.1088/1361-6579/aab2ed.

16. Allen JL, Kesar TM, Ting LH: **Motor module generalization across balance and walking is impaired after stroke**. *J Neurophysiol* 2019, **122**:277–289. https://doi.org/10.1152/jn.00561.2018.

17. Brough LG, Kautz SA, Bowden MG, Gregory CM, Neptune RR: **Merged plantarflexor muscle activity is predictive of poor walking performance in post-stroke hemiparetic subjects**. *J Biomech* 2019, **82**:361–367. https://doi.org/10.1016/j.jbiomech.2018.11.011.

18. Israely S, Leisman G, Machluf CC, Carmeli E: **Muscle synergies control during hand-reaching tasks in multiple directions post-stroke**. *Front Comput Neurosci* 2018, **12**:10. https://doi.org/10.3389/fncom.2018.00010.

19. Li S, Zhuang C, Niu CM, Bao Y, Xie Q, Lan N: **Evaluation of functional correlation of task-specific muscle synergies with motor performance in patients poststroke**. *Front Neurol* 2017. https://doi.org/10.3389/fneur.2017.00337.

20. Pan B, Sun Y, Xie B, Huang Z, Wu J, Hou J, Liu Y, Huang Z, Zhang Z: **Alterations of muscle synergies during voluntary arm reaching movement in subacute stroke survivors at different levels of impairment**. *Front Comput Neurosci* 2018, **12**: 69. https://doi.org/10.3389/fncom.2018.00069.

21. Roh J, Rymer WZ, Beer RF: **Evidence for altered upper extremity muscle synergies in chronic stroke survivors with mild and moderate impairment**. *Front Hum Neurosci* 2015, **9**:6. https://doi.org/10.3389/fnhum.2015.00006.

22. * Wang C, Peng L, Hou Z-G, Li J, Zhang T, Zhao J: **Quantitative assessment of upper-limb motor function for post-stroke rehabilitation based on motor synergy analysis and multi-modality fusion**. *IEEE Trans Neural Syst Rehabil Eng Publ – IEEE Eng Med Biol Soc* 2020, **28**:943–952. https://doi.org/10.1109/TNSRE.2020.2978273.

This study developed a novel assessment approach based on the integration of kinematic and muscle synergy quantification to objectively quantify the upper-limb motor function of post-stroke patients. The multi-modal fusion scheme of the study demonstrated superior performance in classifying post-stroke and healthy movements based on machine learning principles.

23. de Kam D, Geurts AC, Weerdesteyn V, Torres-Oviedo G: **Direction-specific instability poststroke is associated with deficient motor modules for balance control**. *Neurorehabilitation Neural Repair* 2018, **32**:655–666. https://doi.org/10.1177/1545968318783884.

24. Yang N, An Q, Kogami H, Yamakawa H, Tamura Y, Takahashi K, Kinomoto M, Yamasaki H, Itkonen M, Shibata-Alnajjar F, Shimoda S, Hattori N, Fujii T, Otomune H, Miyai I, Yamashita A, Asama H: **Temporal features of muscle synergies in sit-to-stand motion reflect the motor impairment of post-stroke patients**. *IEEE Trans Neural Syst Rehabil Eng Publ – IEEE Eng Med Biol Soc* 2019, **27**:2118–2127. https://doi.org/10.1109/TNSRE.2019.2939193.

25. Barroso FO, Torricelli D, Molina-Rueda F, Alguacil-Diego IM, Cano-de-la-Cuerda R, Santos C, Moreno JC, Miangolarra-Page JC, Pons JL: **Combining muscle synergies and biomechanical analysis to assess gait in stroke patients**. *J Biomech* 2017, **63**:98–103. https://doi.org/10.1016/j.jbiomech.2017.08.006.

26. McMorland AJC, Runnalls KD, Byblow WD: **A neuroanatomical framework for upper limb synergies after stroke**. *Front Hum Neurosci* 2015. https://doi.org/10.3389/fnhum.2015.00082.

27. Alessandro C, Delis I, Nori F, Panzeri S, Berret B: **Muscle synergies in neuroscience and robotics: from input-space to task-space perspectives**. *Front Comput Neurosci* 2013. https://doi.org/10.3389/fncom.2013.00043.

28. ** Pierella C, Pirondini E, Kinany N, Coscia M, Giang C, Miehlbradt J, Magnin C, Nicolo P, Dalise S, Sgherri G, Chisari C, Van De Ville D, Guggisberg A, Micera S: **A multimodal approach to capture post-stroke temporal dynamics of recovery**. *J Neural Eng* 2020, **17**:45002. https://doi.org/10.1088/1741-2552/ab9ada.

This study developed an advanced multivariate methodology that combined clinical evaluations with multimodal instrumental evaluations to provide a more complete characterization of the neuro-biomechanical status of stroke survivors and their changes via rehabilitation protocols.

29. Alnajjar FS, Moreno JC, Ozaki K-I, Kondo I, Shimoda S: **Motor control system for adaptation of healthy individuals and recovery of poststroke patients: a case study on muscle synergies**. *Neural Plast* 2019:8586416. https://doi.org/10.1155/2019/8586416.

30. Hesam-Shariati N, Trinh T, Thompson-Butel AG, Shiner CT, McNulty PA: **A longitudinal electromyography study of complex movements in poststroke therapy. 1: heterogeneous changes despite consistent improvements in clinical assessments**. *Front Neurol* 2017, **8**:340. https://doi.org/10.3389/fneur.2017.00340.

31. Tan CK, Kadone H, Watanabe H, Marushima A, Yamazaki M, Sankai Y, Suzuki K: **Lateral symmetry of synergies in lower limb muscles of acute post-stroke patients after robotic intervention**. *Front Neurosci* 2018, **12**:276. https://doi.org/10.3389/fnins.2018.00276.

32. Hashiguchi Y, Ohata K, Kitatani R, Yamakami N, Sakuma K, Osako S, Aga Y, Watanabe A, Yamada S: **Merging and fractionation of muscle synergy indicate the recovery process in patients with hemiplegia: the first study of patients after subacute stroke**. *Neural Plast* 2016:5282957. https://doi.org/10.1155/2016/5282957.

33. Ambrosini E, Parati M, Peri E, De Marchis C, Nava C, Pedrocchi A, Ferriero G, Ferrante S: **Changes in leg cycling muscle synergies after training augmented by functional electrical stimulation in subacute stroke survivors: a pilot study**. *J Neuroeng Rehabil* 2020, **17**:35. https://doi.org/10.1186/s12984-020-00662-w.

34. Bosecker C, Dipietro L, Volpe B, Igo Krebs H: **Kinematic robot-based evaluation scales and clinical counterparts to measure upper limb motor performance in patients with chronic stroke**. *Neurorehabilitation Neural Repair* 2010. https://doi.org/10.1177/1545968309343214.

35. Harrison JK, McArthur KS, Quinn TJ: **Assessment scales in stroke: clinimetric and clinical considerations**. *Clin Interv Aging* 2013. https://doi.org/10.2147/CIA.S32405.

36. * Niu CM, Bao Y, Zhuang C, Li S, Wang T, Cui L, Xie Q, Lan N: **Synergy-based FES for post-stroke rehabilitation of upper-limb motor functions**. *IEEE Trans Neural Syst Rehabil Eng* 2019, **27**:256–264. https://doi.org/10.1109/TNSRE.2019.2891004.

This study showed that synergy-based FES can change muscle synergy toward the expected form of muscle synergy and enhance motor behavior. The results provide promising evidence of the potential benefits of using synergy-based FES for upper-limb rehabilitation after stroke.

37. Ferrante S, Chia Bejarano N, Ambrosini E, Nardone A, Turcato AM, Monticone M, Ferrigno G, Pedrocchi A: **A personalized multi-channel FES controller based on muscle synergies to support gait rehabilitation after stroke**. *Front Neurosci* 2016, **10**:425. https://doi.org/10.3389/fnins.2016.00425.

38. Berger DJ, D'Avella A: **Towards a myoelectrically controlled virtual reality interface for synergy-based stroke rehabilitation**. In *Biosyst. Biorobotics*; 2017. https://doi.org/10.1007/978-3-319-46669-9_156.

39. Berger DJ, d'Avella A: **Effective force control by muscle synergies**. *Front Comput Neurosci* 2014. https://doi.org/10.3389/fncom.2014.00046.

40. Berger DJ, Gentner R, Edmunds T, Pai DK, D'Avella A: **Differences in adaptation rates after virtual surgeries provide direct evidence for modularity**. *J Neurosci* 2013. https://doi.org/10.1523/JNEUROSCI.0122-13.2013.

41. Latash ML: **The bliss (not the problem) of motor abundance (not redundancy)**. *Exp Brain Res* 2012. https://doi.org/10.1007/s00221-012-3000-4.

42. Meyer AJ, Eskinazi I, Jackson JN, Rao AV, Patten C, Fregly BJ: **Muscle synergies facilitate computational prediction of subject-specific walking motions**. *Front Bioeng Biotechnol* 2016. https://doi.org/10.3389/fbioe.2016.00077.

43. ** Togo S, Imamizu H: **Empirical evaluation of voluntarily activatable muscle synergies**. *Front Comput Neurosci* 2017. https://doi.org/10.3389/fncom.2017.00082.

This study showed that individual muscle synergy extracted by non-negative matrix factorization was voluntarily and independently activatable, which suggests the potential to train individual muscle synergy for a rehabilitation purpose.

44. Lunardini F, Casellato C, D'Avella A, Sanger TD, Pedrocchi A: **Robustness and reliability of synergy-based myocontrol of a multiple degree of freedom robotic arm**. *IEEE Trans Neural Syst Rehabil Eng* 2016. https://doi.org/10.1109/TNSRE.2015.2483375.

45. Lunardini F, Antonietti A, Casellato C, Pedrocchi A: **Synergy-based myocontrol of a multiple degree-of-freedom humanoid robot for functional tasks**. In *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS*; 2019. https://doi.org/10.1109/EMBC.2019.8857809.

46. Rinaldi L, Yeung L-F, Lam PC-H, Pang MYC, Tong RK-Y, Cheung VCK: **Adapting to the mechanical properties and active force of an exoskeleton by altering muscle synergies in chronic stroke survivors**. *IEEE Trans Neural Syst Rehabil Eng Publ - IEEE Eng Med Biol Soc* 2020. https://doi.org/10.1109/TNSRE.2020.3017128.

47. Scano A, Chiavenna A, Caimmi M, Malosio M, Tosatti LM, Molteni F: **Effect of human-robot interaction on muscular synergies on healthy people and post-stroke chronic patients**. *IEEE Int Conf Rehabil Robot* 2017:527–532. https://doi.org/10.1109/ICORR.2017.8009302.

48. Scano A, Chiavenna A, Malosio M, Molinari Tosatti L, Molteni F: **Robotic assistance for upper limbs may induce slight changes in motor modules compared with free movements in stroke survivors: a cluster-based muscle synergy analysis**. *Front Hum Neurosci* 2018, **12**:290. https://doi.org/10.3389/fnhum.2018.00290.