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ORIGINAL RESEARCH

Muscle Synergy Analysis for Clinical Characterization of Upper Limb Motor Recovery After Stroke

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Abstract

Objective: To characterize individuals with stroke who responded or did not respond to upper limb motor treatment by analyzing muscle synergy patterns (similarity, merging, and fractionation).

Design: This study is a secondary analysis of a multicenter randomized controlled trial.

Setting: Inpatients of 2 specialized neurorehabilitation hospitals.

Participants: We enrolled individuals (N=62) with a unilateral first-event ischemic or hemorrhagic stroke and severe-to-mild upper limb motor impairment (Fugl-Meyer Assessment-Upper Extremity score of 5-61, of 66). We excluded people with untreated seizure, severe cognitive, or verbal comprehension impairment.

Interventions: After randomization, individuals were allocated to conventional, virtual reality, or robot-assisted treatment groups (20 sessions, 1 h/d, 5 d/wk, 4wk).

Main Outcome Measures: A blinded assessor performed assessments both before and after the intervention. Surface electromyography recordings from 16 muscles during reaching tasks were collected pre- and post-treatment. We extracted muscle synergy patterns (similarity, merging, and fractionation) of the stroke-affected and unaffected upper limb of each subject.

Results: Overall, individuals improved upper limb motor function (Fugl-Meyer Assessment-Upper Extremity change score=7.14±7.46; P<.001). We identified 34 responders to treatment showing clinically significant improvement (over the Minimal Clinically Important Difference of 5 points on the Fugl-Meyer Assessment-Upper Extremity). The responders showed decreased merging of synergies (P=.016) as compared with the non-responders (P=.025), who conversely showed improved similarity of synergies (P=.006).

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Conclusions: In individuals with stroke undergoing upper limb motor rehabilitation, changes in the synergy merging pattern may serve as a potential marker to distinguish responders from non-responders.

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Upper limb motor impairment affects ∼50% of survivors to a stroke and often persists beyond 6 months from onset, resulting in long lasting limitation of upper limb function.[1,2] Early assessment of upper limb motor impairment is recommended to predict an accurate prognosis of recovery, and to assess objectively the effectiveness of rehabilitation treatments.[3-6] Instrumental assessments are increasingly used to complement the clinical assessment of motor functions.[6] In recent years, muscle synergies (modular patterns generated by linear combination of muscle activations to coordinate voluntary movements[7]) have been explored as a means to characterize the level of upper limb motor impairment after stroke.[8-16] Muscle synergies are extracted by applying decomposition algorithms to surface electromyography (sEMG) signals, recorded while participants perform motor tasks.[17,18] Upper limb motor impairment has been found to be associated with alteration in the organization of these muscle synergy modules.[19,20] More precisely, 3 distinct reorganization patterns have been described after stroke.[11] The first pattern is preservation of modules, which refers to the extraction of similar synergies from both the unaffected and affected upper limb.[11] The modules preservation is explained by quantitative similarity indexes, indicating the similarity between the same module extracted both in the affected and unaffected side.[11] The second pattern is the module merging, with a synergy from the affected limb corresponding to the combination of two or more synergies extracted from the unaffected limb.[11,19] Evidence supports an increasing of merging that corresponds to an increased severity of motor impairment.[21] The third pattern is module fractionation, where 2 or more synergies from the affected limb can be combined to resemble a single synergy extracted from the unaffected limb.[11,19] Fractionation has been reported to positively correlate with time since stroke onset.[11]

Despite relationships between clinical outcomes and muscle synergy patterns reported in the literature,[11,19] evidence of strong relationships is limited. Moreover, no studies applied the muscle synergy analysis to identify the responsiveness to a rehabilitation treatment.

This study aims to investigate whether the muscle synergy patterns characterized upper limb motor recovery according to clinical outcomes in stroke rehabilitation. We compared clinical outcome measures and muscle synergy patterns extracted before and after 20 sessions of conventional, robotic-assisted, or virtual reality-based treatment. We characterized the muscle synergy patterns of individuals who clinically responded (ie, responders) and not responded (ie, non-responders) to the upper limb treatment.

Methods

Participants

All individuals were informed on the aims and modalities of the study and provided the informed written consent. Inclusion criteria included: (1) adults (>18y), (2) diagnosis of unilateral first stroke (hemorrhagic or ischemic), (3) impairment of upper limb motor function defined as a score between 5 and 61 points at the Fugl-Meyer Assessment-Upper Extremity scale (FMA-UE). Moreover, individuals reporting untreated seizures, or severe impairment in cognitive or verbal comprehension function were excluded.

List of abbreviations:

FMA-UE **Fugl-Meyer Assessment-Upper Extremity**
sEMG **surface electromyography**

Study design

The study is a secondary analysis of a multicenter randomized controlled trial. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee for Clinical Experimentation (CESC) of Venice and San Camillo IRCCS hospital (Prot. No. 2015.14) and the written informed consent from all participants enrolled.

After enrolment, individuals received a rehabilitation intervention targeting the upper limb, administered for 1 hour a day, 5 times a week, for 4 weeks (20 sessions overall). Randomization and allocation procedures were conducted by an independent researcher, and a blinded assessor was responsible for screening and clinical assessment before and after the treatment. A random number sequence was computer-generated, and blinded allocation was ensured through sequentially numbered sealed envelopes. Individuals were allocated randomly to robotic-assisted, virtual reality, or conventional treatment. Robotic-assisted treatment was provided by the Braccio di Ferro[a] (Celin s.r.l.) device[22] and virtual reality treatment was delivered by the Virtual Reality Rehabilitation System[b] (VRRS, Khymeia Group Ltd.).[23-25] The conventional treatment consisted of a physiotherapy program with specific exercise for upper limb (a detailed description of 3 treatment modalities is presented in supplemental appendix S1, available online only at http://www.archives-pmr.org/).

Outcome measures

To detect the effect of upper limb treatment, individuals were assessed before and after the treatment by a blinded assessor. The primary outcome of the study was FMA-UE, a reference standard for the assessment of upper limb gross motor function after stroke.[26,27] The FMA-UE score ranges from a minimum of 0 (no motor function) to a maximum of 66 (normal function) points. The secondary outcome measures included: Fugl-Meyer Assessment-sensory function, to quantify the level of sensation impairment (maximum score 24 points, normal sensation); the Fugl-Meyer Assessment-pain and joint functioning, to quantify the pain and range of motion of upper limb joints (maximum score 48 points, normal function); the Modified Ashworth Scale[28] to assess the muscle tone (maximum score 20 points, hypertonia) in 5 key-muscles (pectoralis major, biceps brachialis, flexor carpii, flexor digitorum profundus, flexor digitorum superficialis); Functional Independence Measure[29] to assess the level of the independence in daily

activities (maximum score 126 points, full independence). Demographic and medical history data included: (1) age, (2) sex, (3) type of lesion (ie, ischemic or hemorrhagic), (4) lesioned hemisphere (ie, left or right), and (5) time from stroke onset.

sEMG acquisition

sEMG data were acquired using the EMG-USB2+ (OT Bioelettronica) at a sampling frequency of 2000 Hz. We acquired sEMG from 16 upper limb muscles (triceps brachii, medial and lateral heads; biceps brachii, short and long heads; deltoideus anterior, medialis, posterior; trapezius superior; rhomboid major; brachioradialis; brachialis; supinator; pronator teres; pectoralis major; infraspinatus; teres major) by following the SENIAM guidelines.[30] sEMG were acquired separately from both unaffected and affected limb, whereas the participants performed 7 unilateral voluntary reaching tasks (10 repetitions/task, 70 trials totally) using the VRRS system[b] (Khymeia Group Ltd.). The tasks included elevation, elevation with restriction, forward reaching, shoulder abduction, forearm pronation-supination, shoulder internal-rotation, and shoulder external-rotation.[31]

sEMG feature extraction

sEMG signal preprocessing involved the following steps: (1) band-pass filtering (10-500 Hz), (2) normalization to unit variance, (3) rectification, and (4) low-pass filtering at 12 Hz.[32] Muscle synergies were then extracted separately for the affected and unaffected limbs using the nonnegative matrix factorization algorithm. The number of synergies retained was determined via cross-validation, based on the amount of variance explained of sEMG reconstruction (R^2>80%).[11] Detailed description of the procedures is provided in previous studies.[8,11]

After synergies extraction, we computed the parameters: (1) the number of synergies extracted; (2) the median scalar product between synergies of the affected and unaffected limb, used as a measure of similarity (with higher values indicating greater similarity); (3) the number of preserved synergies, defined as pairs of synergies with a scalar product >0.80.[31] Additionally, we quantified merging and fractionation muscle synergy patterns in the affected limb relative to the total number of synergies in the unaffected limb, using nonnegative least squares (Matlab function *lsqnonneg*).[11] In line with previous work,[11] an unaffected limb synergy was considered to contribute to the merging or fractionation if its weight was >0.20.

Statistical analysis

We reported descriptive statistics for demographics, clinical, and muscle synergies parameters to characterize the sample.[6,11] The overall treatment effect was defined using either parametric (eg, *t* test) or nonparametric tests (eg, Wilcoxon test), depending on the outcome of the Shapiro test for normality. Then, we identified responders and non-responders groups. Responders were defined as individuals who demonstrated an improvement of greater than the Minimal Clinically Important Difference of 5 points on the FMA-UE and non-responders were defined as individuals who improved by ≤5 points on the FMA-UE.[33] We then compared clinical outcome and muscle synergy patterns between the 2 subgroups. Differences across treatment interventions were analyzed using one-way analysis of variance (ANOVA), corrected post hoc by the Tukey test for pairwise. A significance level of P<.05 was adopted for all statistical tests.

Muscle synergies clustering and functions

Cluster analysis was performed to group similar muscle synergies together. Three "vocabularies" were created, each representing the set of muscle synergies extracted from the affected upper limb before treatment, after treatment, and from the unaffected limb. Clustering prototypes were derived using a hierarchical clustering algorithm with Ward's linkage method.[34] The optimal number of clusters for each vocabulary was determined using the Silhouette algorithm.[35] Within each vocabulary, we characterized the relationship between muscle synergies and motor functions by assuming that each muscle within a synergy contributed with its specific biomechanical upper limb functions (ie, shoulder flexion, shoulder extension, shoulder abduction, shoulder adduction, elbow flexion, elbow extension, forearm pronation, forearm supination). A muscle synergy was considered associated with specific biomechanical motor functions when the average weight of all the muscles contributing to those functions exceeded a predefined threshold. The threshold was defined as the smallest maximum average weight observed across all functional mappings within the vocabulary. This analysis was conducted for the overall cohort of participants, as well as separately for responders and non-responders.

Results

Sample characteristics

We included 62 individuals with stroke, all completing the 20 treatment sessions. Detailed participant characteristics are reported in Table 1.

Clinical outcome

Overall, participants showed significant improvement in the FMA-UE, by increasing 7.14 points on average (P<.001), surpassing the established Minimal Clinically Important Difference threshold of 5 points.[33] A comprehensive summary of these results is represented in supplemental appendix S2 (available online only at http://www.archives-pmr.org/).

Responders and non-responders

We identified 34 responders to treatment (improvement over the Minimal Clinically Important Difference of 5 points on the FMA-UE[33]). Among them, 18 individuals received virtual reality treatment, 13 robotic-assisted treatment, and 3 conventional treatments. Clinical outcomes for both responders and non-responders are reported in Table 2.

Responders achieving the greatest motor recovery, expressed by the FMA-UE score change, were those with the most severe impairment at baseline (FMA-UE<20 points). Conversely, non-responders demonstrated more uniform scores changes at FMA-UE, regardless of the score at baseline (Fig 1).

Muscle synergy parameters

By considering the whole sample (n=62), after treatment only the similarity improved significantly (P=.004), whereas the number of

Table 1 Demographic and clinical characteristics of the patients.

Sample Characteristics	Value (n = 62)
Sex, male/female	42 (68%) / 20 (32%)
Age (y)	62.02 (±13.68)
Diagnosis, ischemic/hemorrhagic	50 (81%) /12 (19%)
Hemisphere, left/right	30 (48%) / 32 (52%)
Time-stroke (mo)	13.95 (±30.54)
Recovery phase, early subacute/late subacute/chronic	30 (48%) / 9 (15%) / 23 (37%)
Level of UL motor impairment, severe/mild	18 (29%) / 44 (71%)
Type of treatment, CT/VRT/RT	8 (13%) / 34 (55%) / 20 (32%)
Treatment output, responder/non-responder	34 (55%) / 28 (45%)

NOTE. Values are expressed as mean±standard deviation (SD) for quantitative measures, and number (n) and frequency percentages (%) for all the discrete variables. The level of upper limb (UL) motor impairment was defined as severe (0<FMA-UE<31 points), or mild (FMA-UE ≥31 points). The recovery phase after stroke was defined according to the ESO guidelines as early subacute (from 7d to 3mo), late subacute (from 3 to 6mo), and chronic (after 6mo).
Abbreviations: CT, conventional treatment; RT, robotic-assisted treatment; UL, upper limb; VRT, virtual reality treatment.

muscle synergies (*P*=.374), merging (*P*=.068), and fractionation (*P*=.952) did not change. Full results of the whole sample are reported in supplemental appendix S2.

Between responders and non-responders groups, analysis showed that at baseline the number of muscle synergies (*P*=.552), merging (*P*=.171), and fractionation (*P*=.136) were comparable. Notably, responders (n=8) with most severe impairment (FMA-UE<20 points) exhibited greater synergy merging (Fig 2).

Post-treatment, merging changes differed significantly between responders and non-responders (*P*=.025). Specifically, responders showed a significant reduction in merging (*P*=.016), whereas non-responders exhibited a significant increase in similarity (*P*=.006). There were no significant between-groups differences in fractionation (*P*=.952), nor significant within-group changes for either responders (*P*=.247) or non-responders (*P*=.176) (Table 3).

The one-way ANOVA showed a significant effect of treatment modality on merging changes (*F*=3.52; *P*=.036), confirmed for both virtual reality and robotic-assisted treatments after post hoc Tukey correction (*F*=18.8; 95% CI, 1.4-36.1; *P*=.031). Participants in the robotic-assisted group exhibited greater merging change. However, baseline merging scores significantly differed between the virtual reality (52.59%) and the robotic-assisted groups (69.66%) (*P*=.001).

Cluster analysis

Before treatment, the affected limb exhibited a synergy vocabulary of 13 components, which increased to 14 after the treatment. The unaffected limb exhibited a vocabulary of 16 synergies. In responders, the vocabulary of the affected limb was associated with 2.54 upper limb motor functions before treatment, and 1.37 functions after treatment. In non-responders, these values were 2.61 and 1.42, respectively. Overall, the vocabulary of the unaffected limb was associated with 1.33 motor functions. The vocabularies are represented in supplemental appendix S3 (available online only at http://www.archives-pmr.org/). No significant differences in motor function distributions were observed between responders and non-responders (Fig 3). In both groups, after treatment, the motor function representation of the affected limb became more similar to that of the unaffected limb.

Table 2 Clinical outcome measures at baseline and after treatment in responder and non-responder subgroups.

Clinical Outcomes Measures	Responder (n = 34)			Non-Responder (n = 28)			Between Groups
	T0	T1	Δ (T1 − T0)	T0	T1	Δ (T1 − T0)	p
FMA-UE	34.96 ± 16.2	46.85 ± 14.3	11.9 ± 6.7	45.71 ± 11.7	47.11 ± 12.5	1.4 ± 2.9	<0.000†
	35 [29.5]	46 [23.25]	10 [5.8]*	49.5 [18]	50 [20.25]	1.5 [3.3]*	
FMA-S	19.29 ± 5.28	21.68 ± 3.7	2.4 ± 4.2	21.64 ± 3.2	22.43 ± 2.56	0.8 ± 2.3	0.098
	20.5 [6.75]	23.5 [4]	1 [3.8]*	22.5 [4]	24 [2.25]	0 [1]	
FMA-P	43.74 ± 3.86	44.53 ± 4.1	0.8 ± 3.5	43.46 ± 4.9	44.32 ± 4.04	0.9 ± 3.6	0.715
	44.5 [5.75]	45.5 [5.75]	0.5 [3.5]	45 [6.25]	45 [5.25]	0 [2.3]	
MAS	3.85 ± 4.08	2.5 ± 3.3	−1.4 ± 2.4	2.96 ± 2.9	2.57 ± 3.16	−0.4 ± 2.5	0.085
	2 [7.5]	1 [3]	−1 [1.8]*	2 [3.5]	2 [3.25]	0 [1.3]	
FIM	96.06 ± 21.16	106.8 ± 19.7	10.9 ± 12.4	101.3 ± 15.6	109.6 ± 15.42	8.3 ± 8.4	0.413
	101.5 [23]	113.0 [19]	11 [11]*	104 [24.5]	116 [20.75]	7.5 [10.3]*	

NOTE. Values are expressed as Mean ± SD and median [IQR]. *P* values < 0.05 using Wilcoxon Test.
Abbreviations: FIM, Functional Independence Measure; FMA-P, Fugl-Meyer Assessment-Pain and ROM; FMA-S, Fugl-Meyer Assessment-sensitivity; FMA-UE, Fugl-Meyer Assessment-Upper Extremity; MAS, Modified Ashworth Scale.
* statistically significance within group.
† statistically significance between groups.

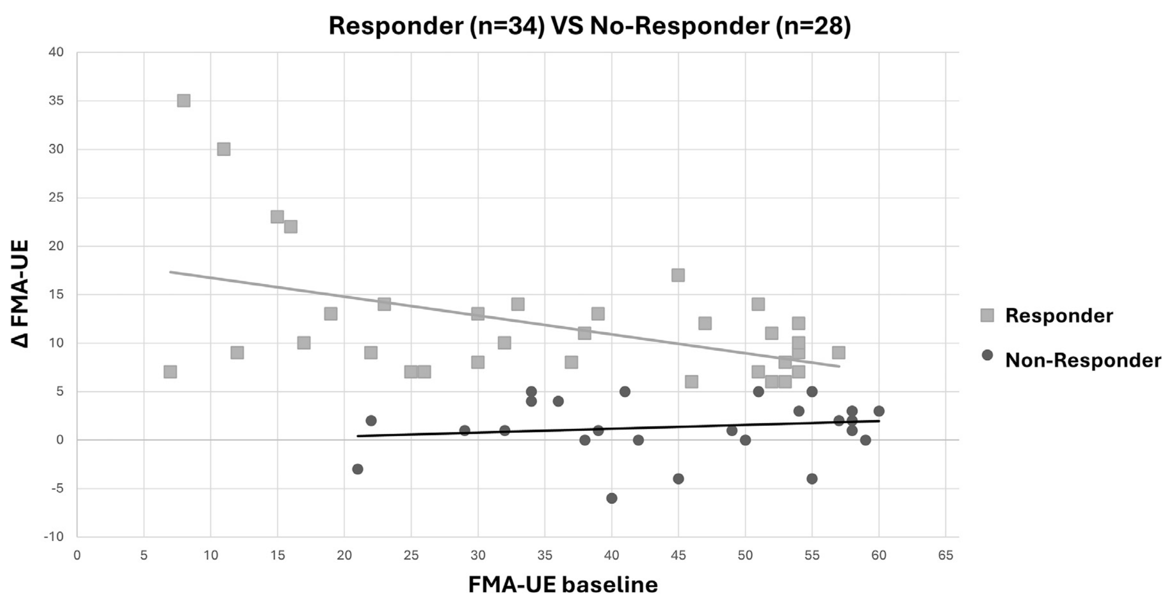

Fig 1 The relationship between the motor impairment (FMA-UE score) at the baseline and the amount of recovery in responders and non-responders. Each symbol represents a participant, from responders (grey squares) and non-responders (black dots). On the x-axis, the Fugl-Meyer Upper Extremity score at baseline (FMA-UE baseline) and on the y-axis, the change (Δ FMA-UE) between the final score and the baseline. Overall (N=62) we found a significant negative correlation (Spearman's rank correlation, ρ=−0.373; 95% CI, −0.136 to −0.569; P=.0029). Thus, we separated the results in responders (Spearman's rank correlation, ρ=−0.325; 95% CI, 0.15 to −0.598; P=.0606) and non-responders (Spearman's rank correlation, ρ=0.128, 95% CI, 0.478 to −0.258; P=.5175).

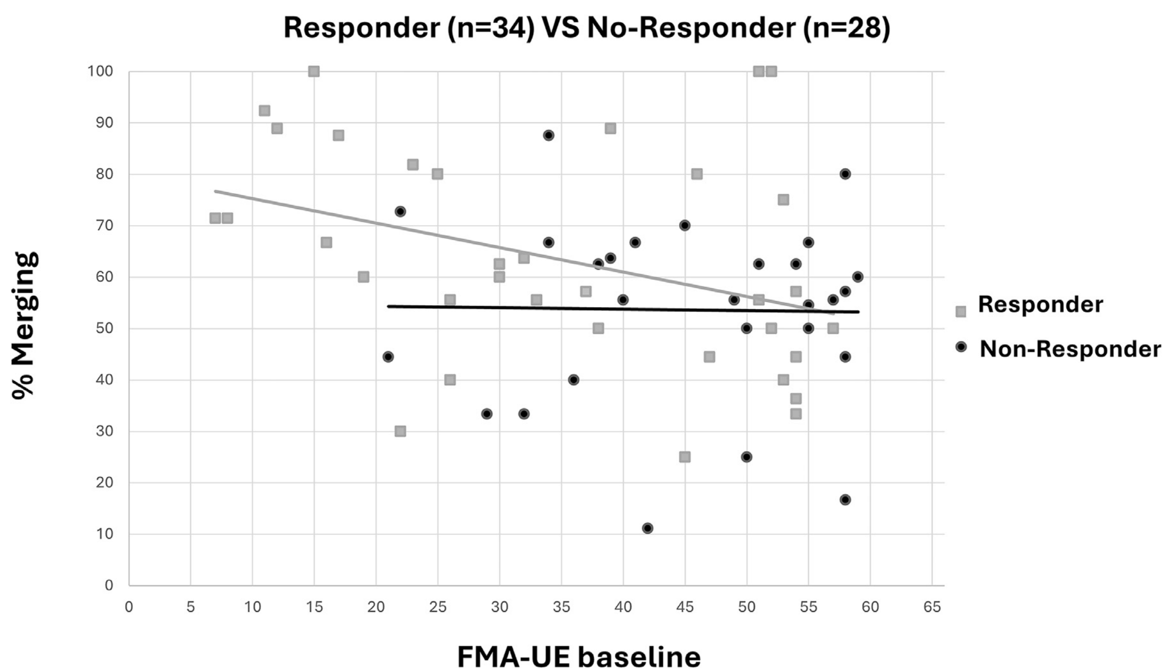

Fig 2 Relationship between the motor impairment (FMA-UE score) at the baseline and the amount of merging at the baseline in responders and non-responders. Each symbol represents a participant, from responders (grey squares) and non-responders (black dots). On the x-axis, the Fugl-Meyer Upper Extremity score at baseline (FMA-UE baseline) and on the y-axis, the percentage of the merging (% Merging) at the baseline. Overall (N=62), we found a significant negative correlation (Spearman's rank correlation, ρ=−0.275; 95% CI, −.028 to −0.491; P=.030). Thus, we separated the results in responders (Spearman's rank correlation, ρ=−0.438; 95% CI, −0.118 to −0.676; P=.009) and non-responders (Spearman's rank correlation, ρ=0.042; 95% CI, 0.409 to −0.336; P=.832).

Table 3 Change of muscle synergies after treatment, in the responders and non-responder subgroups.

	Responder (n = 34)		Non-Responder (n = 28)		Between Groups
Muscle Synergy Parameters	T0	T1	T0	T1	p
N-aff	8.94 ± 1.54 9 [2]	8.59 ± 1.31 9 [1]	8.68 ± 1.44 9 [1.25]	8.75 ± 1.46 9 [2]	0.180
N-un	8.71 ± 1.36 9 [2]	8.68 ± 1.17 9 [1]	8.5 ± 1.2 8.5 [1]	8.64 ± 0.87 9 [1]	0.586
N-sh	6.94 ± 1.30 7 [2]	6.79 ± 1.49 6.5 [2]	6.54 ± 1.58 7 [1]	6.65 ± 1.44 7 [1.75]	0.269
M-sp	0.87 ± 0.07 0.89 [0.12]	0.90 ± 0.06 0.92 [0.1]	0.88 ± 0.06 0.89 [0.08]	0.91 ± 0.06 0.92 [0.09] *	0.181
Me (%)	63.37 ± 21.15 60 [30]	51.17 ± 22 50 [29.2] *	54.27 ± 18.1 56.4 [22.3]	56.11 ± 19.3 52.27 [30.2]	0.025†
Fr (%)	5.67 ± 8.49 0 [10]	7.67 ± 8.58 4.5 [13.8]	9.35 ± 12.2 10.1 [12.5]	6.80 ± 10.34 7 [11.11]	0.070

NOTE. Values are expressed as Mean ± SD and median [IQR]. *P* values < 0.05 using Wilcoxon Test.
Abbreviations: Fr, fractionation index; M-sp, median of scalar product; Me, merging index; N-aff, number of synergies extracted from affected upper limb; N-sh, number of synergies shared between upper limbs; N-un, number of synergies extracted from unaffected upper limb.
* statistically significance within group;
† statistically significance between groups.

Discussion

In this study, we applied muscle synergy analysis to characterize individuals with stroke who did or did not show clinically important improvement after upper limb motor rehabilitation. Classification as a responder or non-responder was based on the Minimal Clinically Important Difference of the FMA-UE,[33] the most reported outcome measure in studies investigating recovery of upper limb motor function after stroke, with a clinical meaning and translation.[4,36,37]

Our analysis showed that all participants (n=62) preserved the number of muscle synergies and exhibited increased similarity

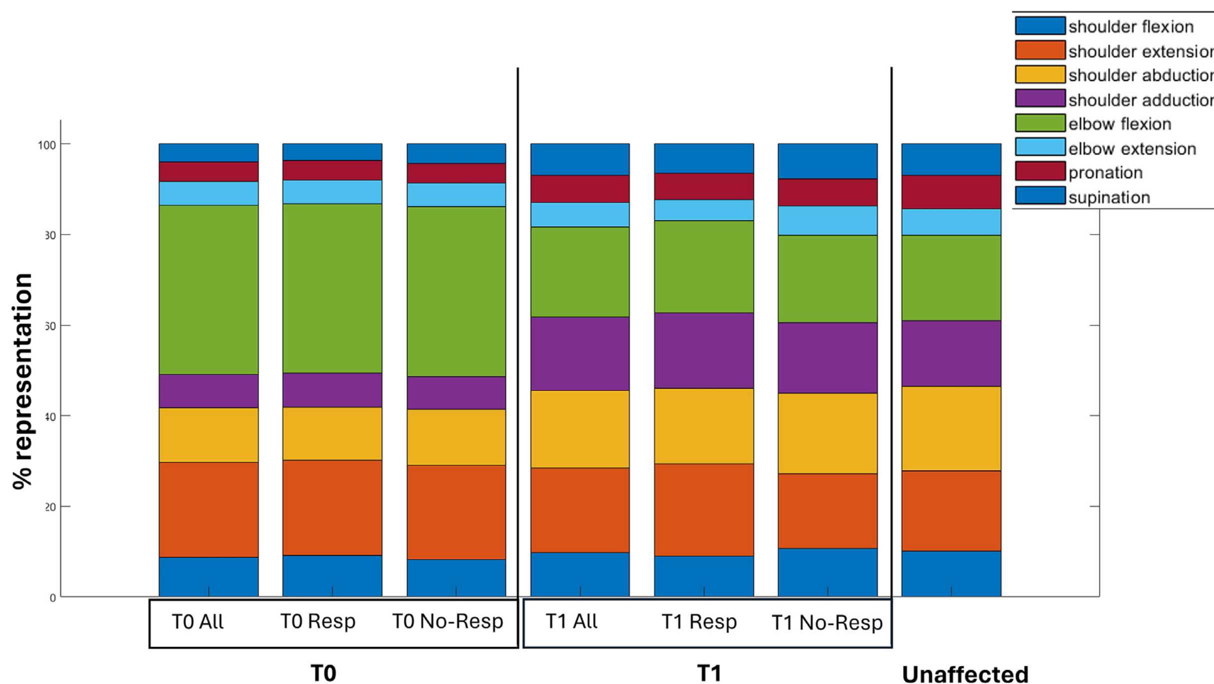

Fig 3 The representation map of upper limb motor functions, in 3 synergies vocabularies. The representation of each synergies vocabulary of the affected upper limb for all (All), in responders (Resp), and non-responders (No-Resp), before (T0) and after (T1) treatment; then, the synergies vocabulary of unaffected upper limb (Unaffected). We identified 8 motor functions based on the degrees of freedom captured by the function-specific tasks adopted in the protocol and the muscles we recorded: shoulder flexion, shoulder extension, shoulder abduction, shoulder adduction, elbow flexion, elbow extension, forearm pronation, and forearm supination. After treatment, shoulder extension (T1 Responders=20.46%; T1 No-Responders=16.51%), and adduction (T1 Responders=16.62%; T1 No-Responders=17.74%) were slightly more represented in the responders, whereas shoulder flexion (T1 Responders=8.95%; T1 No-Responders=10.70%) and elbow extension (T1 Responders=4.60%; T1 No-Responders=6.42%) were more represented in non-responders.

between the affected and unaffected limbs after treatment. Notably, increased similarity index has been previously associated with motor recovery and reduction of spasticity.[11,38,39] By comparing muscle synergy patterns between responders and non-responders, in responders, the level of merging significantly decreased after treatment, reaching levels comparable to those of the non-responders. In addition, we observed that higher levels of merging significantly characterized responders with severe impairment at baseline (FMA-UE<20 points). These results disclosed the potential role of rehabilitation in promoting "de-merging" of muscle synergies in individuals with severe impairment of the upper limb.[40] Conversely, non-responders showed a significant increase in muscle synergy similarity, indicating that the treatment induced more similarity in muscle activation between affected and unaffected limbs. These results are particularly relevant for individuals with mild impairment, who did not demonstrate a significant clinical improvement but exhibited neural adaptations at the level of muscle synergies.[41,42]

Our findings reinforce the evidence that motor recovery after stroke rehabilitation has different expressions, as reflected by the variability of muscle synergy patterns.[14,43,44] The variability in synergy patterns highlights the need for personalized approaches to stroke rehabilitation.[42] The treatment interventions delivered in our trial, especially robot-assisted therapy, may be more effective for individuals with lower baseline motor function. By contrast, individuals with mild impairments may benefit more from virtual reality or task-specific practice,[45] which provides repetitive and task-oriented training shaped on the subjects' functional needs.[46,47] Further studies should more specifically investigate whether different intervention modalities differentially influence the modulation of the muscle synergy patterns.

Contrary to previous findings in a smaller sample, muscle synergy fractionation patterns were not informative in our cohort.[11] This discrepancy may be because of the heterogeneous time since onset in our sample, which included a wide distribution of individuals in both the early and late subacute phase.

The innovative clustering analysis approach grouped synergy to their corresponding functional representations, thereby defining muscle synergies "vocabularies." Overall, participants exhibited unbalanced muscle contributions in the affected limb, with over-representation of elbow flexion and under-representation of shoulder adduction/abduction and forearm pronation/supination. These results are consistent with previous studies describing key motor deficits in reaching tasks among people after stroke.[10,48] Comparing with healthy subjects, individuals with stroke showed a higher activation of pectoralis major and elbow flexor muscles (biceps brachii and brachioradialis), and a lower activation of elbow extensor muscles (triceps brachii).[10,48]

At baseline, no differences were observed between the synergy vocabularies of responders and non-responders. However, after treatment, in both groups, the synergy vocabularies of the affected limb became more similar to the vocabulary of the unaffected limb. This reorganization was reflected in a reduction in the number of motor functions represented per synergy. These findings suggested that, regardless of clinical responsiveness, rehabilitation induced functional reorganization of muscle synergies, in the direction of the unaffected counterpart. Thus, the upper limb rehabilitation could be guided by the functional organization of the unaffected limb, or that unaffected upper limb still preserves a physiological functioning serving as a reference model.[49] Nevertheless, those hypotheses need specific proof-of-concept studies to be tested and falsified or accepted.

Cluster analysis underlined the importance of targeted training to improve or reduce the muscle activation, to avoid maladaptive movement patterns.[50] In this regard, motor interventions should be designed to prevent compensatory strategies, especially in individuals with severe impairment.[51] Mapping motor function representations could contribute to personalize the rehabilitation programs, supporting strategies focused on "restitution" versus "compensatory" behaviors.[45,52] Finally, the synergy-based characterization may be considered in the development of control strategies for technological-based intervention in stroke rehabilitation. Individuals with severe impairment may benefit from tasks with constrained degrees of freedom to facilitate device control.[41] Conversely, individuals with mild impairment may require tasks with greater variability and complexity, controlling high degrees of freedom,[41] fostering advanced control strategies, tailored to individual capabilities.[42,44,53]

Study limitations

This study has several limitations. First, the number of identified synergies was influenced by the acquisition protocol,[19,54] highlighting the urgency to develop guidelines based on experts' consensus.[54,55] Additionally, we predefined the threshold for clinically significant improvement using the Minimal Clinically Important Difference of the FMA-UE.[33] This threshold may vary depending on individual characteristics or when using other outcome measures. Indeed, although the FMA-UE has been used to assess motor function impairments in people after stroke, it may not be appropriate for identifying specific deficits in upper limb activity. Future clinical trials should aim to better characterize the profile of individuals who benefit from stroke rehabilitation,[3] incorporating outcome measures more used in the clinical setting to assess the functional activity of the upper limb. The Action Research Arm Test,[4,56,57] the Wolf Motor Function Test,[58] or the Motor Activity Log assessment[59] should be considered with muscle synergy analysis to thoroughly characterize the upper limb functionality in stroke rehabilitation.[60] Finally, the composition of synergy vocabularies was defined using unimpaired biomechanical functions as a reference, which may not accurately reflect the altered motor patterns observed in individuals with stroke-related impairments.[61]

Conclusions

In this study, we investigated whether muscle synergy patterns could characterize motor recovery, as measured by outcome measures coming from validated clinical assessment of individuals with stroke undergoing upper limb rehabilitation. Our results revealed that who responded clinically to the treatment showed a significant reduction in muscle synergy merging. Conversely, individuals who did not respond clinically, showed an increase in muscle synergy similarity. These results suggest that muscle synergy analysis may convey prognostic value, thus contributing to the personalization of the upper limb rehabilitation after stroke.

Suppliers

[a]Braccio di Ferro; Celin s.r.l.
[b]Virtual Reality Rehabilitation System; Khymeia Group.

Authorship Contributions

G.P., G.S., A.T. contributed to the experimental process, manuscript drafting, and reviewing. A.T., G.P., T.L., M.F., and J.J. contributed to the clinical trial design and the participant management. I.C. implemented the robot-training protocol in Milan. G.P., D.R., I.C., and T.L. participated in acquisition and processing the instrumented data. G.P., L.M., and G.S. contributed to data analysis. M.F. and J.J. coordinated the team in Milan. I.C., T.L., M.F., J.J., and V.C.K.C. critically reviewed the manuscript. A.T. was the PI of the grants GR-2011-02348942 and RF-2019-12371486 sustaining the trial and conceived the study and coordinated the whole projects. All authors read and approved the final manuscript.

Keywords

Motor control; Muscle synergies; Neurorehabilitation; Rehabilitation; Stroke; Surface Electromyography; Upper extremity

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