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Lesion side influences the effects of bilateral upper-limb robotic-assisted training on motor recovery in chronic stroke

Stroke remains a leading cause of long-term disability worldwide affecting over ninety millions individuals and resulting in persistent motor impairments, including upper limb dysfunction, which compromise independence in a substantial proportion of survivors.[1] This condition significantly restricts autonomy in activities of daily living (ADL), as many essential tasks — such as dressing, bathing, or manipulating objects — require the coordinated use of both hands.[2] Restoring bimanual coordination is therefore a critical goal in neurorehabilitation, especially since older adults tend to rely more heavily on bilateral hand use for everyday activities.[3] While robotic-assisted therapy (RAT) has emerged as a promising intervention to provide high-intensity, repetitive training, there is currently no consensus on its optimal application or the factors that predict individual response to treatment.[4] In this study, we aimed to address these gaps by investigating how the side of the brain lesion (dominant *versus* non-dominant hemisphere) influences the effectiveness of bilateral robotic-assisted training (BRAT) in right-handed chronic stroke survivors.[5] Our hypothesis was rooted in the understanding that bimanual movements are predominantly governed by the dominant hemisphere;[6-8] therefore, damage to this area might fundamentally alter the mechanisms of motor recovery and the response to bilateral stimuli.

This study was approved by the Comitato Etico Regione Toscana – Area Vasta Nord Ovest (approval no. 17605) on September 10th, 2020, chairperson of the ethics committee: Prof. Romano Danesi. All participants, recruited at the Neurorehabilitation Unit of Pisa University Hospital, signed a written informed consent form in accordance with the requirements of the Declaration of Helsinki. In this pilot study, we enrolled 24 right-handed outpatients with chronic unilateral stroke (at least six months post-onset) who exhibited upper limb paresis but retained the ability to perform antigravity movements. Patients were stratified into groups based on the side of the affected hemisphere: the left hemispheric stroke (LHS) group (N.=12, 5 females) and the right hemispheric stroke (RHS) group (N=12, 3 females). Demographic and clinical information is reported in Table I. Importantly, the LHS and RHS groups did not differ significantly in terms of median age and duration of illness as assessed by Mann-Whitney tests (both P>0.05).

TABLE I.—*Patients' characteristics.*

Patient #	Gender	Age	Duration of illness (months)	Affected hemisphere	Lesion location	FMA baseline score
1	Male	70	168	Right	Not available	54
2	Male	60	84	Right	Subcortical	102
3	Male	59	108	Left	Cortico-subcortical	101
4	Male	73	24	Left	Subcortical	94
5	Male	54	18	Right	Cortico-subcortical	99
6	Female	40	36	Left	Subcortical	110
7	Male	73	48	Left	Subcortical	108
8	Male	65	60	Right	Cortico-subcortical	46
9	Male	76	96	Left	Subcortical	65
10	Male	76	24	Right	Subcortical	103
11	Male	41	60	Left	Subcortical	94
12	Female	78	24	Left	Cortico-subcortical	92
13	Female	54	36	Right	Subcortical	74
14	Female	70	48	Right	Cortico-subcortical	80
15	Female	69	12	Left	Cortico-subcortical	116
16	Female	78	48	Right	Subcortical	84
17	Male	63	60	Right	Cortico-subcortical	89
18	Male	80	132	Right	Cortico-subcortical	71
19	Male	20	216	Left	Not available	87
20	Male	53	12	Right	Cortico-subcortical	113
21	Female	46	48	Left	Cortico-subcortical	77
22	Male	71	24	Right	Subcortical	92
23	Female	63	30	Left	Cortico-subcortical	55
24	Male	65	48	Left	Subcortical	105

Our participants underwent a three-week intensive BRAT program consisting of five 45-minute sessions per week using the ALEx-RS exoskeleton, a robotic system capable of covering nearly the entire natural workspace of the human arm. The training integrated cognitively engaging "serious games" that combined symmetric and asymmetric tasks, such as virtual tray-carrying and archery, to promote interlimb coordination. Clinical assessments were conducted at baseline, immediately post-treatment, and at a two-month follow-up using the Fugl–Meyer Assessment (FMA), the Bimanual Activity Test (BAT),[9] and the Motricity Index (MI). The BAT was used to assess the functional involvement of the paretic upper limb during bimanual activities of daily living, with particular focus on the extent and quality of its contribution to task execution. Two outcomes were considered for each task: execution time and a quality score. The quality score ranged from 0 to 4, with higher scores indicating greater functional involvement and active integration of the paretic limb. A detailed description of the BAT tasks, experimental procedure, and scoring criteria is provided in Supplementary Digital Material 1 (Supplementary Text File 1, Supplementary Table I). To move beyond purely subjective scales, we also performed a kinematic evaluation of movement smoothness, quantified *via* the Spectral ARC length (SPARC) metric during a standardized reaching task with the robot, and movement duration.

All between-groups comparisons were performed with Mann-Whitney two-tailed tests whereas the within-group comparisons (*i.e.*, treatment effects) were performed with one-tailed Wilcoxon signed-rank tests. We corrected for multiple comparisons using Benjamini/Hochberg FDR correction.

Our findings revealed improvements in both groups on most scales following the three-week training period, with these gains successfully maintained at the two-month follow-up (Figure 1). No differences between RHS and LHS were observed at baseline on any of the scales (all P>0.05). This underscores and confirm that even in the chronic phase — long considered a stage of limited recovery potential — intensive bilateral robotic intervention can still drive meaningful motor improvements (median FMA and MI post-training improvements equal or higher than 6 (raw scale scores) in both groups: RHS FMA: 7; 95% CI: 2.5, 10.5; LHS FMA: 6; 95% CI: 3, 11.5; RHS MI: 6; 95% CI: 5, 10; LHS MI: 6.5; 95% CI: 5, 16)[10] by restoring interhemispheric balance and enhancing connectivity within motor-related neural networks.[11, 12]

However, a more detailed analysis based on the side of the lesion uncovered distinct recovery profiles. We observed that patients with left hemiparesis (RHS group, where the dominant left hemisphere was spared) showed significant gains in bimanual task quality (Figure 1B) and a greater improvement in movement smoothness in the task with the robot (Figure 2A), although this difference did not reach statistical significance. In contrast, pa-

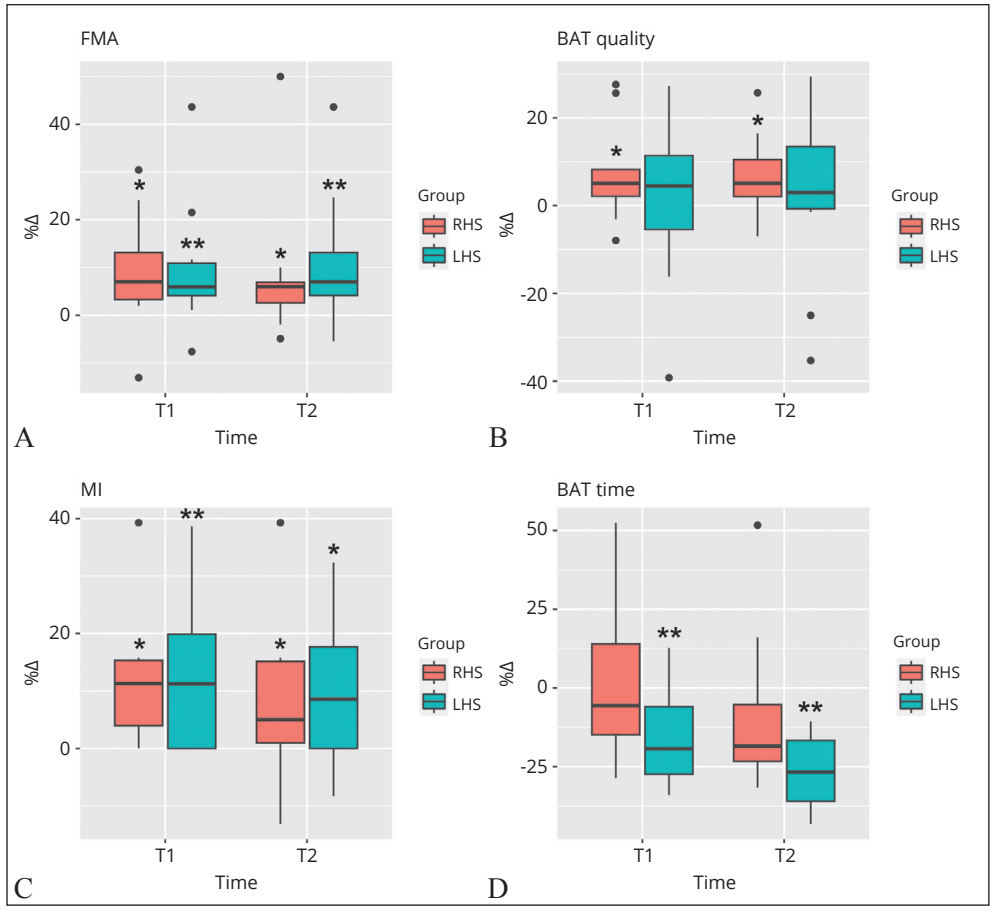


Figure 1.—Training effect in the RHS and LHS groups on the FMA, BAT quality, MI and BAT time clinical scales. Boxplots show the Δ% distribution between T1-T0 and T2-T0 in the RHS group (red) and LHS group (cyan). Horizontal lines indicate medians. Whiskers extend to points that lie within 1.5 interquartile ranges of the lower and upper quartile. Black dots show outliers. Asterisks indicate median significantly different from zero, reflecting a significant percentage change from baseline (T0). *P<0.05, **P<0.01.

tients with right hemiparesis (LHS group, where the dominant hemisphere was lesioned) primarily improved their execution time (Figure 1D) rather than the kinematic quality of their movements (Figure 1B and 2A). This asymmetry suggests the presence of two different recovery processes: the RHS group appeared to engage in a more physiological motor recovery oriented toward quality, while the LHS group potentially relied more heavily on compensatory strategies to improve temporal efficiency.

These results align with current models of hemispheric specialization, which posit that the dominant hemisphere plays a superior role in predictive control and trajectory planning, while the non-dominant hemisphere is more involved in feedback-based stabilization.[13] Therefore, in our LHS group, damage to the dominant hemisphere likely impaired the capacity to generate skilled, fluid, and coordinated bimanual actions, forcing a reliance on alternative pathways that prioritize task completion over movement quality. Conversely, we found that patients with an intact dominant hemisphere were better able to leverage the bilateral training to restore more natural motor patterns.

This was further supported by our correlation analysis (Figure 3), which showed that in the RHS group, milder initial impairment predicted larger gains in movement smoothness. In contrast, the LHS group showed no clear relationship, suggesting a more heterogeneous recovery process. Additionally, the strong correlation between baseline clinical scores and kinematic gains in RHS patients indicates that BRAT may be particularly effective for individuals with higher initial functional levels, enabling them to benefit from high-intensity repetitive training and achieve more physiological movement patterns.[14]

In order to also explore the contribution of the lesion site, beyond lesion laterality, we investigated in 22 patients whether the location of the damage (cortical-subcortical, CS *vs.* subcortical, S) affected the response to BRAT; 2 patients were excluded from analyses since the lesion site could not be determined. These new groups did not differ neither in terms of median age and duration of illness (both P>0.05) nor in terms of baseline score at the clinical scales (all P>0.05). Following this analysis, we observed that patients with purely subcortical strokes achieved greater kinematic benefits, with significant improvements in both smoothness and duration, whereas cortico-subcortical patients showed improve-

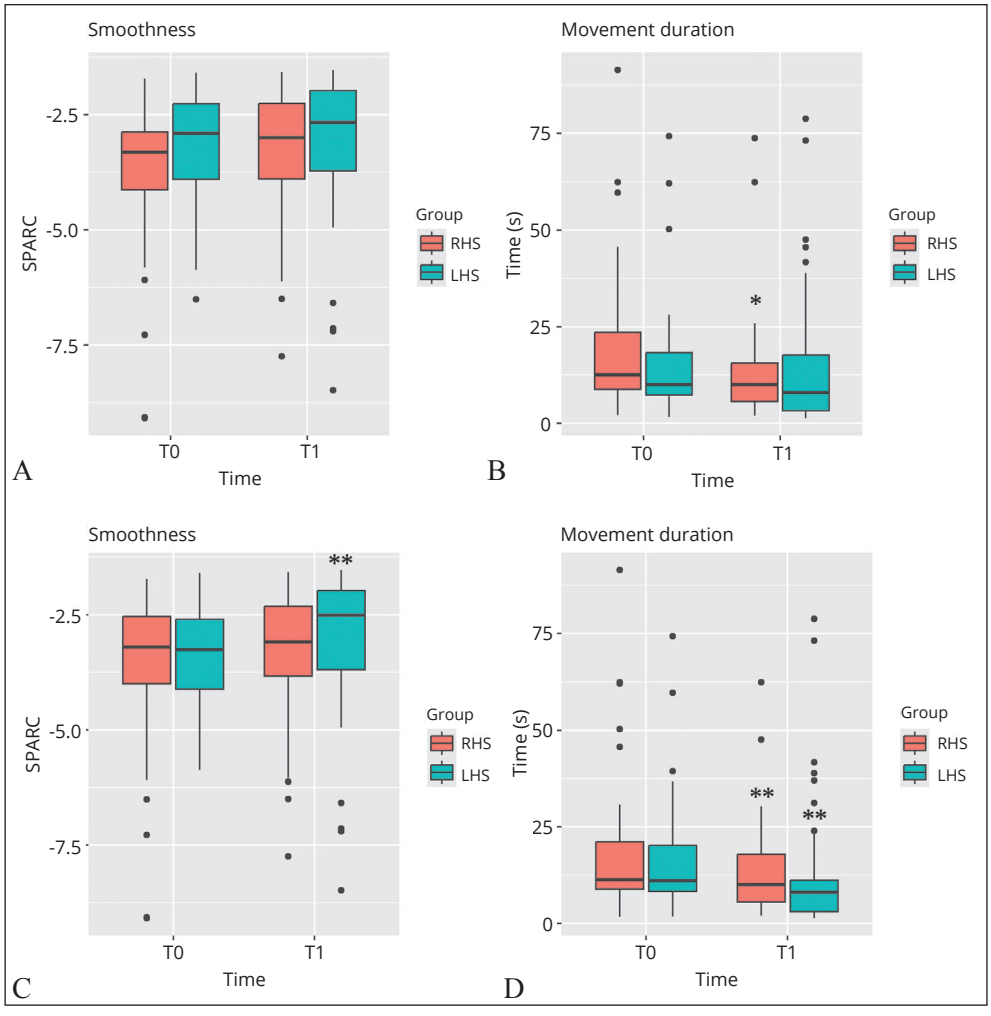


Figure 2.—Training effect on smoothness and movement duration by side and lesion location. A) Boxplots show the SPARC scores distributions at T0 and T1 by lesion side using the same graphical conventions as in Figure 1. Smoothness at the baseline did not significantly differ in RHS and LHS (P>0.05). B) Boxplots show the movement duration distributions at T0 and T1 by lesion side. Movement duration at the baseline did not significantly differ in RHS and LHS (P>0.05). Asterisk indicates significantly faster movements at T1 than T0 in RHS group (*P<0.05). C) Boxplots show the SPARC scores distributions at T0 and T1 by lesion location using the same graphical conventions as in Figure 1. Smoothness at the baseline did not significantly differ in CS and S (P>0.05). Asterisks indicate significantly improved smoothness at T1 in S group. D) Boxplots show the movement duration distributions at T0 and T1 by lesion location. Movement duration at the baseline did not significantly differ in CS and S (P>0.05). Asterisks indicate significantly faster movements at T1 than T0 in both groups (**P<0.01).

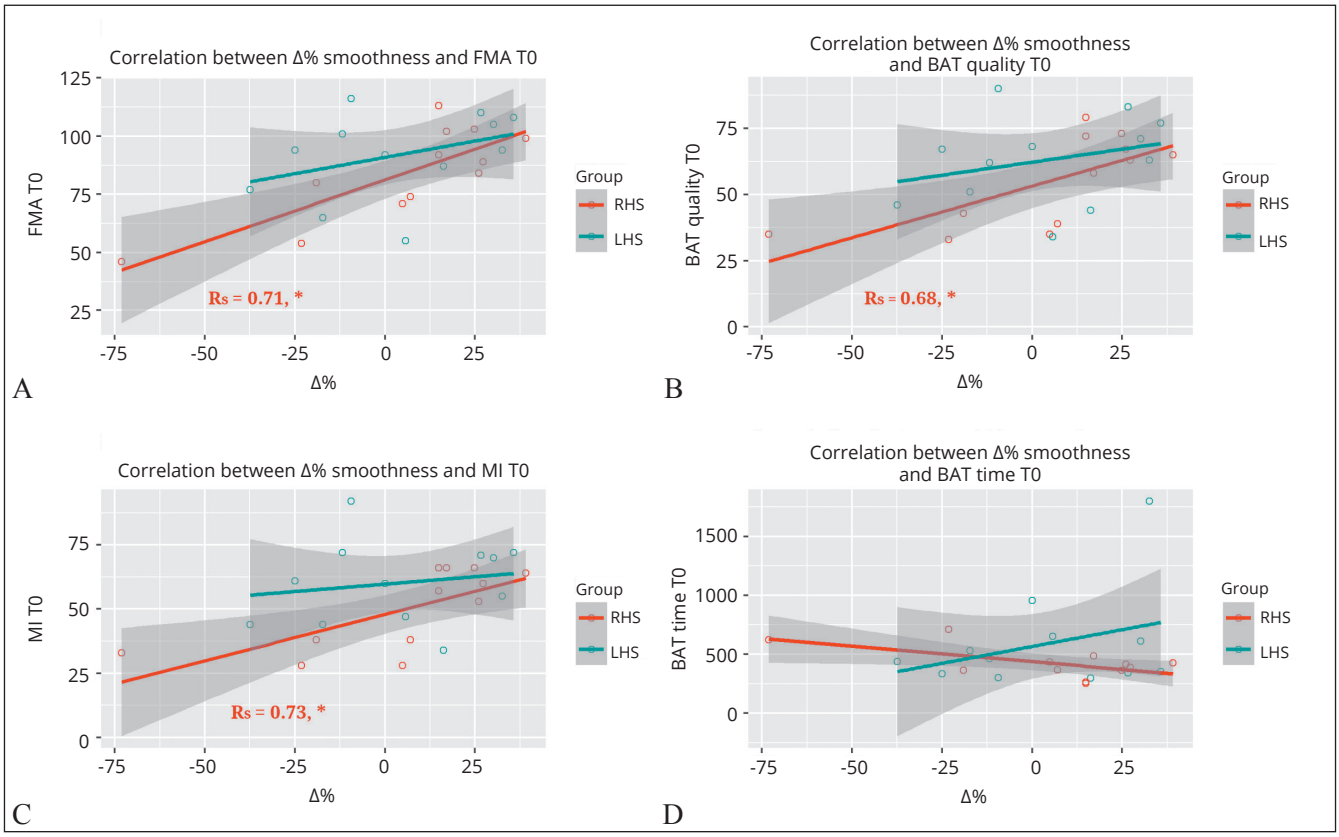


Figure 3.—Spearman correlations between movement smoothness in the BRAT and the score in the FMA, BAT quality, MI, BAT time clinical scale at the baseline by lesion side. The straight lines show the linear trend. The grey areas show the confidence interval (95%) around the linear trend. *P<0.05.

ments only in movement speed (Figure 2C and D). Subcortical lesions often spare cortical hubs essential for motor control, such as the supplementary motor area (SMA), which is pivotal for coordinating bilateral movements and initiating complex sequences.[15] The preservation of these areas likely facilitates a more robust response to intensive interventions like BRAT that depend on interlimb coordination. From a neurophysiological perspective, bilateral training is thought to restore the excitatory-inhibitory balance between hemispheres, reducing the maladaptive transcallosal inhibition often seen after stroke. By simultaneously engaging both limbs, the training promotes more symmetrical activation of motor networks, including the primary motor cortex (M1) and the cerebellum.

In interpreting these results, we must acknowledge certain limitations, including the relatively modest sample size, the use of the Bimanual Activity Test (BAT), which has not yet undergone formal validation, and the absence of a direct comparison with a unilateral robotic protocol. Such a comparison would be necessary to isolate the specific added value of the bilateral component. Since this is a pilot study, these preliminary results are intended to provide insights and suggestions for future large-scale investigations. Nonetheless, our data provide initial evidence that BRAT may be an effective tool for chronic stroke rehabilitation. The integration of serious games further enhanced this effect by engaging additional visuomotor networks and providing the enriched sensory input necessary for sustained learning. In conclusion, our findings suggest that lesion characteristics, particularly hemispheric dominance, and lesion location, are key factors that may influence how a patient responds to bilateral robotic interventions. We believe these results have important implications for personalized rehabilitation planning, as they suggest that clinicians should tailor robotic protocols to the specific lesion side of each survivor to optimize functional outcomes.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Data availability
The data associated with the paper are available from the corresponding author upon reasonable request.

Ethical approval
All procedures performed in this study involving human participants received ethical approval from the competent authorities, as described in the appropriate section of the manuscript, and have been conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed consent
Written informed consent was obtained from all participants prior to inclusion in the study and for publication of their data, as described in the appropriate section of the manuscript.

Authors' contributions
Stefania Dalise: conceptualization, methodology, writing – original draft, review and editing. Fabrizio Leo: formal analysis, data curation, writing – original draft. Nicoletta Falcone: investigation, data curation, writing – original draft. Luca Maggiani: investigation, data curation. Valentina Azzollini: investigation, writing – original draft, project administration. Carmelo Chisari: conceptualization, methodology, writing – review and editing, project administration. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Bimanual Activity Test

The Bimanual Activity Test (BAT) evaluates the functional integration of the impaired upper limb during ecologically valid activities of daily living (ADLs) requiring coordinated use of both upper limbs. Developed to assess upper-limb functional recovery in individuals with unilateral motor impairment, such as hemiparesis after stroke, the BAT is specifically designed to capture the contribution of the impaired limb during bimanual activities. A key methodological feature of the BAT is that all tasks require the use of both upper limbs, allowing the contribution of the impaired limb to be assessed directly within functional activities. This reduces the influence of compensatory one-handed strategies that may lead to apparently successful task completion on conventional measures. The BAT therefore captures not only whether a task is completed, but also the extent and quality of the impaired limb's involvement in task execution.

Experimental setup: Participants are seated comfortably in front of a table, with both upper limbs resting on the surface in a standardized starting position. The objects required for each task are placed in the central workspace between the two hands. Tasks involve object manipulation, tool use, object transport, or fine motor interactions requiring coordinated bimanual control.

Procedure: Participants are instructed to perform a standardized set of 25 ADL tasks (listed in Table 1). Participants are free to adopt their preferred strategy regarding limb dominance and division of roles, allowing naturalistic behavior and individual adaptation strategies to be captured. Each task starts from the standardized resting position and ends when the participant returns both hands to the starting position.

Supplementary Table I.—Bimanual Activity Test (BAT).

1	Loosen and tighten the cap of a bottle
2	Open and close a padlock
3	Cut a piece of modeling paste using fork and knife
4	Loosen and tighten the cap of a 10 cm jar
5	Tear a piece of paper in four parts
6	Draw a line using a pencil and a ruler
7	Cut a piece of paper in two using scissors
8	Open a closed paper bag
9	Fold a piece of paper and place it in a paper bag
10	Staple two pages
11	Tie a bow on a gift box
12	Tie a scarf
13	Shuffle playing cards
14	Open and close a zip-bag
15	Fast and unfasten a belt buckle
16	Squeeze toothpaste onto a toothbrush
17	Spread a tablecloth over a table
18	Roll a poster and secure it with an elastic band
19	Unscrew a bolt
20	Open a safety closure cap
21	Open a glasses case
22	Open a pack of handkerchiefs and take one
23	Move a 1-kg shoe box horizontally
24	Move one shoe box over another
25	Move a ball from the floor to a table

Scoring: Two primary outcome measures are extracted:

- **Execution time:** time in seconds from task initiation, defined by the experimenter's "Go!" command, to task completion, defined as the participant returning both hands to the starting position.
- **Quality score:** 5-point Likert Scale assessing the degree to which the impaired limb is functionally integrated into task execution

0: unable to complete the task;

1: completes the task without using the impaired limb;

2: completes the task with minimal use of the impaired limb, limited to passive stabilization of objects;

3 = completes the task with moderate use of the impaired limb, including functional grasp or pinch, although altered or weak;

4 = completes the task with full active integration of the impaired limb in coordination with the intact limb.