

SUPPLEMENTAL MATERIAL

Evidence of motor skill learning in acute stroke patients without lesions to the thalamus and internal capsule

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Supplementary Methods

Baseline Assessment of the acute stroke patients

Fugl-Meyer Upper Extremity Assessment (FMUE)¹⁶

The FMUE is a reliable and valid tool for the evaluation of motor function (Saes et al. 2019). It is composed of 33 items distributed in 4 sections⁶⁰ : (1) Upper Extremity; (2) Wrist; (3) Hand and (4) Coordination and speed. Each item is scored on an ordinal scale of 0 (absent), 1 (partial impairment), and 2 (no impairment) resulting in a maximal score of 66 (normal).

Test for Upper-Limb Apraxia (TULIA)¹⁷

The TULIA is a bedside test⁶¹ including 2 items evaluating meaningless gestures, 7 intransitive gestures and 3 tool-related gestures. Each item is dichotomized as 1 point = succeed and 0 = fail resulting in a maximal score of 12, with cut-off scores of 9 for mild apraxia and 5 for severe apraxia.

Montreal Cognitive Assessment (MoCA)⁶²

The MoCA is a 10-minutes cognitive screening tool assessing the following cognitive functions: the short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, language and orientation. The maximal score is 30, with a cut-off score of 26 for possible mild cognitive impairment^{63,64}.

Corsi Block tapping test¹⁹

The Corsi Block tapping test is a widely used assessment of the visuospatial short-term memory and working memory. This test is composed by 9 blocks placed on a board and requires a quick administration. The participants are asked to repeat sequences of blocks which are shown by an examiner. The length of the sequence increases gradually through the task.

Box and Blocks test (B&BT)²⁴

The B&BT is a widely used assessment for the evaluation of gross manual dexterity. This test consists of moving a maximum number of blocks one by one from one side of a box to the other one. The score is the number of blocks moved in 1 minute^{65, 66}.

Grip force (GF) measurement²⁴

The GF was quantified using a whole-hand Jamar dynamometer. The subject is comfortably seated, shoulder adducted with no rotation, elbow flexed to 90 degrees and wrist in neutral position. Each evaluation is composed of 3 trials (with 1 min rest between trials) where maximal isometric force is recorded in each hand alternately. Then, the 3 measurements are averaged separately for each hand^{67, 24}.

Supplementary Tables

Supplementary Table I – Patients characteristics

Patients	Gender	Age (Year)	Time @incl. (days)	Handines s	Damaged hemisphere	Type of stroke	Localization	NIHSS total adm	NIHSS arm	NIHSS leg	Fugl- Meyer	MoCA	Tulia
1	M	63	2	R	Non-dom (R)	I	Cx-SubCx	9	3	3	66	23	12
2	M	71	5	R	Dom (L)	I	Cx-SubCx	4	1	1	63	26	12
3	M	59	2	R	Dom (L)	I	Cx	3	1	0	66	29	12
4	F	79	3	R	Non-dom (R)	I	Cx-SubCx	5	2	1	43	24	12
5	M	74	3	L	Dom (R)	I	Cx-SubCx	7	1	1	50	28	12
6	M	46	2	L	Dom (R)	H+	Cx	3	1	0	65	30	12
7	M	68	4	R	Non-dom (R)	I	Cx-SubCx	2	1	0	54	25	12
8	F	67	1	R	Non-dom (R)	I	Cx	3	0	0	66	23	12
9	M	68	2	L	Non-dom (L)	I	Cx	2	1	0	60	21	12
10	M	70	3	R	Dom (L)	I	Cx	1	0	0	60	21	12
11	M	67	2	R	Non-dom (R)	I	Cx-SubCx	3	0	0	65	29	11
12	M	41	3	R	Dom (L)	I	Cx-SubCx	4	0	0	66	23	12
13	M	45	3	R	Dom (L)	I	Cx-SubCx	4	1	1	55	24	12
14	F	49	2	R	Dom (L)	I	Cx-SubCx	3	0	0	56	27	12
15	F	85	1	R	Non-dom (R)	I	Cx-SubCx	4	1	1	59	22	10
16	M	40	2	R	Dom (L)	I	Cx	6	1	0	62	28	11
17	F	60	2	L	Dom (R)	I	Cx-SubCx	5	3	0	51	30	12
18	M	73	2	R	Non-dom (R)	I	Cx	3	1	0	66	26	11
19	F	83	1	R	Non-dom (R)	I	Cx-SubCx	3	1	1	56	24	11
20	F	82	3	R	Non-dom (R)	I	Cx	0	0	0	51	23	5
Mean	13 M	64.5	2.4	16 R	10 Dom	19 I	12 Cx-SubCx	3.7	1	0.5	59	25.3	11.3
±SD	7 F	±13.9	±1	4 L	10 Non-Dom	1 H	8 Cx	±2	±0.9	±0.8	±6.7	±2.9	±1.6

M: male, F: female, R: right, L: left, Dom: dominant, Non-dom: non-dominant, I: ischemic, H+: hemorrhagic, Cx: cortical, SubCx: subcortical, NIHSS total adm: total NIHSS at admission, NIHSS arm: NIHSS sub-item 5 (contralesional arm), NIHSS leg: NIHSS sub-item 6 (contralesional leg).

Supplementary Table II - Healthy Individuals characteristics

HI	Gender	Age (Years)	Handiness
1	M	51	R
2	F	63	R
3	M	52	R
4	F	59	R
5	F	50	R
6	M	53	R
7	F	51	R
8	M	64	R
9	F	66	R
10	F	55	R
11	F	55	R
12	F	50	R
13	M	55	R
14	M	75	R
15	M	51	R
16	M	52	R
17	M	51	R
18	F	54	R
19	F	51	R
20	M	59	L
21	M	60	R
22	F	71	R
23	M	72	R
24	F	52	R
25	F	79	R
26	F	82	R
27	F	72	R
28	M	59	R
29	F	51	R
30	F	59	R
31	F	56	R
32	F	52	R
33	M	62	R
34	F	55	R
35	F	52	R
Mean	14 M	58.6	34 R
±SD	21 F	±8.9	1 L

Supplementary Table III: Comparison between HI and patients (SAT a.u.)

					Difference progression				Ratio progression			
	Measures	Time	HI	S	d-Baseline HI	d-Baseline S	d-Group	p-value	r-Baseline HI	r- Baseline S	r-Group	p-value
CIRCUIT	SAT	D1T1	12,9	7,4	NA	NA	NA		NA	NA	NA	
	SAT	D3T10	34,3	19,4	21.4 [19.3;23.5]	12.1 [9.3;14.9]	-9.3 [-12.8; -5.9]	6.0e-15	2.8 [2.50; 3.14]	2.5 [2.17; 2.95]	0.9 [0.74; 1.09]	0.12
	SAT	G1	23,7	13,9	10.8 [8.7;12.9]	6.6 [3.7; 9.4]	-4.2 [-7.7; -0.7]	0.00046	1.9 [1.73; 2.18]	1.9 [1.63; 2.23]	1 [0.81; 1.19]	0.81
	SAT	G3	29,4	17,6	16.5 [14.4;18.6]	10.2 [7.4;13.0]	-6.3 [-9.8; -2.8]	0.07	2.4 [2.14; 2.70]	2.3 [1.98; 2.71]	1 [0.80; 1.17]	0.61
REACHING	SPARC	D1T1	2,9	3,6	NA	NA	NA		NA	NA	NA	
	SPARC	D1T15	1,9	3,1	-1 [-1.79; -0.20]	-0.6 [-1.62; 0.51]	0.4 [-0.89; 1.77]	0.36	0.7 [0.57;0.81]	0.8 [0.66;1.05]	1.2 [0.91;1.62]	0.061
	SPARC	D2T15	1,9	2,7	-1 [-1.77; -0.18]	-0.9 [-1.93; 0.17]	0.1 [-1.22; 1.41]	0.84	0.7 [0.56;0.80]	0.7 [0.58;0.92]	1.1 [0.82;1.45]	0.42
	SPARC	D3T15	1,7	2,3	-1.2 [-2.01; -0.42]	-1.3 [-2.33; -0.23]	-0.1 [-1.38; 1.25]	0.89	0.6 [0.52;0.73]	0.6 [0.49;0.78]	1 [0.76;1.35]	0.88

SAT: speed/accuracy trade-off, SPARC: Spectral Arc Length (movement's smoothness), D: day, T: time (block), D1T1: Baseline, G: Generalization, HI: healthy individuals, S: stroke patients, Difference progression: in absolute value, Ratio progression: ratio

Supplementary Figures and Figure Legends

Supplementary Figure I. Patients characteristics: Brain imaging of the 20 acute stroke patients

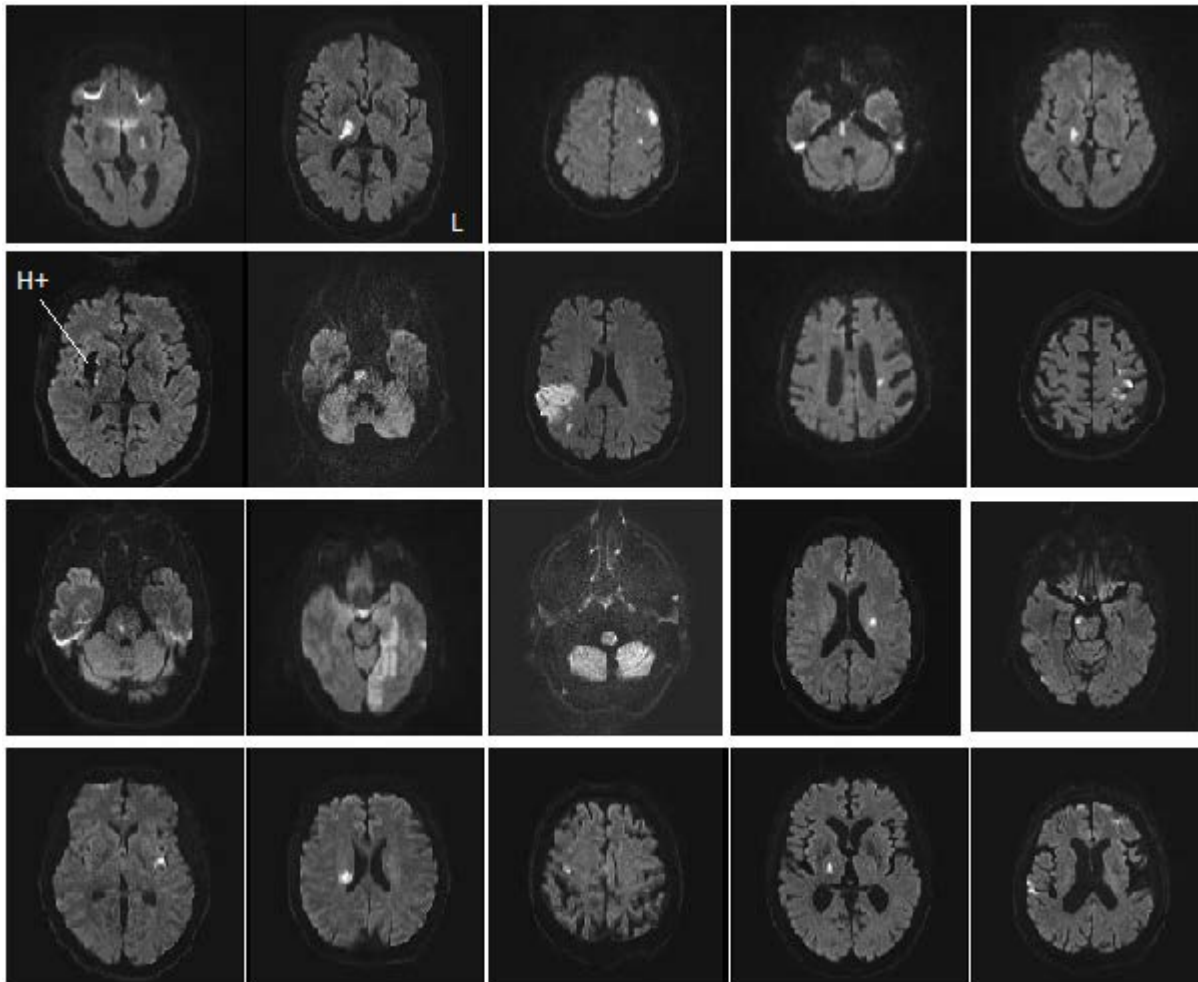


Figure legend. MRI scanners of the acute stroke patients. Diffusion-Weighted Imaging (DWI) showing the acute infarction. Only patient #6 had a subcortical haemorrhagic stroke. L: left.

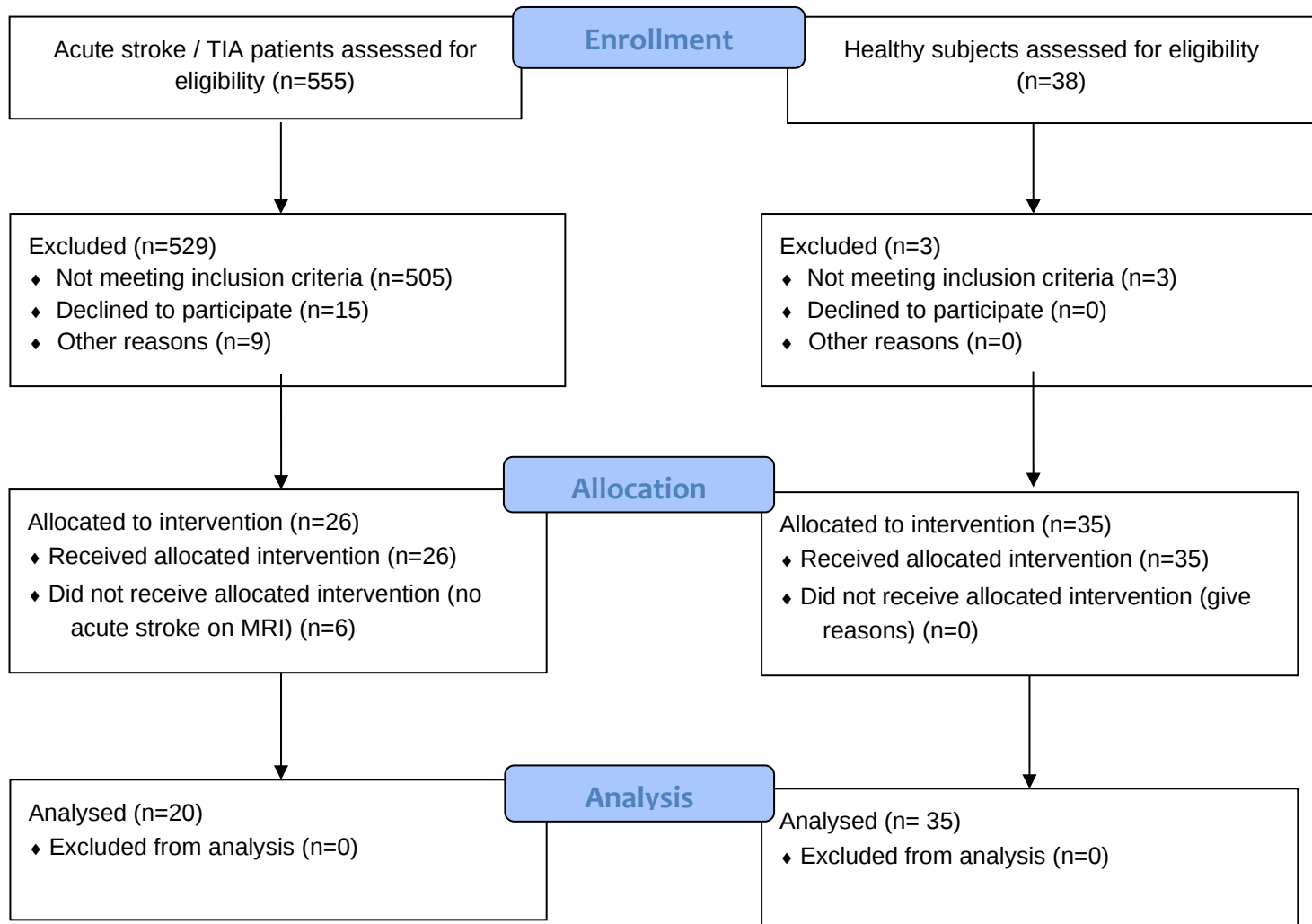
Supplementary Method. TREND reporting guideline for non-randomized intervention studies⁶⁸

Paper Section/ Topic	Item No	Descriptor	Reported?	
				Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	V	2
		• Structured abstract recommended	V	2
		• Information on target population or study sample	V	2
Introduction				
Background	2	• Scientific background and explanation of rationale	V	4-5
		• Theories used in designing behavioral interventions	V	4-5
Methods				
Participants	3	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	V	6
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	V	6
		Recruitment setting	V	6
		Settings and locations where the data were collected	V	6
Interventions	4	Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:		
		o Content: what was given?	V	
		o Delivery method: how was the content given?	V	7-8
		o Unit of delivery: how were the subjects grouped during delivery?	V	6
		o Deliverer: who delivered the intervention?	X	
		o Setting: where was the intervention delivered?	V	6
		Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	V	7
		o Time span: how long was it intended to take to deliver the intervention to each unit?	V	7
o Activities to increase compliance or adherence (e.g., incentives)	X			
Objectives	5	• Specific objectives and hypotheses	V	5
Outcomes	6	• Clearly defined primary and secondary outcome measures	V	9
		Methods used to collect data and any methods used to enhance the quality of measurements	V	7-9
		Information on validated instruments such as psychometric and biometric properties	V	
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	X	
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	V	6-7
		Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	X	
		Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	X	

Blinding (masking)	9	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment;if so, statement regarding how the blinding was accomplished and how it was assessed.	X	
Unit of Analysis	10	Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	V	10-11
		If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	V	
Statistical Methods	11	Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	V	10-11
		Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	V	10-11
		Methods for imputing missing data, if used	X	
		Statistical software or programs used	V	9&11
Results				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (adiagram is strongly recommended)		
		Enrollment: the numbers of participants screened for eligibility,found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	V	6
		Assignment: the numbers of participants assigned to a study condition	V	6
		Allocation and intervention exposure: the number of participantsassigned to each study condition and the number of participants who received each intervention	V	6
		Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	N/A	
		Analysis: the number of participants included in or excluded from the main analysis, by study condition	N/A	6
		Description of protocol deviations from study as planned, along with reasons	X	
Recruitment	13	Dates defining the periods of recruitment and follow-up	X	6
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	V	SUPPL
		Baseline characteristics for each study condition relevant to specific disease prevention research	V	SUPPL
		Baseline comparisons of those lost to follow-up and those retained, overalland by study condition	X	
		Comparison between study population at baseline and target populationof interest	X	
Baseline equivalence	15	Data on study group equivalence at baseline and statistical methods usedto control for baseline differences	X	

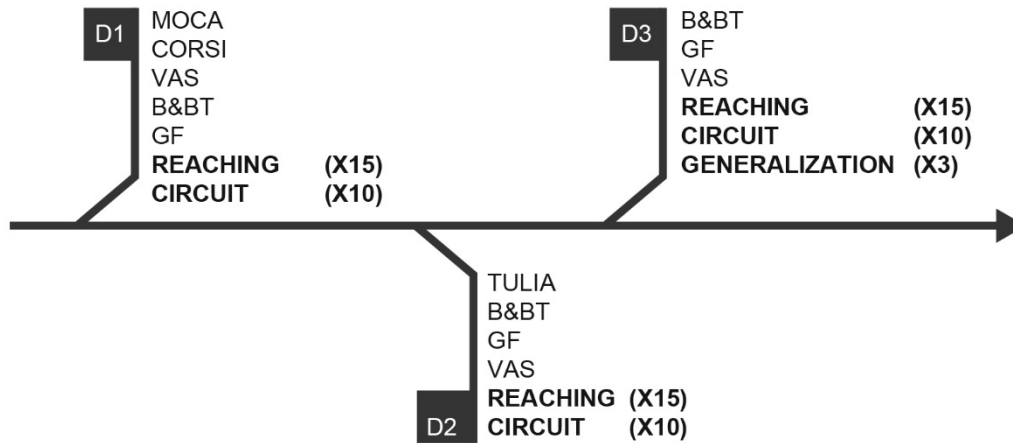
Number s analyze d	16	Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	V	6
		Indication of whether the analysis strategy was “intention to treat” or, if not, description of how non-compliers were treated in the analyses	X	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	XV	12-14
		• Inclusion of null and negative findings	X	12-14
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	X	
Ancillary analyses	18	Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	V	12-14
2 Adverse events	19	Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	V	
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	V	14-17
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	V	14-17
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	V	17-18
		Discussion of research, programmatic, or policy implications	V	17-17
Generalizability	21	Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	V	17-18
Overall Evidence	22	General interpretation of the results in the context of current evidence and current theory	V	14-17

Supplementary Figure II. Patient flow diagram



TIA: transient ischemic attack.

Supplementary Figure III. Study design



Patients and HI completed the same protocol over three consecutive days. On day 1 (D1), they trained with their paretic (or non-dominant UL for HI) on the serious game CIRCUIT, a MSkL task with a SAT. In order to quantify motor control/impairment, they performed a REACHING task, the Box and Blocks Test (B&BT) and a grip force (GF) measure which were all three replicated on day 2 and 3 (D2, D3). A visual analogic scale (VAS) of fatigue was completed at the end of each session. At the end of D3, generalisation was evaluated with another version of the CIRCUIT. Additionally, patients underwent a structural MRI (Diffusion-Weighted Imaging and 3D-FLAIR) and a Fugl-Meyer Upper Extremity Assessment.

Spectral arc length (SPARC)

The SPARC quantifies movement smoothness, and it was calculated from the arc length of the power spectrum of a Fourier transformation of the velocity signal (Gulde and Hermsdörfer 2018).

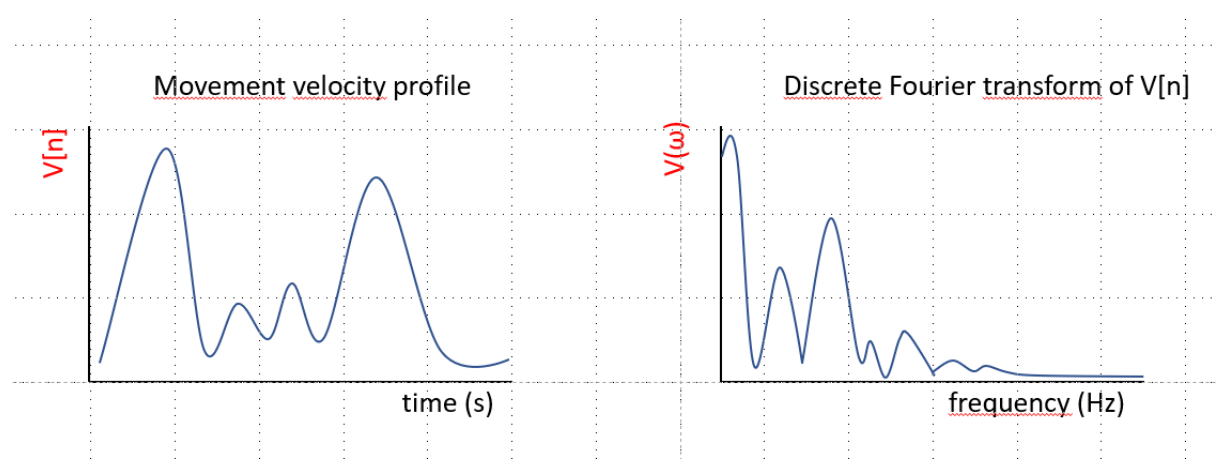
$$\text{SPARC} = - \int_0^{\omega_c} \left[\left(\frac{1}{\omega_c} \right)^2 + \left(\frac{d\hat{V}(\omega)}{d\omega} \right)^2 \right]^{\frac{1}{2}} d\omega; \quad \hat{V}(\omega) = \frac{V(\omega)}{V(0)}$$

$$\omega_c = \min \{ \omega_c^{max}, \min \{ \omega, \hat{V}(\omega) < \bar{V} \forall \omega > \omega \} \}$$

$V(\omega)$ is the Fourier magnitude spectrum and $[0, \omega_c]$ frequency band (Balasubramanian et al. 2015a; Balasubramanian, Melendez-Calderon, and Burdet 2012). The SPARC was computed with a sampling rate of 80 Hz and a maximum cut-off frequency ω_c^{max} of 20 Hz, and then concatenated for all the targets and trials separately for each session. The default value for $\bar{V}$ threshold was kept at 0.05, as in the original Matlab algorithm provided by Balasubramanian et al. signal (Gulde and Hermsdörfer 2018). SPARC values closer to 0 reflect smoother movements.

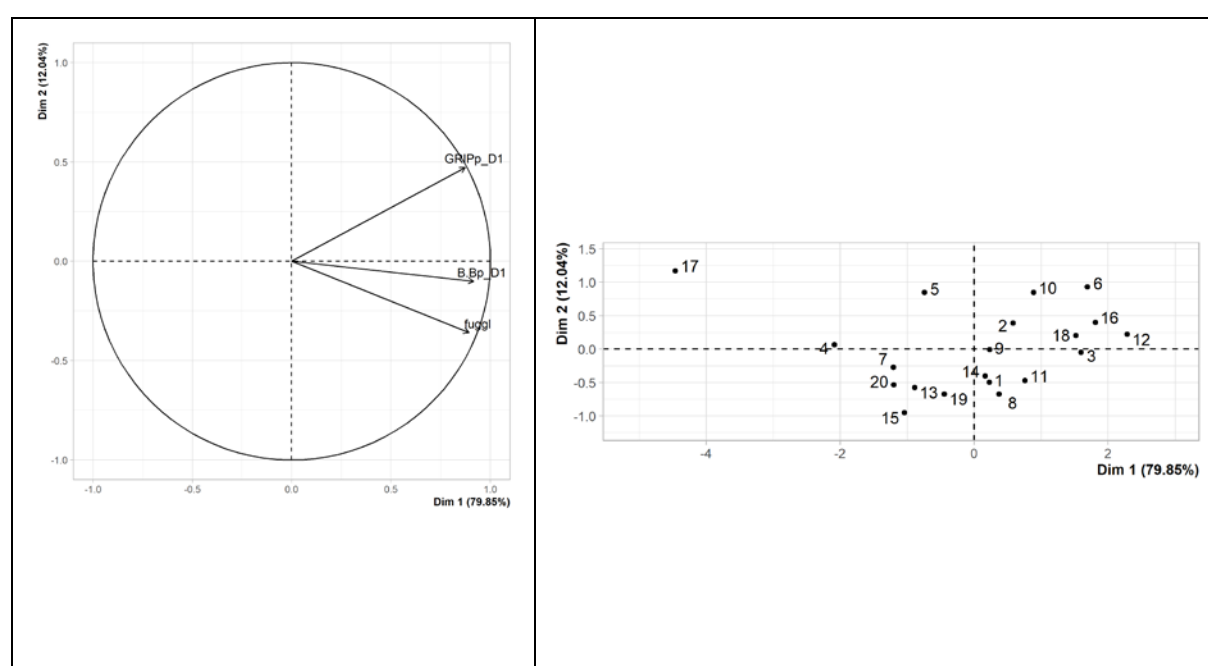
The Supplementary Figure IV below (adapted from Balasubramanian et al. (Gulde and Hermsdörfer 2018)) schematically illustrates schematically the SPARC. The left panel shows the velocity profile of a movement and the right panel shows a Fourier transformation of the velocity signal.

Supplementary Figure IV. SPARC.



The SPARC quantifies movement smoothness and is independent from the duration of the movement (Balasubramanian et al. 2015b). In other words, two movements with identical shapes of velocity profiles (e.g., a gaussian for point-to-point movement) but of different path lengths and durations will have identical SPARC scores. In addition, contrary to other metrics based on acceleration or jerk, the SPARC is valid for both discrete and rhythmic movements²⁸⁻³⁰.

Supplementary Figure V. PCA



For patients, a subset of correlations between baseline CIRCUIT performance and impairments were computed with Pearson's correlation coefficients using a Composite Motor Score (CMS). The CMS was generated using the first component of a Principal Component Analysis (PCA) performed on the FMUE, BBT and GF scores of each patient to estimate the overall paretic UL impairment.

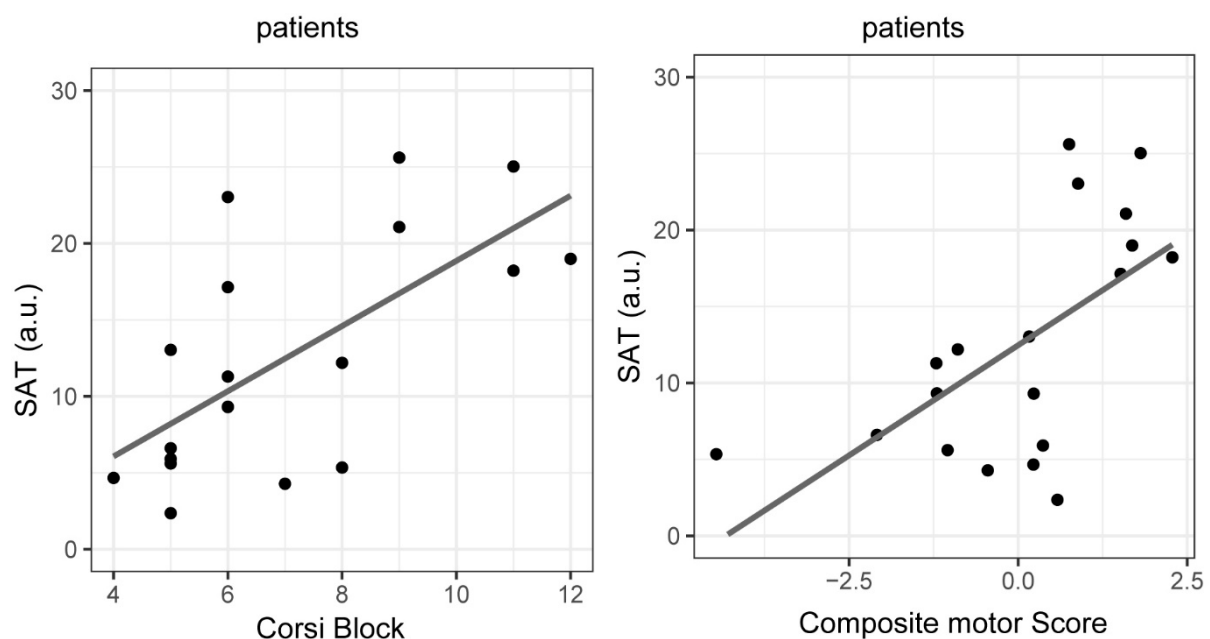
On the left panel, the first dimension of the PCA (Dim 1, 79.85%) and the second dimension (Dim 2, 12.04%) of the PCA are represented as eigen vectors, showing that the first dimension of the PCA explains the three scores (FMUE, BBT and GF). On the right panel, the distribution of the 20 patients

along the first and second dimension of the PCA is depicted. The (first dimension) of the PCA is an interesting estimate of the overall paretic UL impairment

Supplementary Methods: MRI & VLSM

In addition to routine clinical MRI sequences, a 3D-FLAIR covering the whole brain (1 mm³, TR=5000 ms, TE=402 ms, FA= 20°, matrix size= 512×512, FOV= 256×256 mm³, 160 slices, slice thickness= 1 mm, no gap) and a Diffusion-Weighted Imaging (DWI: 2 mm³, TR=7800 ms, TE=99ms, diff directions: 64, b value1: 0, b-value2: 1000, epi factor: 128, matrix size= 128×128, FOV= 256×256 mm³, 50 slices, slice thickness= 2 mm, no gap) were acquired on a 3T scanner with a 32-channel head coil (Siemens Verio, Erlangen, Germany).

Supplementary Figure VI. Correlation between baseline SAT (a.u.) and impairments



Pearson correlation for the stroke patients between the progression of SAT (a.u.) from D1T1 to D3T10 (overall MSKL) and the Corsi Score backward (left) or the CMS (composite motor Score, right). Pearson correlations were .66 and .61 respectively.

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