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ABSTRACT

Objective: To determine similarities and differences in key predictors of recovery of bimanual hand use and unimanual motor impairment after stroke.

Method: In this prospective longitudinal study n = 89 first-ever stroke patients with arm paresis, were assessed at 3 weeks, 3 and 6 months after stroke onset. Bimanual activity performance was assessed with the Adult Assisting Hand Assessment Stroke (Ad-AHA), unimanual motor impairment with the Fugl-Meyer Assessment (FMA). Candidate predictors included shoulder abduction and finger extension measured by the corresponding FMA-items (FMA-SAFE, range 0-4) and sensory and cognitive impairment. MRI was used to measure weighted corticospinal tract lesion load (wCST-LL) and resting-state interhemispheric functional connectivity (FC).

Results: Initial Ad-AHA performance was poor but improved over time in all (mild-severe) impairment subgroups. Ad-AHA correlated with FMA at each time-point ($r>0.88$, $p<0.001$) and recovery trajectories were similar. In patients with moderate-severe initial FMA, FMA-SAFE was the strongest predictor of Ad-AHA outcome ($R2 = 0.81$) and degree of recovery ($R2 = 0.64$). Two-point discrimination explained additional variance in Ad-AHA outcome ($R2 = 0.05$). Repeated analyses without FMA-SAFE identified wCST-LL and cognitive impairment as additional predictors. A wCST-LL above 5.5cc strongly predicted low-to-minimal FMA/Ad-AHA recovery (≤10/20p, specificity = 0.91). FC only explained some additional variance to FMA-SAFE in unimanual recovery.

Conclusion: Although recovery of bimanual activity depends on the extent of CST injury and initial sensory and cognitive impairments, FMA-SAFE captures most of the variance

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explained by these mechanisms. FMA-SAFE, a straightforward clinical measure, strongly predicts bimanual recovery.

Classification of Evidence: This study provides Class I evidence that the FMA-SAFE predicts bimanual recovery after stroke.

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INTRODUCTION

Stroke survivors with arm and hand motor impairment[1] often experience reduced daily life activities and participation[2]. Many daily tasks require skilful and coordinated use of the hands together, but bimanual recovery after stroke remains largely unstudied. One accelerometer-based study has indicated increased bimanual hand use, during the first 3 months after stroke[3]. Impaired inter-limb coordination[4] and grip force matching between hands[5] have also been reported.

Recently, the Adult Assisting Hand Assessment Stroke (Ad-AHA), has shown to produce valid and reliable measures for the adult stroke population[4, 5]. How often and how effectively the more affected arm and hand is spontaneously involved during the performance of bimanual tasks is evaluated. However, how bimanual performance evolves after stroke is unknown.

Using Ad-AHA, we aimed to investigate how bimanual activity performance recovers over time compared to unimanual motor impairment, and to identify key predictors of recovery. We hypothesized that initial motor impairment, indicated by shoulder abduction and finger extension strength, would be a weaker predictor of bimanual performance than it is for unimanual motor impairment, because Ad-AHA is a measure of spontaneous hand incorporating task goals and inter-limb coordination[6]. Furthermore, given the importance of somatosensory[7-9] and cognitive impairment[10, 11] for more complex tasks, we expected that bimanual recovery would be more strongly associated with initial somatosensory and cognitive status than unimanual recovery. Finally, we also assessed the contribution of simple structural and functional imaging variables, namely CST lesion load and interhemispheric connectivity, to bimanual recovery.

METHODS

Study design and participants

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This prospective observational study (ClinicalTrials.gov Identifier: NCT02878304) characterized similarities and differences in key predictors of recovery of bimanual hand use in relation to unimanual motor impairment after stroke (Class I evidence). Patients admitted to a sub-acute in-patient neurorehabilitation clinic, for persons of working age (18-70), at a university hospital in Sweden, were recruited (**figure 1**). First assessment was performed at admission (on average at 3 weeks post stroke, T1). Follow-up assessments were performed at three (T2) and six (T3) months after stroke onset. All patients participated in interdisciplinary rehabilitation.

Inclusion criteria were a first-ever stroke within 2-6 weeks, with upper extremity hemiparesis, verified by clinical examination performed by the admitting physician, using the MRC Manual Muscle Test and the arm and hand items of the National Institute of Health Stroke Scale (NIHSS). Exclusion criteria were inability to comply with or understand instructions, disorders other than stroke affecting hand function, a cerebellar lesion, and contraindications for MRI.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Regional Ethical Review Board in Stockholm (DNR: 2011/1510-31/3). Before inclusion, written informed consent was obtained from all participants. Speech and language therapists were consulted in recruitment of patients with aphasia, to ensure their ability to provide an informed consent.

Main outcome assessment

The adult version of Assisting Hand Assessment Stroke (Ad-AHA Stroke, for brevity hereafter referred to as Ad-AHA)[4] was used to evaluate how effectively the patients used their contra-lesional hand together with the ipsi-lesional hand during activity performance. This observation-based assessment comprises performance of one of two tasks (lasting ~10 min), either preparing a sandwich or wrapping a present. Both tasks require the use of the hands together and comprise gross and fine hand use (e.g. opening/closing containers, cutting, folding, stabilizing and using different grips) and are equally challenging[4]. The Ad-AHA measure bimanual activity performance, i.e. actual spontaneous performance as opposed to best capacity. The assessment is video-recorded and later scored by a certified assessor. Nineteen items are rated on a four-level ordinal scale: 4=effective, 3=somewhat effective, 2=ineffective, and 1=does not do. The scale is developed using a Rasch measurement model, and the scores are transformed to a logit-based Ad-AHA-unit scale, range 0–100. A higher unit indicates higher ability. Ad-AHA produce a valid measure of bimanual performance[4, 5] with good to excellent interrater and intrarater reliability for patients with subacute stroke[5]. In this study, each task was performed at least once by each patient and tasks were alternated between assessment occasions.

Unimanual arm and hand motor impairment was assessed with Fugl-Meyer Assessment for the Upper Extremity (FMA-UE)[12, 13]. The three reflex-items were omitted to exclusively reflect voluntary movement functions, yielding maximum 60 points[14]. Distal motor impairment was assessed using the FMA-Hand subscale (0-14 points)[15].

Other clinical assessments

Independent variables included in the prediction models and clinical assessment instruments used at baseline were:

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- Since finger extension and shoulder abduction strength is predictive of hand motor outcome[16, 17], a sum-score of rated shoulder abduction and finger extension was derived from the corresponding FMA-UE items, yielding the variable "FMA-SAFE", range 0-4.
- Proprioception – FMA subdomain for position sense[13], categorized to normal-near normal/impaired/absent.
- Pain – FMA subdomain for pain during passive movement[13]. A score of ≤23/24 indicated pain.
- Discriminative sensation (two-point discrimination, 2pD) – Index and thumb finger pads were tested with a Disc-Criminator (Dellon-McKinnon). Unable to detect 12mm indicated impairment.
- Touch – Monofilaments (5 item-kit, North Coast Medical) were applied to the index and thumb finger-pads. Categorized to; normal-near normal/impaired/absent.
- Vibration – A tuning fork was applied to the MCP bone 1. Intact vibration sense required ability to i) distinguish vibration from no vibration and ii) indicate when the vibration stopped.
- Aphasia Index – the Swedish Neurolinguistic Instrument A-ning[18], range 0-5.
- Cognitive status – the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS)[19], range 0-50.
- Anxiety/depression – Hospital Anxiety and Depression Scale (HADS-A/HADS-D), range 0-21 for the respective domain[20].
- Neglect – Baking Tray Task, (yes/no).
- Neural resistance of wrist and finger flexor muscles – the NeuroFlexor method[21].
- Demographic data obtained from patients' records were age, ischemic/haemorrhagic stroke, affected hemisphere and dominant hand.

Magnetic Resonance Imaging

Brain imaging was performed at baseline (T1) with an Ingenia 3.0T MR system (www.usa.philips.com) with an 8HR head coil. High-resolution T1-weighted anatomical images were acquired using TFE 3D (3-dimensional gradient echo-based sequence): field of view, 250×250×181 mm; matrix, 228×227; slice thickness, 1.2 mm; slice spacing, 0.6 mm; and number of slices, 301 (echo time, shortest; relaxation time, shortest). T2 FLAIR images were also acquired. Resting-state fMRI consisted of a gradient echo-planar sequence (echo time [TE] = 35 ms, flip angle = 90°, voxel size of 1.8 x 1.8 x 4 mm, repetition time [TR] = 3000ms) sensitive to BOLD contrast. The acquisition time was 6 minutes. Patients were instructed to keep eyes closed, to think about nothing in particular and to not fall asleep.

Anatomical T1-images were normalized to Montreal Neurological Institute template using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/). Cost function masking was used to avoid distortion of lesion by normalization procedure. The images were inspected visually to ensure adequate normalization. Lesion maps were manually drawn on all axial slices of native space T1 weighted anatomical images using MRIcron (https://people.cas.sc.edu/rorden/mricron/index.html) by a researcher (J.P.) and verified by an experienced neurologist (J.-C.B.) who was blinded to all clinical data. Lesion location was verified on fluid attenuated inversion recovery images, and lesion maps were binarized. Normalization parameters for T1 images were applied to lesion maps using the SPM12 tool *Old Normalize*.

Lesion maps were used to calculate weighted CST lesion load (wCST-LL, unit: cubic centimetre, cc) using previously constructed CST template based on regions of interest in the

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precentral gyri, posterior limb of internal capsule, cerebral peduncle, and anteromedial pons[22].

Resting-state functional connectivity analysis

Seed-based functional connectivity analysis was performed in 57 patients with complete resting-state fMRI data. Pre-processing was performed using SPM12b software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and included (i) head movement correction, (ii) co-registration of resting-state EPI images to T1-weigted anatomical images, (iii) segmentation (grey matter/white matter/CSF), (iv) normalization with cost-function masking of lesion using Clinical Toolbox, and (v) smoothing (8 mm).

Motor cortex connectivity has been shown to explain a portion of the variance in motor recovery[23] and the supplementary motor area (SMA) was also analysed since it is crucial for bimanual coordination[24].

We calculated interhemispheric functional connectivity (FC) between regions of interest (ROIs) including: ipsi-lesional and contra-lesional primary motor cortex/precentral gyrus (PCG) and SMA ROIs from the FSL´s Harvard-Oxford cortical and subcortical structural atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Seed-based functional connectivity (FC) was calculated using the Connectivity toolbox[25]. It incorporates the CompCorr strategy for reduction of noise of physiological and other sources[26], that takes into account the non-homogenous distribution of noise signals in the brain. Principal components (PCA) were derived from these noise regions and later included as nuisance parameters within the general linear model.

Head motion parameters and outliers (Artifact Detection toolbox: https://www.nitrc.org/projects/artifact_detect) were also included as regressors since it has been shown that this strategy improves motion artefact correction when studying FC[27]. White matter and CSF masks were used for partial volume correction. The principal components of signal from white matter and CSF masks were regressed out during the analysis. A temporal band pass filter (0.01-0.08Hz) was applied covering approximately the range between 10 s and 100 s which is standard for resting-state connectivity analyses[28]. The toolbox computed the average BOLD time series across all the voxels within each ROI.

Bivariate correlation and regression analyses were performed giving beta values (from linear regression results) reflecting the level of linear association of the bold time series between each pair of ROIs. The beta value reflecting PCG FC (FC_{PCG}) and SMA FC (FC_{SMA}) was extracted for each patient.

Statistical methods

Longitudinal bimanual activity was assessed with regard to *outcome* at 6 months, and *recovery*, which was calculated as the ratio between *actual change from T1 to T3* and *residual impairment at T1* (i.e. the scale´s maximum score minus initial score).

$$recovery = \frac{(\mathrm{T3} - \mathrm{T1})}{(\text{the scale´s maximum score} - \mathrm{T1})}$$

Unimanual motor impairment data was described using the same approach.

One patient was lost to follow up at 3 months due to illness and 5 patients could not be reached or had moved to another city at 6 month's follow-up. Last value was carried over compensated for missing data at 6 months.

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A Linear Mixed Effect Model with subject ID included as random effect was used to calculate the overall effect of time on Ad-AHA and FMA-UE/FMA-Hand, and effect of time by impairment subgroup.

Prediction analysis first involved univariate linear regression analysis to determine the strength of the univariate associations. Secondly, multivariable regression analysis was undertaken. A stepwise procedure using forward selection was used. The independent variables were carried forward, one by one, in order of univariate association strength (i.e. the highest R square). Included variables that did not contribute with a significant F-change were discarded. For evaluation of alternative prediction candidates, the analysis procedure was repeated without the strongest predictor identified in the first model.

Regarding wCST-LL, further analysis assessed its ability to distinguish patients experiencing a clinically meaningful difference in FMA-UE (≥ 10 points) from T1 to T3[29], from those who did not. To this end, a ROC curve analysis was performed, and sensitivity values (true positive rate) and 1 minus specificity values (false positive rate) were plotted. Area under the curve and ±95% confidence intervals were also calculated. A second multivariable regression analysis was performed in patients with wCST-LL below the ROC-identified negative predictive threshold for FMA-UE recovery. This sub-sample was determined using the FMA-derived threshold, since clinical meaningful difference has yet not been determined for the Ad-AHA.

The level of significance was set at 0.05.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

RESULTS

Eighty-nine patients were included at 25±7 (mean±SD) days from stroke onset, at which n = 23 had mild initial sensorimotor impairment (FMA-UE ≥ 48), n = 19 had moderate (FMA-UE = 20-47) and n = 47 severe (FMA-UE ≤19). Demographical and clinical characteristics are presented in **table 1.**

Association between bimanual activity performance and unimanual motor impairment over time

Ad-AHA and FMA-UE/FMA-Hand showed high inter-individual variability regarding status at each time-point and recovery **(figure 2, A-C).** Ad-AHA correlated strongly with FMA-UE (r_s range = 0.877-0.938, $p < 0.001$) **(figure 2A)** and FMA-Hand (r_s range = 0.886-0.923, $p < 0.001$) at each time-point. Ad-AHA recovery correlated with FMA-UE recovery ($r_s = 0.839$, $p < 0.001$), and FMA-Hand recovery ($r_s = 0.824$, $p < 0.001$), **(figure 3B-C)**. In patients with mild unimanual impairment, Ad-AHA and FMA-UE/FMA-Hand correlations were low or non-significant (r_s range = 0.188-0.322, $p > 0.05$ and r_s range = 0.367-0.469, $p \geq 0.027$ respectively) while patients with moderate and severe impairment showed significant positive correlations (r_s range = 0.564-0.826, $p < 0.015$).

There was a significant effect of time on Ad-AHA ($F(2, 87) = 30.0$, $p < 0.001$), FMA-UE ($F(2, 87) = 40.5$, $p < 0.001$) and FMA-Hand ($F(2, 87) = 24.3$, $p < 0.001$). The time-effects on Ad-AHA were significant in all three impairment groups **(figure 2D)**. However, there was a significant effect of time on FMA-UE and FMA-Hand in the moderate and severe impairment groups, but not in the mild group **(figure 2E-F)**.

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Prediction of bimanual and unimanual outcome and recovery

To avoid known ceiling effects of the FMA-UE[13], mildly impaired patients (n = 23), who had a minimal residual arm and hand motor impairment (FMA-UE = 56±3.6 points [mean±SD]) at 3 weeks, were not included in the prediction analysis, yielding a sample of n = 66. Univariate associations are shown in **etable 1** (available from Dryad: https://doi.org/10.5061/dryad.866t1g1qq) and multivariable results in **table 2**. The strongest association was with FMA-SAFE, shown in **figure 3 (D-G)**.

Prediction of outcome

The multivariable linear regression analysis showed that Ad-AHA outcome was best predicted by FMA-SAFE and 2pD, together explaining 86% of the variance, 2pD contributing with 5% **(table 2)**. When repeating the analysis without FMA-SAFE, alternative independent predictors were wCST-LL (44%), 2pD (15%), BNIS (7%) and pain (3%), which together explained 70% of the variance.

In comparison, FMA-UE outcome was best predicted by FMA-SAFE and interhemispheric FC_{PCG}, together explaining 87% of the variance, of which FC_{PCG} accounted for 3%. The best fitted model without FMA-SAFE included wCST-LL (49%), 2pD (7%) and BNIS (6%), together explaining 62% of the variance. Results for FMA-Hand were almost identical **(table 2)**.

Prediction of recovery

Ad-AHA recovery was best predicted by FMA-SAFE as a single predictor, explaining 64% of the variance. Without FMA-SAFE, the best model included wCST-LL (31%) combined with 2pD (9%), together explaining 40% of the variance **(table 2)**.

In comparison, FMA-UE recovery was also best predicted by FMA-SAFE as a single predictor, explaining 72% of the variance. Without FMA-SAFE, the best prediction model included wCST-LL (36%) and 2pd (5%), together explaining 41% of the variance. Results for FMA-Hand were similar to FMA-UE but more variance was explained by interhemispheric FC_{PCG} **(table 2)**.

ROC analysis of CST integrity

Sensitivity and specificity of CST lesion load

The ROC analysis on wCST-LL data for the moderate and severe impairment groups revealed a predictive threshold of 5.5cc, separating patients who showed a clinically meaningful increase in FMA-UE, ≥10 points, from those who did not **(figure 4A-B)**. The sensitivity of this predictive threshold was 0.73 and specificity was 0.91 (AOC=0.889, SE=0.043, p<0.001, 95%CI: 0.802-0.971). Two patients only out of n=28 with wCST-LL >5.5cc recovered ≥10 points in FMA-UE **(figure 4B)**. The variability of actual change in FMA-UE was high among individuals with wCST-LL < 5.5cc (summary score = 19.4±10.6 [mean ±SD], range 0-37, corresponding to recovery ratio of 0.54±0.30, range 0-1; **figure 4**).

Figure 4C illustrates changes in Ad-AHA between 3 weeks and 6 months in relation to the same wCST-LL cut-off. Ad-AHA recovery was poor in patients with wCST-LL >5.5cc and more variable in patients with wCST-LL<5.5cc, with no patient with wCST-LL >5.5cc having Ad-AHA increase above ~20. Conversely, Ad-AHA recovery was highly variable in patients with wCST-LL<5.5cc (**figure 4C**). Given this high variability in unimanual and bimanual recovery, multivariable linear regression was therefore implemented in the subsample of n=38 patients with wCST-LL <5.5cc **(figure 4B)**.

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Outcome and recovery in patients with CST lesion load <5.5cc

Multivariable regression identified FMA-SAFE, 2pD and BNIS as the main predictors of Ad-AHA outcome as well as recovery in this subgroup. Haemorrhagic stroke was also identified as favourable for outcome and recovery **(table 3)**.

The main predictors of FMA-UE and FMA-Hand outcome and recovery were FMA-SAFE, 2pD, FC_{PCG} and BNIS, with lower total amount of variance explained, compared to the previous models **(table 2)**.

DISCUSSION

This study cohort had poor initial bimanual performance (mean Ad-AHA of 37, max 100) and considerable unimanual motor impairment (mean FMA-UE of 24, max 60). Bimanual activity performance improved significantly over time across all impairment severity levels (mild, moderate and severe), while in no significant effect of time was observed for unimanual impairment in group with mild initial impairment. Unexpectedly and contrary to our hypothesis, bimanual and unimanual recovery trajectories were strikingly similar and were explained by similar factors. Both were to a large extent explained by early FMA-SAFE score, which captured variance explained by CST injury and initial sensory and cognitive impairments. In addition, CST lesion load >5.5 cc was associated with poor bimanual and unimanual outcome and recovery. However, despite these similarities, some differences were apparent. Initial sensory impairment had additional predictive value, above that explained by FMA-SAFE, for bimanual but not for unimanual outcome and recovery. Conversely, interhemispheric FC_{PCG} explained some additional variance in unimanual outcome and recovery above that explained by FMA-SAFE.

FMA-SAFE - a key determinant of bimanual outcome and recovery

FMA-SAFE was the strongest univariate and multivariable predictor of outcome and recovery of bimanual performance. The multivariable analyses showed that FMA-SAFE explained 81% of the variance in bimanual outcome, with some additional variance explained by sensory impairment (5%). FMA-SAFE alone explained bimanual recovery over time (64%). These results suggest that basic movement capacity, i.e. finger extension and shoulder abduction, important for recovery of bimanual hand use in stroke patients with moderate-to-severe initial unimanual motor impairment. The strong association between bimanual outcome and recovery and FMA-SAFE in the severe impairment group **(figure 3D-E)** further indicates that recovery of unimanual motor control is one essential step in recovery of bimanual hand use. Additionally, correlation strength between bimanual and unimanual scores increased from the first to later time points. Finally, correlations between Ad-AHA and FMA-UE outcome and recovery were stronger in the moderate and severe impairment groups ($R = 0.50\text{-}0.89$, $p < 0.028$) as compared to the mild group ($R = 0.188\text{-}0.322$, $p > 0.05$). These results point to the importance of unimanual motor control functions for bimanual recovery in patients with moderate-to-severe motor impairment.

FMA-SAFE was also the strongest predictor of unimanual motor impairment (FMA-UE) regarding both outcome (84% explained) and recovery (74% explained), confirming previous findings[30]. We had expected an even lower degree of variance explained by FMA-SAFE for bimanual recovery given that bimanual tasks require greater sensorimotor integration to manipulate objects and adaptation of movements during task. Typically, interacting with various objects, as in Ad-AHA tasks, comprises reaching and grasping actions, which involves the ability to stabilize the arm and hand while moving towards a target and during fine hand use[31]. FMA-SAFE assesses shoulder abduction which is involved in arm transport

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and finger extension which is necessary for opening fingers before grasping[32]. Recovery of distal movement functions (FMA-Hand score of 14 points) was not sufficient for full recovery on the Ad-AHA **(figure 3C)**, while patients obtaining a full score on the FMA-UE scale (that includes proximal movement control items) recovered equally well on the Ad-AHA **(figure 3B)**. Previous research has highlighted the importance of proximal movement control function for reaching[33], and Ghaziani, Couppe, Siersma, Christensen, Magnusson, Sunnerhagen, Persson and Alt Murphy [34] showed that individual FMA-rated finger extension, shoulder abduction, and elbow extension was useful in predicting arm function at six months after stroke. Our findings show that FMA-SAFE is also important for recovery of bimanual performance.

Some other predictors showed strong associations with bimanual outcome in the univariate tests, but did not reach significance in the final multivariable regression models. This was the case for spasticity (neural resistance). Severe hand spasticity (neural resistance >8N) may be negatively associated with hand motor recovery, while hand spasticity in the lower range (<8N) is not[35]. In the present analysis (**etable 1** available from Dryad: https://doi.org/10.5061/dryad.866t1g1qq) neural resistance did not remain significant when including the SAFE-score or two-point discrimination and CST integrity. These variables co-varied reflecting common sources of variance.

Neuroimaging predictors

An analysis of predictors masked by and co-varying with FMA-SAFE showed that CST lesion load was a highly significant predictor of bimanual recovery, explaining a similar amount of variance in bimanual (44% of outcome and 31% of dynamic recovery) and unimanual recovery (49% of outcome and 35% of dynamic recovery). This extends previous findings[36, 37]. showing that CST lesion load is important for recovery of bimanual activity performance. However, the modest variance explained also suggests a contribution by other neural substrates and multiple pathways supporting recovery such as cortico-cortical connections[38] cortico-basal ganglia loops, other descending motor pathways such as the reticulospinal tract and CST projections from primary somatosensory cortex, and afferent somatosensory input[39]. The ROC analysis further showed that a lesion load > 5.5 cc was highly predictive of both poor bimanual and unimanual recovery **(figure 4)**. Feng, Wang, Chhatbar, Doughty, Landsittel, Lioutas, Kautz and Schlaug [36] also reported that a wCST-LL >5.5 cc in the acute phase, was a strong predictor of unimanual motor recovery (FMA-UE outcome score >25) at three months and Pennati, Plantin, Carment, Roca, Baron, Pavlova, Borg and Lindberg [7] found that wCST-LL >6cc indicated absence of recovery of dynamic precision grip. The present findings show that a similar wCST-LL threshold (>5.5 cc) is also a strong predictor of bimanual hand recovery. The CST is well developed in humans[40] and is essential for dexterity and its recovery post-stroke[7, 22]. The present findings show that CST integrity is important for bimanual recovery.

In patients with CST lesion load <5.5cc, the predictors of bimanual outcome and recovery did not differ substantially. FMA-SAFE was again the strongest predictor and two-point discrimination was the second strongest predictor of Ad-AHA recovery. Interestingly, stroke type (ischemic or haemorrhagic) explained a significant portion of the variance in recovery of bimanual activity performance, but not in unimanual impairment, in line with findings[41] showing a greater change in activity capacity (ARAT) in haemorrhagic as compared to ischemic stroke patients.

Contrary to our expectations, interhemispheric FC did not explain any unique variance in Ad-AHA recovery **(table 2 and 3)**. This agrees with previous reports that failed to show an

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association between FC and unimanual motor recovery[42, 43]. However, in the present study, interhemispheric FC_{PCG} did explain some additional variance in unimanual outcome and recovery, in addition to FMA-SAFE **(table 2)**, in agreement with some other studies[43-45]. Notably, the greatest influence of FC_{PCG} was in predicting recovery of unimanual hand motor function in patients with CST lesion load < 5.5cc (10% additional variance to 50% explained by FMA-SAFE, **table 3**). These findings suggest that interhemispheric motor cortex FC may support unimanual recovery, particularly in patients with relatively spared CST projections, while its role for bimanual recovery is less certain.

Contribution of sensory and cognitive impairments

As expected, sensory impairment explained additional variance in bimanual outcome and recovery when combined with FMA-SAFE. This was not the case for unimanual impairment. Also when FMA-SAFE was excluded from the prediction model, sensory impairment explained more variance in bimanual (15% of outcome and 9% of recovery) than unimanual recovery (7% of outcome and 5% of recovery).

In patients with relatively intact CST (wCST-LL<5.5cc) sensory impairment was the factor that explained most variance of bimanual recovery when excluding FMA-SAFE (30% of outcome and 25% of recovery). Somatosensory function is essential for grasping and skilled object manipulation[9]. Two-point discrimination has been shown to predict recovery of pinch grip over time[7] and, proprioception, quantified using a robotic device, explained treatment gains after robotic hand therapy[46]. Qualitative reports also suggest a key contribution of sensory impairment that is often neglected by therapists[47]. Our findings provide evidence that sensory function is one key determinant for bimanual recovery, most likely since the activity-based Ad-AHA measure involves object manipulation which requires some residual somatosensation[9].

Cognitive impairment, measured using a comprehensive screening instrument[19], also emerged as a significant predictor of bimanual outcome (adding 7% of variance explained), when FMA-SAFE was not included in the prediction model from the start. The partly shared variance explained by FMA-SAFE and cognitive impairment, suggests a possible cognitive-motor interaction that may deserve further attention in prediction modelling as well as for the design of treatment interventions. Some other studies have suggested a cognitive-motor interaction in recovery from hand motor impairment, particularly attention and executive functions[48].

Cognitive status also explained a significant amount of variance in FMA-Hand outcome and recovery (7% and 10% respectively) that co-varied with FMA-SAFE, comparable to Ad-AHA. It therefore seems that cognitive status may be significant for recovery of more distal unimanual movement control functions. Previous work in subjects with mild cognitive impairment has shown that complex aspects of manual dexterity (e.g., individuated finger movement) correlate with neuropsychological measurements of attention and working memory[11], suggesting cognitive-motor interaction in dexterous tasks. Our findings are consistent with the interpretation that bimanual activity performance require planning and coordination of movements across two hands.

Limitations

This study was not suited for the evaluation of age as a predictor of recovery[30]. The severe motor impairment group included more males and the first measurement point occurred later

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in this group compared to the mild and moderate subgroups **(table 1).** However, including these factors in multivariable analyses did not change the results.

We included 89 patients with stroke, a limited sample size for the number of independent variables tested. We cannot rule out more precise multivariable model results with a larger sample.

We used FMA-SAFE, an adapted version of the original SAFE-score[17] with a lower scale range (0-4). Our FMA-SAFE had a lower scale range (0-4). Potential differences in sensitivity and specificity between the respective scales are yet to be determined.

As with most longitudinal studies, some data were missing. Complete resting-state functional MRI was present in 57 patients. Patients with missing data were excluded from part of the regression analyses. However, wCST-LL data were missing in only 6 patients. Also, FC analysis was limited to M1 and SMA interhemispheric connectivity, based on previous findings[23, 49]. An extended network approach may have provided additional information on FC between other key nodes in the sensorimotor network[50].

Conclusions

This study provides the first detailed comparison of unimanual and bimanual recovery and their predictors after stroke. Recovery of Ad-AHA and FMA-UE over the first six months post stroke was strikingly similar. In the cohort with moderate-to-severe initial motor impairment, the strongest predictor of both Ad-AHA and FMA-UE was the FMA-SAFE score, a quick measure of affected-side shoulder abduction and finger extension. Sensory function explained additional variance in bimanual recovery, and interhemispheric motor cortex functional connectivity explained additional variance in unimanual outcome and recovery. Cognitive impairment and CST integrity were other important predictors for both bimanual and unimanual outcome and recovery. Notably, a CST lesion load >5.5 cc was associated with poor bimanual and unimanual outcome and recovery. Taken together, the findings point to similarities and differences in mechanisms driving bimanual and unimanual recovery and indicate that future prediction models and patient stratification strategies should include measures of FMA-SAFE, CST lesion load, and sensory and cognitive functions.

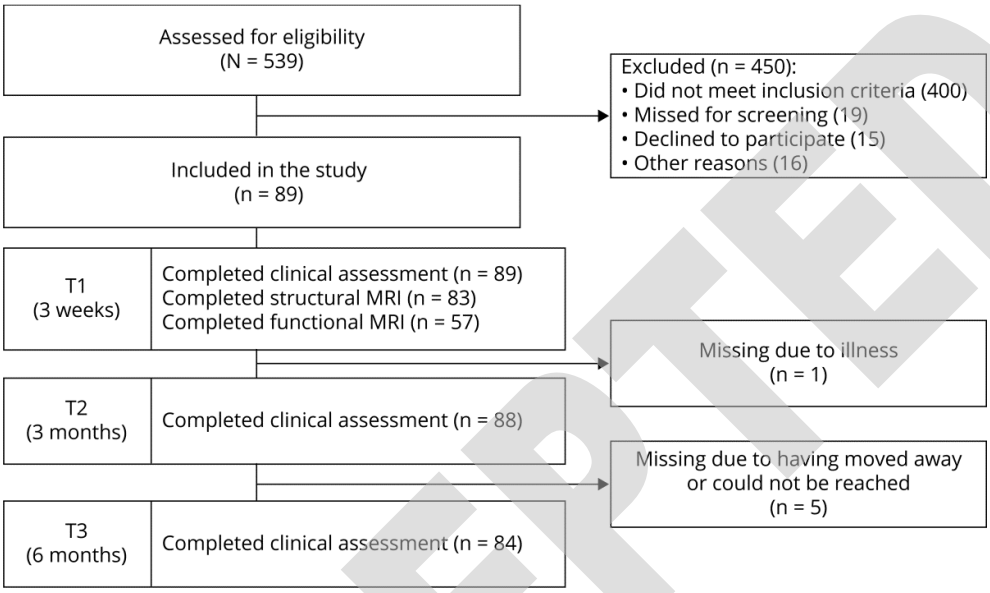
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Tables and Figures

Figure 1 Flowchart of the recruitment process

Flowchart of the recruitment process. Recruitment was initiated in March 2013 and ended in September 2019.

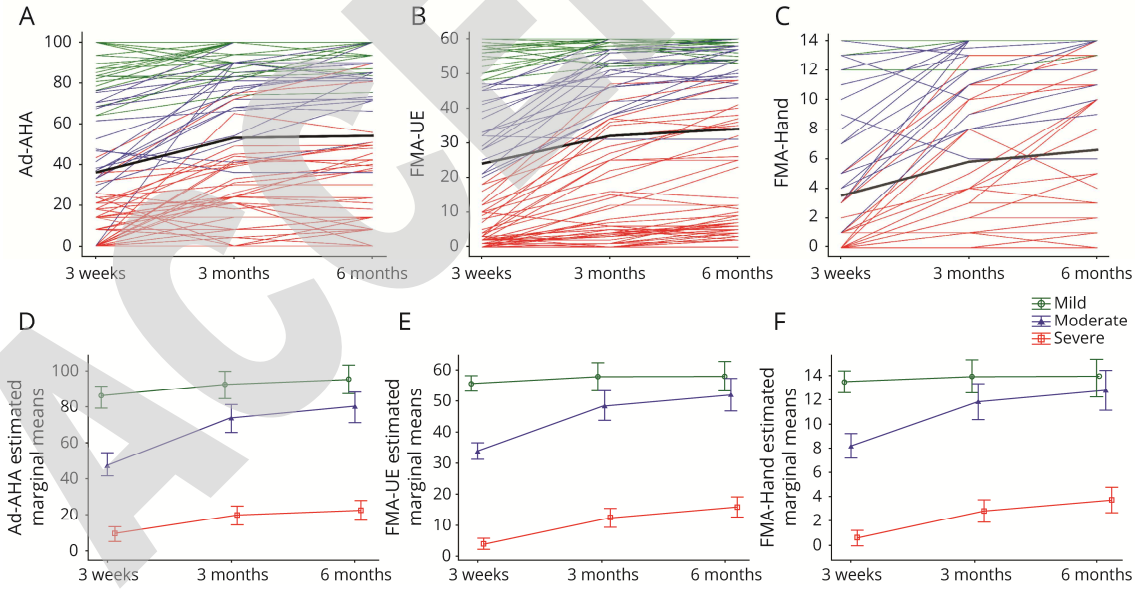


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Figure 2 Individual case profiles and group mean (A-C) and bimanual activity performance (D), arm (E) and hand (F) motor impairment estimated marginal means across impairment severity subgroups.

(A-C): Individual case profiles (raw scores) of Ad-AHA – Adult Assisting Hand Assessment Stroke (A), FMA-UE – Fugl-Meyer Assessment for the Upper 13 Extremity (B) and FMA-Hand – Fugl-Meyer Assessment Hand subscale (C). Colours illustrate initial motor impairment sub-groups according to the FMA-UE (MILD >47p (in green), MODERATE 20-47p (in blue), and SEVERE ≤19p, (in red). Dark bars represent whole group mean. (D-F): Effects of time by group, analysed using Linear Mixed Effects Model. Each marker represents the Estimated Marginal Means per subgroup and time-point. Vertical bars are 95% confidence intervals.



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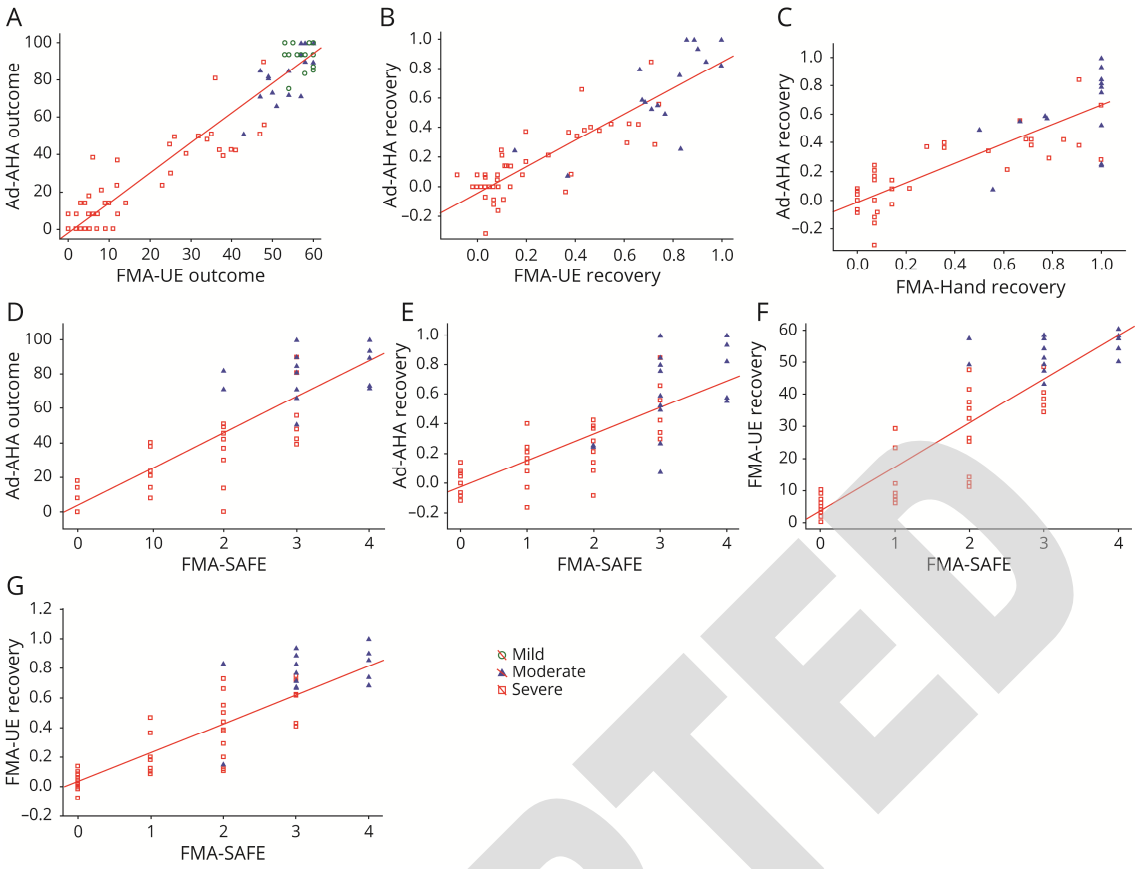
Figure 3 Scatterplots illustrating linear association between dependent variables (Ad-AHA and FMA), and with FMA-SAFE.

A positive linear association was found between bimanual activity performance (Ad-AHA) and arm and hand motor impairment (FMA-UE) (A). A similar pattern was found regarding recovery, both between Ad-AHA and FMA-UE (B) and Ad-AHA and the FMA-Hand (C). However, note that a full recovery in FMA-Hand (recovery ratio = 1), did not equal a correspondingly full recovery in the Ad-AHA (C).

Strong associations were also found between bimanual and unimanual outcome and recovery and FMA-SAFE, most prominent in the severe impairment group (D-F). Ad-AHA outcome vs FMA-SAFE: moderate: $R = 0.38$, $p = 0.109$ and severe: $R = 0.82$, $p < 0.0001$ (D), Ad-AHA recovery vs FMA-SAFE: moderate: $R = 0.50$, $p = 0.028$, severe: $R = 0.76$, $p < 0.0001$ (E), FMA-UE outcome vs FMA-SAFE: moderate: $R = 0.42$, $p = 0.077$, severe: $R = 0.89$, $p < 0.0001$ (F). FMA-UE recovery vs FMA-SAFE: moderate: $R = 0.36$, $p = 0.137$, severe: $R = 0.86$, $p < 0.0001$ (G).

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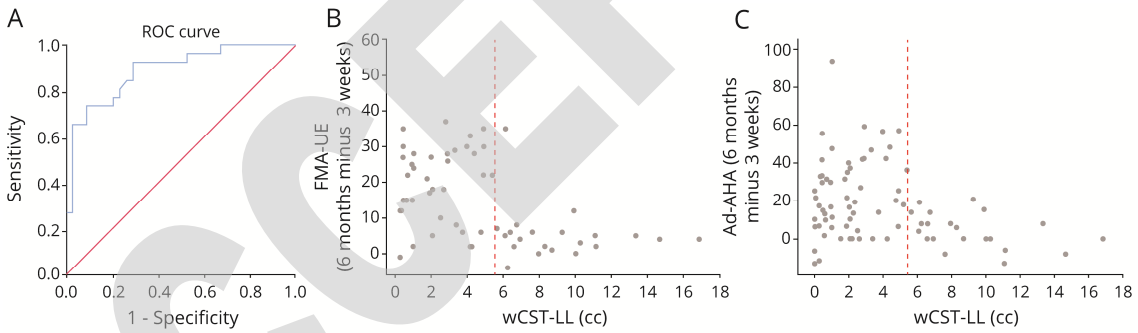


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Figure 4 A predictive threshold of CST injury (wCST-LL) of 5.5 cubic centimetres (cc) was identified by Receiver Operating Characteristic (ROC) curve analysis separating patients who showed a minimum clinically meaningful change in FMA-UE of 10 points from those who did not.

The ROC derived predictive threshold of 5.5cc CST lesion load had a sensitivity of 0.73 and specificity of 0.91 (1 minus 0.09) (A). Unimanual arm and hand actual change (Fugl-Meyer for the upper extremity, FMA-UE, 6-month status minus status at 3 weeks) against CST lesion load (wCST-LL) (B). The red dotted line (B and C) demarks 5.5cc. Adult Assisting Hand Assessment Stroke (Ad-AHA) against wCST-LL illustrating a similar pattern as FMA-UE, with a limited amount of actual change in patients with a wCST-LL >5.5 cc and high inter-individual variance in patients with a wCST-LL <5.5cc (C).



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Table 1. Patient characteristics and demographical data at baseline (mean 3 weeks from stroke onset)								
Variables		ALL n=89	MILD n=23	MODERATE n=19	SEVERE n=47	Group difference (sig.)[k]		
						MILD-MODERATE	MILD-SEVERE	MODERATE-SEVERE
Days from stroke onset to inclusion		25±7	23±7	24±6	27±7	0.742	0.012	0.022
Age		52.3±9.4	52±10	52±9	53±9	0.742	0.885	0.650
Sex	Females	23 (26)	9 (39)	7 (37)	7 (15)	0.881	0.024	0.050
	Males	66 (74)	14 (61)	12 (63)	40 (85)			
Higher education[a]		40 (45)	14 (61)	9 (47)	17 (36)	0.387	0.052	0.403
Lesion location	Left	40 (44.9)	11 (47.8)	11 (57.9)	27 (57.4)	0.521	0.451	0.974
	Right	49 (55.1)	12 (52.2)	8 (42.1)	20 (42.6)			
Stroke type	Ischemic	61 (68.5)	17 (73.9)	13 (68.4)	31 (66.0)	0.698	0.504	0.849
	Haemorrhagic	28 (31.4)	6 (26.1)	6 (31.6)	16 (34.0)			
NIH Stroke Scale (acute, day 1 to 3)		11 (5-16)	6 (3-9)	8 (5-11)	16 (13-19)	0.578	0.001	<0.001
NIH Stroke Scale (at inclusion)		7 (3-12)	3 (2-4)	3 (2-4)	12 (9-15)	0.276	<0.0001	<0.0001
wCST-LL (cc)		3.83 (3.7)	1.31 (1.3)	1.79 (1.7)	6.085 (3.8)	0.338	<0.0001	<0.0001
Neglect[b]		21 (24)	0 (0)	2 (10)	19 (40)	0.115	0.0004	0.191
Aphasia[c]		30 (34)	8 (35)	3 (16)	19 (40)			
Cognitive impairment (0-50p)[d]		38 (31-44)	40 (37-46)	40.5 (35-46)	35 (28-42)	0.817	0.050	0.076
Barthel Index (0-100p)		60 (43-100)	100 (95-100)	90 (60-100)	45 (20-55)	0.004	<0.0001	0.009
Dominant hand affected		41 (41)	14 (34)	8 (20)	19 (46)	0.231	0.148	0.993
Neural Component (N)[e]		3.78±5.6	1.58±2.9	1.68±2.0	5.71±6.9	0.304	<0.0001	
Pain during passive movement[f]		39 (44)	3 (13)	5 (26)	31 (66)	0.281	<0.0001	0.0036
Two-point discrimination (absent)[g]		48 (54)	4 (17)	4 (21)	40 (85)	0.766	<0.0001	<0.0001
Vibration (absent)[h]		24 (29)	1 (4)*	3 (16)	20 (48)	0.214	0.0004	0.185
Touch (impaired or absent)[i]		60 (67)	7 (30)	10 (53)	43 (92)	0.242	<0.0001	<0.0001
Proprioception (impaired or absent)[j]		51 (58)	4 (17)	9 (47)	38 (83)	0.032	<0.0001	0.001
FMA-SAFE (0-4)		3(1-4)	4(4-4)	3(3-4)	1(0-2)	<0.0001	<0.0001	<0.0001

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Ad-AHA (0-100p)	37.1±35.0	85.3±11.3	47.9±20.4	9.5±11.9	<0.0001	<0.0001	<0.0001
FMA-UE (60p)	23.7±23.0	55.6±3.6	33.9±8.9	4.0±5.1	<0.0001	<0.0001	<0.0001
FMA-Hand (14p)	5.5±6.0	13.5±1.0	8.2±4.2	0.6±1.4	<0.0001	<0.0001	<0.0001

Data are mean±SD, number (%) or median (IQR) unless otherwise stated. Abbreviations: NIH Stroke Scale – National Institute of Health Stroke Scale, wCST-LL – weighted corticospinal tract lesion load, FMA-UE – Fugl-Meyer Assessment for the Upper Extremity, FMA-Hand – Fugl-Meyer Assessment Hand sub-scale (C), Ad-AHA – Adult Assisting Hand Assessment Stroke.

a) Post-secondary education/degree (yes/no).

b) According to the Baking Tray Task (BBT).

c) Aphasia was indicated by and index ≤4.7p on the Swedish Neurolinguistic Instrument A-ning.

d) Cognitive status according to the Barrow Neurological Institute Screen for Higher Cerebral Functions, BNIS. A score ≤47p indicated impairment.

e) Neural Component in Newton, i.e. neural resistance at passive wrist extension assessed with the NeuroFlexor© device. A neural component ≥3.4 N indicate spasticity in the muscles controlling wrist and finger flexor muscles.

f) Fugl-Meyer subscale for pain during passive movement. A score of ≤23 (of24) indicated pain.

g) Index and thumb finger pads were tested. Unable to detect 12mm indicated impairment.

h) Tested using a tuning fork.

i) Index and thumb finger pads were tested using Monofilaments, categorized to normal-near normal/impaired/absent.

j) Fug-Meyer Subscale for proprioception categorized to normal-near normal/impaired/absent.

k) Kruskal-Wallis H or Pearson Chi-square tests.

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Table 2 Multivariable linear regression prediction models* of outcome and recovery

Dependent variables	Model*	Independent variables	Unstandardized Coefficients			95% Confidence Interval for B		Change statistics		
			B	Std. Error	Sig.	Lower Bound	Upper Bound	R2 Accumulated	R2 Change	Sig. F change
Ad-AHA Outcome		(Constant)	2.931	2.522	0.250	-2.113	7.975			
	1	FMA-SAFE	18.165	1.332	0.000	15.501	20.828	.808	0.808	0.000
	2	2pD	18.084	3.963	0.000	10.159	26.009	.857	0.049	0.000
		(Constant)	45.990	14.979	0.004	15.838	76.142			
	1	wCST-LL	-3.988	0.804	0.000	-5.606	-2.370	0.444	0.444	0.000
	2	2pD	19.987	7.123	0.007	5.649	34.324	0.595	0.151	0.000
	3	BNIS	0.772	0.258	0.005	0.252	1.292	0.664	0.068	0.003
	4	Pain	-13.694	6.347	0.036	-26.470	-0.918	0.694	0.031	0.036
Ad-AHA Recovery		(Constant)	-.020	0.037	0.591	-0.095	0.055			
	1	FMA-SAFE	0.180	0.017	0.000	0.146	0.215	0.639	0.639	<.0001
		(Constant)	0.364	0.071	0.000	0.222	0.506			
	1	wCST-LL	-0.034	0.010	0.001	-0.053	-0.015	0.314	0.314	0.000
	2	2pD	0.227	0.078	0.005	0.072	0.383	0.405	0.091	0.005
FMA-UE Outcome		(Constant)	-1.300	2.419	0.594	-6.179	3.578			
	1	FMA-SAFE	13.222	.821	0.000	11.565	14.878	0.846	0.846	0.000
	2	FC_{PCG}	10.619	3.610	0.005	3.340	17.899	0.872	0.026	0.005
		(Constant)	21.322	7.018	0.004	7.203	35.441			
	1	wCST-LL	-3.143	0.553	0.000	-4.255	-2.031	0.488	0.488	<.0001
	2	2pD	10.540	4.584	0.026	1.318	19.763	0.561	0.073	0.0069
	3	BNIS	0.471	0.179	0.011	0.111	0.830	0.617	0.057	0.0113
FMA-UE Recovery		(Constant)	0.038	0.033	0.260	-0.028	0.104			
	1	FMA-SAFE	0.191	0.015	0.000	0.161	0.221	0.715	0.715	<.000

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Table 3 Multivariable linear regression prediction models of outcome and recovery in n=38 patients with CST lesion load <5.5cc

Dependent variables	Model	Predictor variables	Unstandardized coefficients			95.0% Confidence interval for B		Change statistics		
			B	Std.	Sig.	Lower	Upper	Accumulated	R2	Sig. F change
FMA-Hand Outcome		(Constant)	0.491	0.071	0.000	0.350	0.633			
	1	wCST-LL	-0.040	0.010	0.000	-0.059	-0.021	0.355	0.355	<.000
	2	2pD	0.168	0.077	0.034	0.013	0.322	0.405	0.049	0.0337
		(Constant)	-1.581	0.747	0.040	-3.089	0.073			
	1	FMA-SAFE	3.547	0.254	0.000	3.035	4.059	0.803	0.803	0.000
	2	FC_{PCG}	3.783	1.115	0.002	1.533	6.033	0.846	0.042	0.002
		(Constant)	4.697	1.982	0.022	0.710	8.684			
	1	wCST-LL	-0.877	0.156	0.000	-1.191	-0.563	0.476	0.476	0.000
	2	2pD	2.614	1.295	0.049	0.009	5.219	0.539	0.063	0.013
	3	BNIS	0.141	0.050	0.007	0.040	0.243	0.605	0.066	0.007
FMA-Hand Recovery		(Constant)	-0.132	0.063	0.041	-0.258	-0.006			
	1	FMA-SAFE	0.233	0.021	0.000	0.190	0.276	0.714	0.714	0.000
	2	FC_{PCG}	0.329	0.093	0.001	0.141	0.517	0.778	0.064	0.001
		(Constant)	0.451	0.161	0.008	0.125	0.776			
	1	wCST-LL	-0.064	0.011	0.000	-0.086	-0.042	0.411	0.411	0.000
	2	BNIS	0.012	0.004	0.004	0.004	0.019	0.510	0.099	0.004
	3	HADS-D	-0.024	0.012	0.048	-0.048	0.000	0.552	0.042	0.048

Abbreviations: wCST-LL – weighted corticospinal tract lesion load, FC – interhemispheric functional connectivity, PGC – precentral gyrus, SMA – supplementary motor area, HADS-D – Hospital Anxiety and depression scale, FMA-SAFE – Sum of the Fugl-Meyer items for shoulder abduction and finger extension, 2pD – Two-point Discrimination and BNIS – Barrow Neurological Institute Screen for Higher Cerebral Functions.

* Each multivariable linear regression analysis was performed in two steps. Firstly, all candidate determinants were entered one at a time, including FMA-SAFE, in order of predictive strength in the univariate analysis. Secondly, to test candidate determinants while leaving out FMA-SAFE (i.e. the variable with the highest explanatory value) the analysis was repeated while excluding FMA-SAFE.

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				Error		Bound	Bound	R2	Change	
		(Constant)	4.103	5.921	.493	-7.929	16.135			
Ad-AHA	1	FMA-SAFE	18.353	2.376	0.000	13.525	23.182	0.699	0.699	0.000
Outcome	2	2pD	16.439	5.532	0.005	5.197	27.681	0.761	0.062	0.005
		(Constant)	5.486	14.139	0.701	-23.351	34.323			
	1	2pD	26.134	8.289	0.004	9.229	43.039	0.305	0.305	0.001
	2	BNIS	1.101	0.399	0.010	0.287	1.914	0.442	0.137	0.010
		(Constant)	-0.059	0.089	0.514	-0.239	0.122			
Ad-AHA	1	FMA-SAFE	0.198	0.032	0.000	0.133	0.264	0.513	0.513	0.000
Recovery										
		(Constant)	-0.001	0.145	0.997	-0.295	0.294			
	1	2pD	0.343	0.089	0.000	0.163	0.524	0.254	0.254	0.001
	2	Stroke type*	0.211	0.096	0.034	0.017	0.406	0.348	0.094	0.034
		(Constant)	0.859	4.629	0.854	-8.609	10.328			
FMA-UE	1	FMA-SAFE	12.788	1.294	0.000	10.142	15.434	0.739	0.739	0.000
Outcome	2	FC_{PCG}	10.259	4.719	0.038	0.607	19.911	0.776	0.037	0.038
		(Constant)	30.842	3.560	0.000	23.623	38.061			
	1	2pD	16.053	5.034	0.003	5.843	26.262	0.220	0.220	0.003
		(Constant)	0.065	0.077	0.403	-0.091	0.222			
FMA-UE	1	FMA-SAFE	0.188	0.028	0.000	0.132	0.245	0.557	0.557	0.000
Recovery										
		(Constant)	0.433	0.065	0.000	0.302	0.564			
	1	2pD	0.206	0.092	0.031	0.020	0.392	0.123	0.123	0.031
		(Constant)	-0.837	1.457	0.570	-3.822	2.148			
FMA-Hand	1	FMA-SAFE	3.381	.407	0.000	2.546	4.215	0.661	0.661	0.000

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Outcome	2	FC_{PCG}	3.731	1.486	0.018	0.688	6.774	0.723	0.062	0.018
		(Constant)	2.202	2.480	0.382	-2.863	7.267			
	1	2pD	3.733	1.454	0.015	0.764	6.703	0.243	0.243	0.004
	2	BNIS	0.162	0.070	0.028	0.019	0.305	0.358	0.114	0.028
		(Constant)	-0.093	0.127	0.470	-0.352	0.166			
FMA-Hand	1	FMA-SAFE	0.218	0.035	0.000	0.146	0.291	0.500	0.500	0.000
Recovery	2	FC_{PCG}	0.349	0.129	0.011	0.085	0.613	0.600	0.101	0.011
		(Constant)	0.076	0.173	0.662	-0.277	0.429			
	1	2pD	0.509	0.150	0.002	0.203	0.815	0.195	0.195	0.009
	2	BNIS	0.016	0.005	0.004	0.006	0.026	0.314	0.119	0.027
	3	Touch	-0.255	0.104	0.020	-0.466	-0.043	0.429	0.115	0.020

Abbreviations: wCST-LL – weighted corticospinal tract lesion load, FC – interhemispheric functional connectivity, PGC – precentral gyrus, SMA – supplementary motor area, FMA-SAFE – Sum of the Fugl-Meyer items for shoulder abduction and finger extension, 2pD – Two-point Discrimination and BNIS – Barrow Neurological Institute Screen for Higher Cerebral Functions.

*Stroke type refers to ischemic or haemorrhagic stroke. The effect of stroke type was in favour of patients with haemorrhagic stroke.

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Appendix 1. Authors

Name	Location	Contribution
Jeanette Plantin, PT, MSc	Karolinska Institutet, Stockholm, Sweden.	Design and conceptualization of the study. Major role in acquisition of the data. Statistical analysis. Analysis and interpretation of data. Drafted and revised the manuscript for intellectual content.
Marion Verneau, PhD	Institut de Psychiatrie et Neurosciences de Paris, Paris, France.	Analysis and interpretation of data.
Alison Kate Godbolt, MD, MRCP	Karolinska Institutet, Stockholm, Sweden.	Analysis and interpretation of data. Revised the manuscript for intellectual content.
Gaia Valentina Pennati, MD	Karolinska Institutet, Stockholm, Sweden.	Acquisition of the data and revised the manuscript for intellectual content.
Evaldas Laurencikas, MD, PhD	Karolinska Institutet, Stockholm, Sweden.	Design and conceptualization of the study.
Birgitta Johansson, OT	Danderyd University Hospital	Analysis and interpretation of data.
Lena Krumlinde Sundholm, OT, PhD	Karolinska Institutet, Stockholm, Sweden.	Design and conceptualization of the study. Revised the manuscript for intellectual content.
Jean-Claude Baron, MD, ScD	Université de Paris, Paris, France.	Analysis and interpretation of data. Revised the manuscript for intellectual content.
Jörgen Borg, MD, PhD	Karolinska Institutet, Stockholm, Sweden.	Design and conceptualization of the study. Analysis and interpretation of data. Revised the manuscript for intellectual content.
Påvel G. Lindberg, PT, PhD	Karolinska Institutet, Stockholm, Sweden Institut de Psychiatrie et Neurosciences de Paris, Paris, France.	Design and conceptualization of the study. Analysis and interpretation of data. Revised the manuscript for intellectual content.

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