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# Recovery and Prediction of Bimanual Hand Use After Stroke

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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, 89 patients with first-ever stroke with arm paresis were assessed at 3 weeks and 3 and 6 months after stroke onset. Bimanual activity performance was assessed with the Adult Assisting Hand Assessment Stroke (Ad-AHA), and unimanual motor impairment was assessed 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 to severe initial FMA, FMA-SAFE score was the strongest predictor of Ad-AHA outcome ($R^2 = 0.81$) and degree of recovery ($R^2 = 0.64$). Two-point discrimination explained additional variance in Ad-AHA outcome ($R^2 = 0.05$). Repeated analyses without FMA-SAFE score identified wCST-LL and cognitive impairment as additional predictors. A wCST-LL >5.5 $cm^3$ strongly predicted low to minimal FMA/Ad-AHA recovery (≤10 and 20 points respectively, specificity = 0.91). FC explained some additional variance to FMA-SAFE score only in unimanual recovery.

### Conclusion

Although recovery of bimanual activity depends on the extent of corticospinal tract injury and initial sensory and cognitive impairments, FMA-SAFE score captures most of the variance explained by these mechanisms. FMA-SAFE score, a straightforward clinical measure, strongly predicts bimanual recovery.

### ClinicalTrials.gov Identifier

NCT02878304.

### Classification of Evidence

This study provides Class I evidence that the FMA-SAFE score predicts bimanual recovery after stroke.

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**Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
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## Glossary

**Ad-AHA** = Adult Assisting Hand Assessment Stroke; **BNIS** = Barrow Neurological Institute Screen for Higher Cerebral Functions; **CST** = corticospinal tract; **FC** = functional connectivity; **FMA** = Fugl-Meyer Assessment; **FMA-Hand** = FMA for the hand; **FMA-SAFE** = FMA for shoulder abduction and finger extension; **FMA-UE** = FMA for the upper extremity; **PCG** = precentral gyrus; **ROC** = receiver operating characteristic; **ROI** = region of interest; **SMA** = supplementary motor area; **2pD** = 2-point discrimination; **wCST-LL** = weighted CST lesion load.

Stroke survivors with arm and hand motor impairment[1] often experience reduced daily life activities and participation.[2] Many daily tasks require skillful 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 interlimb 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.[6,7] How often and how effectively the more affected arm and hand are 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 of unimanual motor impairment because Ad-AHA is a measure of spontaneous hand-use incorporating task goals and interlimb coordination.[8] Furthermore, given the importance of somatosensory[9–11] and cognitive impairment[12,13] 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 corticospinal tract (CST) lesion load and interhemispheric connectivity, to bimanual recovery.

# Methods

### 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 the recruitment of patients with aphasia to ensure their ability to provide informed consent.

### Study Design and Participants

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 subacute inpatient neurorehabilitation clinic for persons of working age (18–70 year) at a university hospital in Sweden were recruited (figure 1). First assessment was performed at admission (on average at 3 weeks after stroke, T1). Follow-up assessments were performed at 3 (T2) and 6 (T3) months after stroke onset. All patients participated in interdisciplinary rehabilitation.

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

### Main Outcome Assessment

The Ad-AHA[6] was used to evaluate how effectively the patients used their contralesional hand together with the ipsilesional hand during activity performance. This observation-based assessment comprises performance of 1 of 2 tasks (lasting ≈10 minutes), 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.[6] The Ad-AHA measures bimanual activity performance, that is, 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 4-level ordinal scale: 4 = effective, 3 = somewhat effective, 2 = ineffective, and 1 = does not do. The scale was developed using a Rasch measurement model, and the scores were transformed to a logit-based Ad-AHA unit scale (range 0–100), with a higher unit indicating higher ability. Ad-AHA produces a valid measure of bimanual performance[6,7] 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 (FMA) for the upper extremity

(FMA-UE).[14,15] The 3 reflex items were omitted to exclusively reflect voluntary movement functions, yielding a maximum of 60 points.[16] Distal motor impairment was assessed with the FMA-Hand subscale (0–14 points).[17]

## Other Clinical Assessments

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

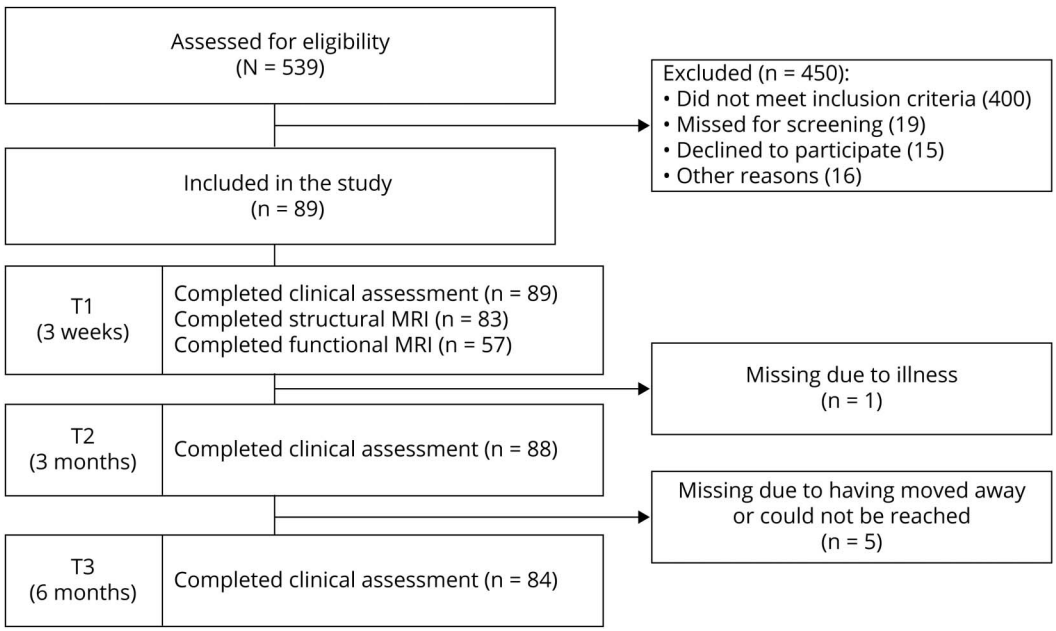
1. Because finger extension and shoulder abduction strength are predictive of hand motor outcome,[18,19] a sum score of rated shoulder abduction and finger extension was derived from the corresponding FMA-UE items, yielding the variable FMA-SAFE (range 0–4).
2. Proprioception: FMA subdomain for position sense,[15] categorized as normal–near normal/impaired/absent.
3. Pain: FMA subdomain for pain during passive movement.[15] A score of ≤23 of 24 indicated pain.
4. Discriminative sensation (2-point discrimination [2pD]): index and thumb finger pads were tested with a DiscCriminator (Dellon-McKinnon). Inability to detect 12 mm indicated impairment.
5. Touch: monofilaments (5 item-kit, North Coast Medical) were applied to the index and thumb finger pads. Touch was categorized to normal–near normal/impaired/absent.
6. Vibration: a tuning fork was applied to the metacarpophalangeal bone 1. Intact vibration sense required the ability to distinguish vibration from no vibration and to indicate when the vibration stopped.
7. Aphasia Index: assessed with the Swedish Neurolinguistic Instrument A-ning[20] (range 0–5).
8. Cognitive status: determined with the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS)[21] (range 0–50).
9. Anxiety/depression: Hospital Anxiety and Depression Scale (range 0–21 for the respective domain).[22]
10. Neglect: baking tray task (yes/no).
11. Neural resistance, indicating spasticity, of wrist and finger flexor muscles: the NeuroFlexor method.[23]
12. Demographic data obtained from patients' records: age, ischemic/hemorrhagic stroke, affected hemisphere, and dominant hand.

## Magnetic Resonance Imaging

Brain imaging was performed at baseline (T1) with an Ingenia 3.0T MR system (Philips, Cambridge, MA) with an 8HR head coil. High-resolution T1-weighted anatomic images were acquired with turbo field echo 3-dimensional 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 fluid-attenuated inversion recovery images were also acquired. Resting-state fMRI consisted of a gradient echo-planar sequence (echo time 35 milliseconds, flip angle 90°, voxel size 1.8 × 1.8 × 4 mm, repetition time 3,000 milliseconds) sensitive to blood oxygen level–dependent 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.

Anatomic T1 images were normalized to Montreal Neurologic Institute template with SPM12 (University College London, UK; fil.ion.ucl.ac.uk/spm/software/spm12/). Cost

**Figure 1** Flowchart of the Recruitment Process




Recruitment was initiated in March 2013 and ended in September 2019.

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 anatomic images using MRIcron (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; in cubic centimeters) using a previously constructed CST template based on regions of interest (ROIs) in the precentral gyri, posterior limb of internal capsule, cerebral peduncle, and anteromedial pons.[24]

## Resting-State Functional Connectivity Analysis

Seed-based functional connectivity (FC) analysis was performed in 57 patients with complete resting-state fMRI data. Preprocessing was performed with SPM12b software (fil.ion.ucl.ac.uk/spm/software/spm12) and included (1) head movement correction, (2) coregistration of resting-state echo planar images to T1-weighted anatomic images, (3) segmentation (gray matter/white matter/CSF), (4) normalization with cost-function masking of lesion using Clinical Toolbox, and (5) smoothing (8 mm).

Motor cortex connectivity has been shown to explain a portion of the variance in motor recovery,[25] and the supplementary motor area (SMA) was also analyzed because it is crucial for bimanual coordination.[26]

We calculated interhemispheric FC between ROIs, including ipsilesional and contralesional primary motor cortex/precentral gyrus (PCG) and SMA ROIs from the FSL Harvard-Oxford cortical and subcortical structural atlases (fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). Seed-based FC was calculated with the Conn toolbox.[27] It incorporates the CompCorr strategy for reduction of noise of physiologic and other sources[28] that takes into account the nonhomogeneous distribution of noise signals in the brain. Principal components 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; nitrc.org/projects/artifact_detect) were also included as regressors because it has been shown that this strategy improves motion artifact correction when studying FC.[29] 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 (0.01–0.08 Hz) was applied covering approximately the range between 10 and 100 seconds, which is standard for resting-state connectivity analyses.[30] The toolbox computed the average blood oxygen level–dependent time series across all the voxels within each ROI.

Bivariate correlation and regression analyses were performed giving z-scores reflecting the level of linear association of the bold time series between each pair of ROIs. The z-score 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., maximum score of the scale minus initial score).

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

Unimanual motor impairment data were 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 the 6-month follow-up. Last value carried over compensated for missing data at 6 months.

A linear mixed-effect model with participant identification included as a random effect was used to calculate the overall effect of time on Ad-AHA and FMA-UE/FMA-Hand score and effect of time by impairment subgroup.

Prediction analysis first involved univariate linear regression analysis to determine the strength of the univariate associations. Second, 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 $R^2$). 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 score (≥10 points) from T1 to T3[31] from those who did not. To this end, a receiver operating characteristic (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 also were 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 subsample was determined from the FMA-derived threshold because a clinical

meaningful difference has not yet 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 score ≥48), n = 19 had moderate (FMA-UE score 20–47), and n = 47 had severe (FMA-UE score ≤19) impairment. 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 scores showed high interindividual 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, $p < 0.001$) scores 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 3, B and C). In patients with mild unimanual impairment, Ad-AHA and FMA-UE/FMA-Hand score correlations were low or nonsignificant ($r_s$ 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 ($F_{2,87} = 24.3$, $p < 0.001$) scores. The time effects on Ad-AHA score were significant in all 3 impairment groups (figure 2D). However, there was a significant effect of time on FMA-UE and FMA-Hand scores in the moderate and severe impairment groups but not in the mild group (figure 2, E and F).

## Prediction of Bimanual and Unimanual Outcome and Recovery

To avoid known ceiling effects of the FMA-UE,[15] mildly impaired patients (n = 23) who had a minimal residual arm and hand motor impairment (FMA-UE score 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 Zenondo: http://doi.org/10.5281/zenodo.5054068), and multivariable results are given in table 2. The strongest association was with FMA-SAFE score (figure 3, D–G).

### Prediction of Outcome

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

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

### Prediction of Recovery

Ad-AHA recovery was best predicted by FMA-SAFE score as a single predictor, explaining 64% of the variance. Without FMA-SAFE score, 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 score as a single predictor, explaining 72% of the variance. Without FMA-SAFE score, the best prediction model included wCST-LL (36%) and 2pd (5%), together explaining 41% of the variance. Results for FMA-Hand score were similar to FMA-UE score, 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 of wCST-LL data for the moderate and severe impairment groups revealed a predictive threshold of 5.5 $cm^3$, separating patients who showed a clinically meaningful increase in FMA-UE score, ≥10 points, from those who did not (figure 4, A and B). The sensitivity of this predictive threshold was 0.73 and the specificity was 0.91 (area under the curve 0.889, standard error 0.043, $p < 0.001$, 95% confidence interval 0.802–0.971). Only 2 patients of 28 with wCST-LL >5.5 $cm^3$ recovered ≥10 points in FMA-UE score (figure 4B). The variability of actual change in FMA-UE score was high among individuals with wCST-LL <5.5 $cm^3$ (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).

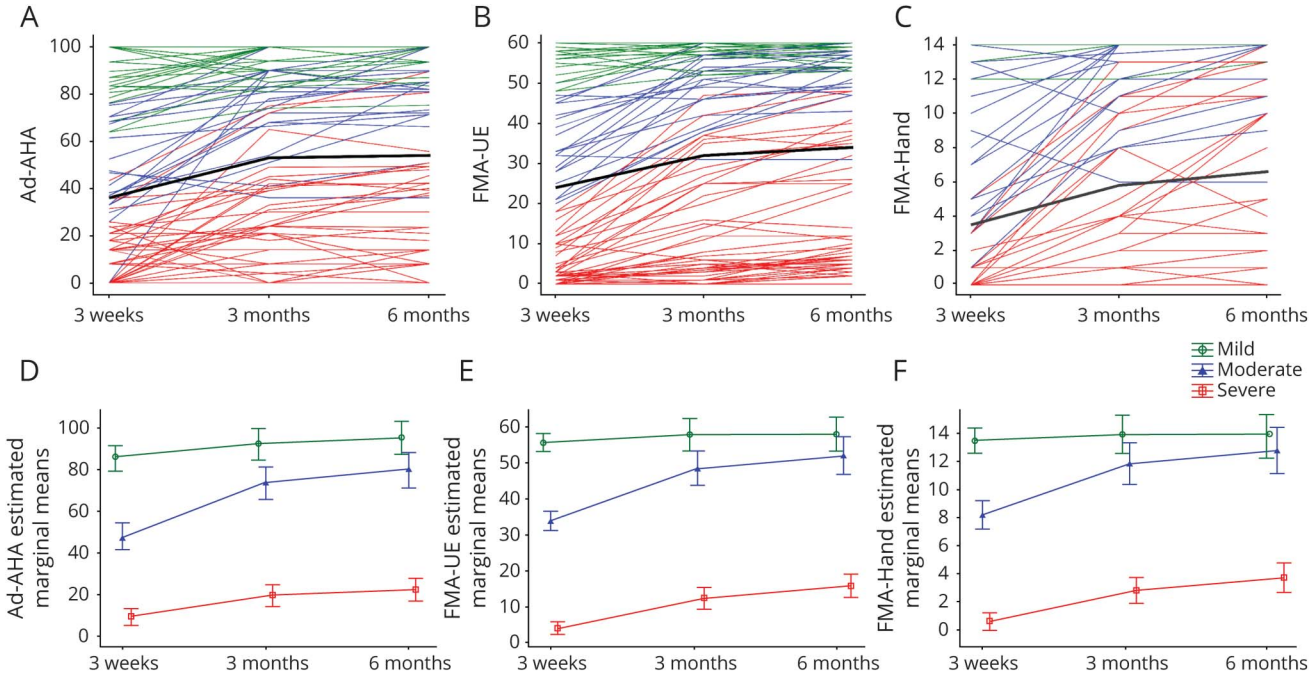
Figure 4C illustrates changes in Ad-AHA score between 3 weeks and 6 months in relation to the same wCST-LL cutoff. Ad-AHA recovery was poor in patients with wCST-LL >5.5 $cm^3$ and more variable in patients with wCST-LL<5.5 $cm^3$, with no patient with wCST-LL >5.5 $cm^3$ having Ad-AHA score increase above ≈20. Conversely, Ad-AHA recovery was highly variable in patients with wCST-LL<5.5 $cm^3$ (figure

**Table 1** Patient Characteristics and Demographic Data at Baseline (Mean 3 Weeks From Stroke Onset)

| | | | | | Group Difference (Significance)[k] | | |
|---|---|---|---|---|---|---|---|
| **Variables** | **All (n = 89)** | **Mild (n = 23)** | **Moderate (n = 19)** | **Severe (n = 47)** | **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, y** | 52.3 ± 9.4 | 52 ± 10 | 52 ± 9 | 53 ± 9 | 0.742 | 0.885 | 0.650 |
| **Sex, n (%)** | | | | | | | |
| **Female** | 23 (26) | 9 (39) | 7 (37) | 7 (15) | 0.881 | 0.024 | 0.050 |
| **Male** | 66 (74) | 14 (61) | 12 (63) | 40 (85) | | | |
| | | | | | | | |
| **Higher education, n (%)[a]** | 40 (45) | 14 (61) | 9 (47) | 17 (36) | 0.387 | 0.052 | 0.403 |
| **Lesion location, n (%)** | | | | | | | |
| **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, n (%)** | | | | | | | |
| **Ischemic** | 61 (68.5) | 17 (73.9) | 13 (68.4) | 31 (66.0) | 0.698 | 0.504 | 0.849 |
| **Hemorrhagic** | 28 (31.4) | 6 (26.1) | 6 (31.6) | 16 (34.0) | | | |
| **NIH Stroke Scale score (acute, day 1–3)** | 11 (5–16) | 6 (3–9) | 8 (5–11) | 16 (13–19) | 0.578 | 0.001 | <0.001 |
| **NIH Stroke Scale score (at inclusion)** | 7 (3–12) | 3 (2–4) | 3 (2–4) | 12 (9–15) | 0.276 | <0.0001 | <0.0001 |
| **wCST-LL, $cm^3$** | 3.83 (3.7) | 1.31 (1.3) | 1.79 (1.7) | 6.085 (3.8) | 0.338 | <0.0001 | <0.0001 |
| **Neglect, n (%)[b]** | 21 (24) | 0 (0) | 2 (10) | 19 (40) | 0.115 | 0.0004 | 0.191 |
| **Aphasia, n (%)[c]** | 30 (34) | 8 (35) | 3 (16) | 19 (40) | | | |
| **Cognitive impairment score (0–50)[d]** | 38 (31–44) | 40 (37–46) | 40.5 (35–46) | 35 (28–42) | 0.817 | 0.050 | 0.076 |
| **Barthel Index score (0–100)** | 60 (43–100) | 100 (95–100) | 90 (60–100) | 45 (20–55) | 0.004 | <0.0001 | 0.009 |
| **Dominant hand affected, n (%)** | 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, n (%)[f]** | 39 (44) | 3 (13) | 5 (26) | 31 (66) | 0.281 | <0.0001 | 0.0036 |
| **2-Point discrimination (absent), n (%)[g]** | 48 (54) | 4 (17) | 4 (21) | 40 (85) | 0.766 | <0.0001 | <0.0001 |
| **Vibration (absent), n (%)[h]** | 24 (29) | 1 (4)* | 3 (16) | 20 (48) | 0.214 | 0.0004 | 0.185 |
| **Touch (impaired or absent), n (%)[i]** | 60 (67) | 7 (30) | 10 (53) | 43 (92) | 0.242 | <0.0001 | <0.0001 |
| **Proprioception (impaired or absent), n (%)[j]** | 51 (58) | 4 (17) | 9 (47) | 38 (83) | 0.032 | <0.0001 | 0.001 |
| **FMA-SAFE score (0–4 points)** | 3(1–4) | 4(4–4) | 3(3–4) | 1(0–2) | <0.0001 | <0.0001 | <0.0001 |
| **Ad-AHA score (0–100 points)** | 37.1 ± 35.0 | 85.3 ± 11.3 | 47.9 ± 20.4 | 9.5 ± 11.9 | <0.0001 | <0.0001 | <0.0001 |
| **FMA-UE score (60 points)** | 23.7 ± 23.0 | 55.6 ± 3.6 | 33.9 ± 8.9 | 4.0 ± 5.1 | <0.0001 | <0.0001 | <0.0001 |
| **FMA-Hand score (14 points)** | 5.5 ± 6.0 | 13.5 ± 1.0 | 8.2 ± 4.2 | 0.6 ± 1.4 | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: Ad-AHA = Adult Assisting Hand Assessment Stroke; FMA-Hand, Fugl-Meyer Assessment hand subscale; FMA-SAFE = Fugl-Meyer Assessment of shoulder abduction and finger extension; FMA-UE = Fugl-Meyer Assessment for the upper extremity; wCST-LL = weighted corticospinal tract lesion load.
Data are mean ± SD, number (percent), or median (interquartile range) unless otherwise stated.
[a] Postsecondary education/degree (yes/no).
[b] According to the baking tray task.
[c] Aphasia was indicated by an index score ≤4.7 points on the Swedish Neurolinguistic Instrument A-ning.
[d] Cognitive status according to the Barrow Neurologic Institute Screen for Higher Cerebral Functions. A score ≤47 points indicated impairment.
[e] Neural component in Newton, that is, neural resistance at passive wrist extension assessed with the NeuroFlexor device. A neural component ≥3.4 N indicates spasticity in the muscles controlling wrist and finger flexor muscles.
[f] Fugl-Meyer subscale for pain during passive movement. A score of ≤23 (of 24) indicates pain.
[g] Index and thumb finger pads were tested. Unable to detect 12 mm indicated impairment.
[h] Tested with a tuning fork.
[i] Index and thumb finger pads were tested with monofilaments, categorized to normal–near normal/impaired/absent.
[j] Fugl-Meyer subscale for proprioception categorized to normal–near normal/impaired/absent.
[k] Kruskal-Wallis *H* or Pearson $\chi^2$ tests.

**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 Adult Assisting Hand Assessment Stroke (Ad-AHA) (A), Fugl-Meyer Assessment for the upper extremity (FMA-UE) (B), and Fugl-Meyer Assessment hand (FMA-Hand) subscale (C). Colors illustrate initial motor impairment sub-groups according to the FMA-UE score (mild >47points [green], moderate 20–47 points [blue], and severe ≤19 points [red]). Dark bars represent whole group absolute mean. (D–F) Effects of time by group analyzed using linear mixed effects model. Each marker represents the estimated marginal means per subgroup and time point. Vertical bars are 95% confidence intervals.

4C). Given this high variability in unimanual and bimanual recovery, multivariable linear regression was therefore implemented in the subsample of 38 patients with wCST-LL <5.5 $cm^3$ (figure 4B).

### Outcome and Recovery in Patients With wCST-LL <5.5 $cm^3$

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

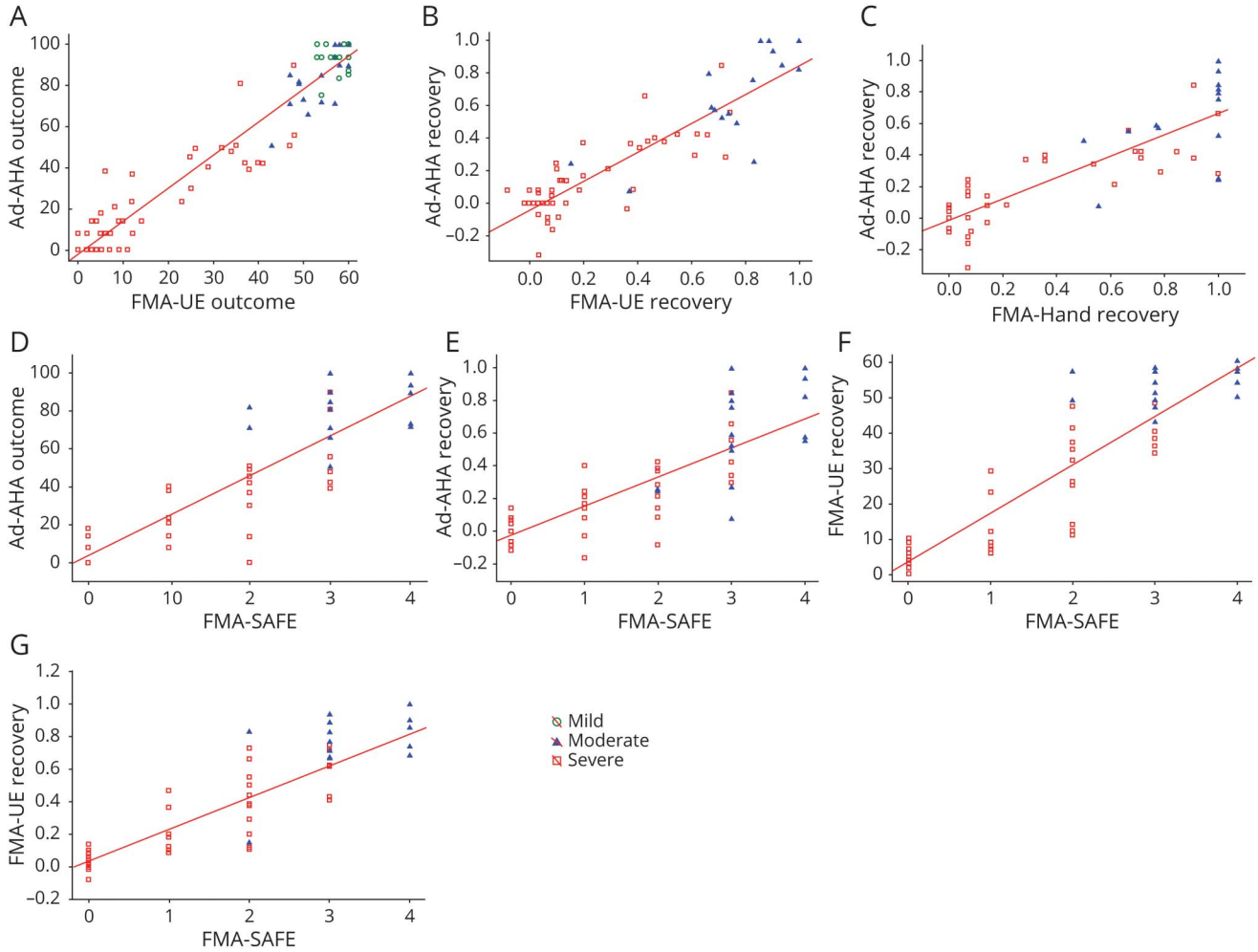
The main predictors of FMA-UE and FMA-Hand outcome and recovery were FMA-SAFE score, 2pD, $FC_{PCG}$, and BNIS score, with lower total amount of variance explained compared to the previous models (table 2).

## Discussion

This study cohort had poor initial bimanual performance (mean Ad-AHA score 37, maximum 100) and considerable unimanual motor impairment (mean FMA-UE score 24, maximum 60). Bimanual activity performance improved significantly over time across all impairment severity levels (mild, moderate, and severe), while unimanual impairment improved in the severe and moderate subgroups only. 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, wCST-LL lesion load >5.5 $cm^3$ 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 score, 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 score.

FMA-SAFE score was the strongest univariate and multivariable predictor of outcome and recovery of bimanual performance. The multivariable analyses showed that FMA-SAFE score explained 81% of the variance in bimanual outcome, with some additional variance explained by sensory impairment (5%). FMA-SAFE score alone explained bimanual recovery over time (64%). These results suggest that basic movement capacity, that is, finger extension and shoulder abduction, is important for recovery of bimanual hand use in patients with stroke with moderate to severe initial unimanual motor impairment. The strong association between bimanual

**Figure 3** Scatterplots Illustrating Linear Association Between Dependent Variables (Ad-AHA and FMA Score) and FMA-SAFE Score




A positive linear association was found between bimanual activity performance (Adult Assisting Hand Assessment Stroke [Ad-AHA]) and arm and hand motor impairment (Fugl-Meyer Assessment for the upper extremity [FMA-UE]) (A). A similar pattern was found regarding recovery, between both Ad-AHA and FMA-UE scores (B) and Ad-AHA and the Fugl-Meyer Assessment of hand (FMA-Hand) (C) scores. However, note that a full recovery in FMA-Hand score (recovery ratio 1) did not equal a correspondingly full recovery in Ad-AHA score (C). Strong associations were also found between bimanual and unimanual outcome and recovery and for Fugl-Meyer Assessment of shoulder abduction and finger extension (FMA-SAFE) score, most prominent in the severe impairment group (D–F). Ad-AHA outcome vs FMA-SAFE score: moderate: $R = 0.38$, $p = 0.109$ and severe: $R = 0.82$, $p < 0.0001$ (D); Ad-AHA recovery vs FMA-SAFE score: moderate: $R = 0.50$, $p = 0.028$ and severe: $R = 0.76$, $p < 0.0001$ (E); FMA-UE outcome vs FMA-SAFE score: moderate: $R = 0.42$, $p = 0.077$ and severe: $R = 0.89$, $p < 0.0001$ (F). FMA-UE recovery vs FMA-SAFE score: moderate: $R = 0.36$, $p = 0.137$ and severe: $R = 0.86$, $p < 0.0001$ (G).

outcome and recovery and FMA-SAFE score in the severe impairment group (figure 3, D and E) further indicates that recovery of unimanual motor control is an essential step in the recovery of bimanual hand use. In addition, 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 ($R = 0.50–0.89$, $p < 0.028$) compared to the mild group ($R = 0.188–0.322$, $p > 0.05$). These results point to the importance of unimanual motor control functions for bimanual recovery in patients with moderate to severe motor impairment.

FMA-SAFE score was also the strongest predictor of unimanual motor impairment (FMA-UE score) regarding both outcome (84% explained) and recovery (74% explained), confirming previous findings.[32] We had expected an even lower degree of variance explained by FMA-SAFE score 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 toward a target and during fine hand use.[33] FMA-SAFE assesses shoulder abduction, which is involved in arm transport, and finger extension, which is necessary for opening fingers before grasping.[34] Recovery of distal movement functions (FMA-Hand score 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

**Table 2** Multivariable Linear Regression Prediction Models[a] of Outcome and Recovery

| Dependent Variables | Model[a] | Independent Variables | Unstandardized Coefficients | | Significance | 95% Confidence Interval for B | | Change Statistics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | B | SE | | Lower Bound | Upper Bound | $R^2$ Accumulated | $R^2$ Change | Significant *F* Change |
| **Ad-AHA outcome** | | (Constant) | 2.931 | 2.522 | 0.250 | −2.113 | 7.975 | | | |
| | 1 | FMA-SAFE score | 18.165 | 1.332 | 0.000 | 15.501 | 20.828 | 0.808 | 0.808 | 0.000 |
| | 2 | 2pD | 18.084 | 3.963 | 0.000 | 10.159 | 26.009 | 0.857 | 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 score | 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) | −0.020 | 0.037 | 0.591 | −0.095 | 0.055 | | | |
| | 1 | FMA-SAFE score | 0.180 | 0.017 | 0.000 | 0.146 | 0.215 | 0.639 | 0.639 | <0.0001 |
| | | (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 score | 13.222 | 0.821 | 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 | <0.0001 |
| | 2 | 2pD | 10.540 | 4.584 | 0.026 | 1.318 | 19.763 | 0.561 | 0.073 | 0.0069 |
| | 3 | BNIS score | 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 score | 0.191 | 0.015 | 0.000 | 0.161 | 0.221 | 0.715 | 0.715 | <0.0001 |
| | | (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 | <0.0001 |
| | 2 | 2pD | 0.168 | 0.077 | 0.034 | 0.013 | 0.322 | 0.405 | 0.049 | 0.0337 |
| **FMA-Hand outcome** | | (Constant) | −1.581 | 0.747 | 0.040 | −3.089 | −0.073 | | | |
| | 1 | FMA-SAFE score | 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 score | 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 score | 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 |

Continued

**Table 2** Multivariable Linear Regression Prediction Models[a] of Outcome and Recovery *(continued)*

| Dependent Variables | Model[a] | Independent Variables | Unstandardized Coefficients | | Significance | 95% Confidence Interval for B | | Change Statistics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | B | SE | | Lower Bound | Upper Bound | $R^2$ Accumulated | $R^2$ Change | Significant *F* Change |
| | 2 | BNIS score | 0.012 | 0.004 | 0.004 | 0.004 | 0.019 | 0.510 | 0.099 | 0.004 |
| | 3 | HADS-D score | −0.024 | 0.012 | 0.048 | −0.048 | 0.000 | 0.552 | 0.042 | 0.048 |

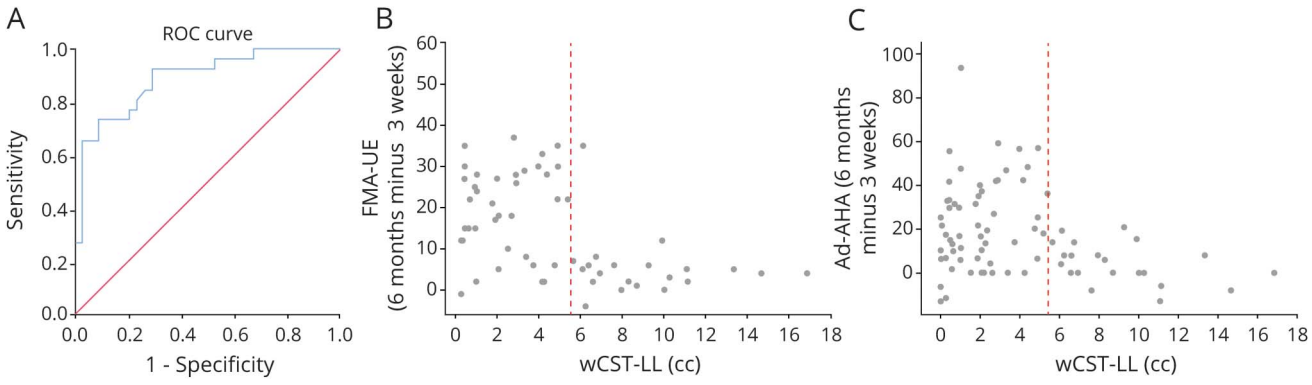
Abbreviations: Ad-AHA = Adult Assisting Hand Assessment Stroke; BNIS = Barrow Neurological Institute Screen for Higher Cerebral Functions; FC = interhemispheric functional connectivity; FMA-Hand = Fugl-Meyer Assessment hand subscale; FMA-SAFE = Fugl-Meyer Assessment for shoulder abduction and finger extension; FMA-UE = Fugl-Meyer Assessment for the upper extremity; HADS-D = Hospital Anxiety and Depression Scale; PGC = precentral gyrus; 2pD, 2-point discrimination; wCST-LL = weighted corticospinal tract lesion load.
[a] Each multivariable linear regression analysis was performed in 2 steps. First, all candidate determinants were entered 1 at a time, including FMA-SAFE score, in order of predictive strength in the univariate analysis. Second, to test candidate determinants while leaving out FMA-SAFE score (i.e., the variable with the highest explanatory value), the analysis was repeated while excluding FMA-SAFE score.

(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,[35] and Ghaziani et al.[36] showed that individual FMA-rated finger extension, shoulder abduction, and elbow extension were useful in predicting arm function at 6 months after stroke. Our findings show that FMA-SAFE score 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 >8 N) may be negatively associated with hand motor recovery, while hand spasticity in the lower range (<8 N) is not.[37] In the present analysis (etable 1 available from Zenondo: http://doi.org/10.5281/zenodo.5054068), neural resistance did not remain significant when we included the FMA-SAFE score or 2pD and CST integrity. These variables covaried, reflecting common sources of variance.

An analysis of predictors masked by and covarying with FMA-SAFE score 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 (49% of outcome and 35% of dynamic recovery) recovery. This extends previous findings[38,39] 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,[40] cortico-basal ganglia loops, other descending motor pathways such as the reticulospinal tract and CST projections from primary somatosensory cortex, and afferent somatosensory input.[41] The ROC analysis further showed that a lesion load >5.5 $cm^3$ was highly predictive of both poor bimanual and unimanual recovery (figure 4). Feng et al.[38] also reported that a wCST-LL >5.5 $cm^3$ in the acute phase was a strong predictor of unimanual motor recovery (FMA-UE outcome score >25) at

**Figure 4** Predictive Threshold of CST Injury (wCST-LL) of 5.5 $cm^3$ Was Identified by ROC Curve Analysis Separating Patients Who Showed a Minimum Clinically Meaningful Change in FMA-UE Score of 10 Points From Those Who did Not




Receiver operating characteristic (ROC) curve–derived predictive threshold of 5.5 $cm^3$ corticospinal tract (CST) lesion load had a sensitivity of 0.73 and specificity of 0.91 (1 − 0.09) (A). Unimanual arm and hand actual change (Fugl-Meyer Assessment for the upper extremity [FMA-UE], 6-month status minus status at 3 weeks) against weighted CST lesion load (wCST-LL) (B). Red dotted line (B and C) demarks 5.5 $cm^3$. Adult Assisting Hand Assessment Stroke (Ad-AHA) score against wCST-LL illustrating a pattern similar to that of FMA-UE score, with a limited amount of actual change in patients with a wCST-LL >5.5 $cm^3$ and high interindividual variance in patients with a wCST-LL <5.5 $cm^3$ (C).

**Table 3** Multivariable Linear Regression Prediction Models of Outcome and Recovery in 38 Patients With wCST-LL <5.5 $cm^3$

| Dependent Variables | Model | Predictor Variables | Unstandardized Coefficients | | Significance | 95% Confidence Interval for B | | Change Statistics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | B | SE | | Lower Bound | Upper Bound | Accumulated $R^2$ | $R^2$ Change | Significant *F* Change |
| **Ad-AHA outcome** | | (Constant) | 4.103 | 5.921 | 0.493 | −7.929 | 16.135 | | | |
| | 1 | FMA-SAFE score | 18.353 | 2.376 | 0.000 | 13.525 | 23.182 | 0.699 | 0.699 | 0.000 |
| | 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 score | 1.101 | 0.399 | 0.010 | 0.287 | 1.914 | 0.442 | 0.137 | 0.010 |
| **Ad-AHA recovery** | | (Constant) | −0.059 | 0.089 | 0.514 | −0.239 | 0.122 | | | |
| | 1 | FMA-SAFE score | 0.198 | 0.032 | 0.000 | 0.133 | 0.264 | 0.513 | 0.513 | 0.000 |
| | | (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[a] | 0.211 | 0.096 | 0.034 | 0.017 | 0.406 | 0.348 | 0.094 | 0.034 |
| **FMA-UE outcome** | | (Constant) | 0.859 | 4.629 | 0.854 | −8.609 | 10.328 | | | |
| | 1 | FMA-SAFE score | 12.788 | 1.294 | 0.000 | 10.142 | 15.434 | 0.739 | 0.739 | 0.000 |
| | 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 |
| **FMA-UE recovery** | | (Constant) | 0.065 | 0.077 | 0.403 | −0.091 | 0.222 | | | |
| | 1 | FMA-SAFE score | 0.188 | 0.028 | 0.000 | 0.132 | 0.245 | 0.557 | 0.557 | 0.000 |
| | | (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 |
| **FMA-Hand outcome** | | (Constant) | −0.837 | 1.457 | 0.570 | −3.822 | 2.148 | | | |
| | 1 | FMA-SAFE score | 3.381 | 0.407 | 0.000 | 2.546 | 4.215 | 0.661 | 0.661 | 0.000 |
| | 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 score | 0.162 | 0.070 | 0.028 | 0.019 | 0.305 | 0.358 | 0.114 | 0.028 |
| **FMA-Hand recovery** | | (Constant) | −0.093 | 0.127 | 0.470 | −0.352 | 0.166 | | | |
| | 1 | FMA-SAFE score | 0.218 | 0.035 | 0.000 | 0.146 | 0.291 | 0.500 | 0.500 | 0.000 |
| | 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 score | 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: Ad-AHA = Adult Assisting Hand Assessment Stroke; BNIS = Barrow Neurological Institute Screen for Higher Cerebral Functions; FC = interhemispheric functional connectivity; FMA-Hand = Fugl-Meyer Assessment hand subscale; FMA-SAFE, Fugl-Meyer Assessment for shoulder abduction and finger extension; FMA-UE = Fugl-Meyer Assessment for the upper extremity; PGC = precentral gyrus; 2pD, 2-point discrimination; wCST-LL = weighted corticospinal tract lesion load.

[a] Stroke type refers to ischemic or hemorrhagic stroke. The effect of stroke type was in favor of patients with hemorrhagic stroke.

3 months, and Pennati et al.[7] found that wCST-LL >6 $cm^3$ indicated absence of recovery of dynamic precision grip. The present findings show that a similar wCST-LL threshold (>5.5 $cm^3$) is also a strong predictor of bimanual hand recovery. The CST is well developed in humans[42] and is essential for dexterity and its recovery after stroke.[9,24] The present findings show that CST integrity is important for bimanual recovery.

In patients with CST lesion load <5.5 $cm^3$, the predictors of bimanual outcome and recovery did not differ substantially. FMA-SAFE score was again the strongest predictor and 2pD was the second strongest predictor of Ad-AHA recovery. Stroke type (ischemic or hemorrhagic) explained a significant portion of the variance in recovery of bimanual activity performance but not in unimanual impairment, in line with findings[43] showing a greater change in activity capacity in patients with hemorrhagic compared to those with ischemic stroke.

Contrary to our expectations, interhemispheric FC did not explain any unique variance in Ad-AHA recovery (tables 2 and 3). This agrees with previous reports that failed to show an association between FC and unimanual motor recovery.[44,45] However, in the present study, interhemispheric $FC_{PCG}$ did explain some additional variance in unimanual outcome and recovery, in addition to FMA-SAFE score (table 2), in agreement with some other studies.[45-47] Notably, the greatest influence of $FC_{PCG}$ was in predicting recovery of unimanual hand motor function in patients with CST lesion load <5.5 $cm^3$ (10% additional variance to 50% explained by FMA-SAFE score, 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.

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

In patients with relatively intact CST (wCST-LL<5.5 $cm^3$), sensory impairment was the factor that explained most variance of bimanual recovery when FMA-SAFE score (30% of outcome and 25% of recovery) was excluded. Somatosensory function is essential for grasping and skilled object manipulation.[11] The 2pD has been shown to predict recovery of pinch grip over time,[9] and proprioception, quantified with a robotic device, explained treatment gains after robotic hand therapy.[48] Qualitative reports also suggest a key contribution of sensory impairment that is often neglected by therapists.[49] Our findings provide evidence that sensory function is a key determinant for bimanual recovery, most likely because the activity-based Ad-AHA measure involves object manipulation, which requires some residual somatosensation.[11]

Cognitive impairment, measured with a comprehensive screening instrument,[21] also emerged as a significant predictor of bimanual outcome (adding 7% of variance explained) when FMA-SAFE score was not included in the prediction model from the start. The partly shared variance explained by FMA-SAFE score and cognitive impairment suggests a possible cognitive-motor interaction that may deserve further attention in prediction modeling and 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.[50]

Cognitive status also explained a significant amount of variance in FMA-Hand outcome and recovery (7% and 10%, respectively) that covaried with FMA-SAFE score, comparable to Ad-AHA score. It therefore seems that cognitive status may be significant for recovery of more distal unimanual movement control functions. Previous work in individuals 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,[13] suggesting cognitive-motor interaction in dexterous tasks. Our findings are consistent with the interpretation that bimanual activity performance requires planning and coordination of movements across 2 hands.

This study was not suited for the evaluation of age as a predictor of recovery.[32] The severe motor impairment group included more men and the first measurement point occurred later 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,[19] with 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 fMRI 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. In addition, FC analysis was limited to M1 and SMA interhemispheric connectivity, on the basis of previous findings.[25,51] An extended network approach may have provided additional information on FC between other key nodes in the sensorimotor network.[52]

This study provides the first detailed comparison of unimanual and bimanual recovery and their predictors after stroke. Recovery of Ad-AHA and FMA-UE scores over the

first 6 months after stroke was strikingly similar. In the cohort with moderate to severe initial motor impairment, the strongest predictor of both Ad-AHA and FMA-UE scores 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 FC 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 $cm^3$ 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 score, CST lesion load, and sensory and cognitive functions.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## Appendix 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, France | Analysis and interpretation of data |
| **Alison K. 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; 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, Stockholm, Sweden | 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, 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, France | Design and conceptualization of the study; analysis and interpretation of data; revised the manuscript for intellectual content |

## References


1. Persson HC, Parziali M, Danielsson A, Sunnerhagen KS. Outcome and upper extremity function within 72 hours after first occasion of stroke in an unselected population at a stroke unit: a part of the SALGOT study. *BMC Neurol.* 2012;12:162.
2. Mayo NE, Wood-Dauphinee S, Cote R, Durcan L, Carlton J. Activity, participation, and quality of life 6 months poststroke. *Arch Phys Med Rehabil.* 2002;83(8):1035-1042.
3. Waddell KJ, Strube MJ, Tabak RG, Haire-Joshu D, Lang CE. Upper limb performance in daily life improves over the first 12 weeks poststroke. *Neurorehabil Neural Repair.* 2019;33(10):836-847.
4. Wu CY, Chou SH, Chen CL, Kuo MY, Lu TW, Fu YC. Kinematic analysis of a functional and sequential bimanual task in patients with left hemiparesis: intra-limb and interlimb coordination. *Disabil Rehabil* 2009;31:958-966.
5. Lodha N, Coombes SA, Cauraugh JH. Bimanual isometric force control: asymmetry and coordination evidence post stroke. *Clin Neurophysiol.* 2012;123:787-795.
6. Krumlinde-Sundholm L, Lindkvist B, Plantin J, Hoare B. Development of the Assisting Hand Assessment for Adults Following Stroke: a Rasch-built bimanual performance measure. *Disabil Rehabil.* 2019;41(4):472-480.
7. Van Gils A, Meyer S, Van Dijk M, et al. The Adult Assisting Hand Assessment Stroke: psychometric properties of an observation-based bimanual upper limb performance measurement. *Arch Phys Med Rehabil.* 2018;99(12):2513-2522.
8. Ivry R, Diedrichsen J, Spencer R, Hazeltine E, Semjen A. A cognitive neuroscience perspective on bimanual coordination and interference. In: Swinnen SP, Duysens J, eds. *Neuro-Behavioral Determinants of Interlimb Coordination: A Multidisciplinary Approach*. Springer US; 2004:259-295.
9. Pennati GV, Plantin J, Carment L, et al. Recovery and prediction of dynamic precision grip force control after stroke. *Stroke.* 2020;51(3):944-951.
10. Meyer S, De Bruyn N, Krumlinde-Sundholm L, et al. Associations between sensorimotor impairments in the upper limb at 1 week and 6 months after stroke. *J Neurol Phys Ther.* 2016;40(3):186-195.
11. Johansson RS, Flanagan JR. Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nat Rev Neurosci.* 2009;10(5):345-359.
12. Rinne P, Hassan M, Fernandes C, et al. Motor dexterity and strength depend upon integrity of the attention-control system. *Proc Natl Acad Sci USA.* 2018;115(3):e536–e545.
13. Carment L, Abdellatif A, Lafuente-Lafuente C, et al. Manual dexterity and aging: a pilot study disentangling sensorimotor from cognitive decline. *Front Neurol.* 2018;9:910.

14. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient, 1: a method for evaluation of physical performance. *Scand J Rehabil Med.* 1975;7(1):13-31.
15. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer Assessment of motor recovery after stroke: a critical review of its measurement properties. *Neurorehabil Neural Repair.* 2002;16(3):232-240.
16. Woodbury ML, Velozo CA, Richards LG, Duncan PW, Studenski S, Lai SM. Dimensionality and construct validity of the Fugl-Meyer Assessment of the upper extremity. *Arch Phys Med Rehabil.* 2007;88(6):715-723.
17. Page SJ, Hade E, Persch A. Psychometrics of the wrist stability and hand mobility subscales of the Fugl-Meyer Assessment in moderately impaired stroke. *Phys Ther.* 2015;95(1):103-108.
18. Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. *Stroke.* 2010;41(4):745-750.
19. Stinear C. Prediction of recovery of motor function after stroke. *Lancet Neurol.* 2010; 9(12):1228-1232.
20. Werner C, Lindberg E. *Aning. Neurolingvistisk Afasiundersökning.* Ersta Diakonisällskap; 1995.
21. Redfors P, Hofgren C, Eriksson I, Holmegaard L, Samuelsson H, Jood K. The Barrow Neurological Institute Screen for Higher Cerebral Functions in cognitive screening after stroke. *J Stroke Cerebrovasc Dis.* 2014;23(2):349-355.
22. Ayis SA, Ayerbe L, Ashworth M, Wolfe CDA. Evaluation of the Hospital Anxiety and Depression Scale (HADS) in screening stroke patients for symptoms: item response theory (IRT) analysis. *J Affect Disord.* 2018;228:33-40.
23. Lindberg PG, Gaverth J, Islam M, Fagergren A, Borg J, Forssberg H. Validation of a new biomechanical model to measure muscle tone in spastic muscles. *Neurorehabil Neural Repair.* 2011;25(7):617-625.
24. Birchenall J, Teremetz M, Roca P, et al. Individual recovery profiles of manual dexterity, and relation to corticospinal lesion load and excitability after stroke: a longitudinal pilot study. *Neurophysiol Clin.* 2019;49(2):149-164.
25. Burke Quinlan E, Dodakian L, See J, et al. Neural function, injury, and stroke subtype predict treatment gains after stroke. *Ann Neurol.* 2015;77(1):132-145.
26. Serrien DJ, Strens LH, Oliviero A, Brown P. Repetitive transcranial magnetic stimulation of the supplementary motor area (SMA) degrades bimanual movement control in humans. *Neurosci Lett.* 2002;328(2):89-92.
27. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* 2012;2(3):125-141.
28. Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage.* 2007;37(1):90-101.
29. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage.* 2012;59(3):2142-2154.
30. Cole DM, Smith SM, Beckmann CF. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Front Syst Neurosci.* 2010;4:8.
31. Arya KN, Verma R, Garg RK. Estimating the minimal clinically important difference of an upper extremity recovery measure in subacute stroke patients. *Top Stroke Rehabil.* 2011;18(suppl 1):599-610.
32. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: a biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol.* 2017;4(11):811-820.
33. Nowak DA, Glasauer S, Hermsdörfer J. Force control in object manipulation: a model for the study of sensorimotor control strategies. *Neurosci Biobehav Rev.* 2013;37(8):1578-1586.
34. Lang CE, DeJong SL, Beebe JA. Recovery of thumb and finger extension and its relation to grasp performance after stroke. *J Neurophysiol.* 2009;102(1):451-459.
35. Lang CE, Wagner JM, Bastian AJ, et al. Deficits in grasp versus reach during acute hemiparesis. *Exp Brain Res.* 2005;166(1):126-136.
36. Ghaziani E, Couppe C, Siersma V, et al. Easily conducted tests during the first week post-stroke can aid the prediction of arm functioning at 6 months. *Front Neurol.* 2019;10:1371.
37. Plantin J, Pennati GV, Roca P, et al. Quantitative assessment of hand spasticity after stroke: imaging correlates and impact on motor recovery. *Front Neurol.* 2019;10:836.
38. Feng W, Wang J, Chhatbar PY, et al. Corticospinal tract lesion load: an imaging biomarker for stroke motor outcomes. *Ann Neurol.* 2015;78(6):860-870.
39. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. *Ann Neurol.* 2015;78(6):848-859.
40. Schulz R, Koch P, Zimerman M, et al. Parietofrontal motor pathways and their association with motor function after stroke. *Brain.* 2015;138(pt 7):1949-1960.
41. Abela E, Missimer J, Wiest R, et al. Lesions to primary sensory and posterior parietal cortices impair recovery from hand paresis after stroke. *PLoS One.* 2012;7(2):e31275.
42. Lemon RN. Descending pathways in motor control. *Annu Rev Neurosci.* 2008;31: 195-218.
43. Persson HC, Opheim A, Lundgren-Nilsson Å, Alt Murphy M, Danielsson A, Sunnerhagen KS. Upper extremity recovery after ischaemic and haemorrhagic stroke: part of the SALGOT study. *Eur Stroke J.* 2016;1(4):310-319.
44. Quinlan EB, Dodakian L, See J, McKenzie A, Stewart JC, Cramer SC. Biomarkers of rehabilitation therapy vary according to stroke severity. *Neural Plast.* 2018;2018:9867196.
45. Grefkes C, Nowak DA, Eickhoff SB, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol.* 2008;63(2):236-246.
46. Carter AR, Astafiev SV, Lang CE, et al. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. *Ann Neurol.* 2010; 67(3):365-375.
47. Baldassarre A, Ramsey L, Rengachary J, et al. Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke. *Brain.* 2016; 139(pt 7):2024-2038.
48. Ingemanson ML, Rowe JR, Chan V, Wolbrecht ET, Reinkensmeyer DJ, Cramer SC. Somatosensory system integrity explains differences in treatment response after stroke. *Neurology.* 2019;92(10):e1098-e1108.
49. Carlsson H, Gard G, Brogardh C. Upper-limb sensory impairments after stroke: self-reported experiences of daily life and rehabilitation. *J Rehabil Med.* 2018;50(1):45-51.
50. Mullick AA, Subramanian SK, Levin MF. Emerging evidence of the association between cognitive deficits and arm motor recovery after stroke: a meta-analysis. *Restor Neurol Neurosci.* 2015;33(3):389-403.
51. Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage.* 2008;41(4):1382-1394.
52. Grefkes C, Fink GR. Connectivity-based approaches in stroke and recovery of function. *Lancet Neurol.* 2014;13(2):206-216.

# Disputes & Debates: Editors' Choice



## Editors' Note: Burden of Chronic and Acute Conditions and Symptoms in People With Epilepsy

Dr. Bensken et al. examined the burden and racial/ethnic disparities of chronic and acute conditions, injuries, and symptoms in 81,963 patients with epilepsy using 5 years of Medicaid claims data. The most common conditions were anxiety and mood disorders, hypertension, back problems, developmental disorders, and headache. Indigenous groups had a substantially higher prevalence of developmental disorders, whereas Black patients had a higher prevalence of hypertension. Those with high healthcare utilization had higher disease burden. In response, Dr. Garg suggests that sleep is another important symptom to consider in people with epilepsy, given that studies have indicated a reciprocal relationship between sleep and epilepsy. Responding to this comment, the authors note that sleep quality may also affect conditions such as anxiety and mood disorders that were examined in their study. However, they note that administrative health data do not capture sleep-related symptoms well. This exchange highlights the protean effects of epilepsy on patients' lives and the challenges of fully capturing the burden of this disease in claims data.

Aravind Ganesh, MD, DPhil, FRCPC, and Steven Galetta, MD
*Neurology*® 2022;98:340. doi:10.1212/WNL.0000000000013283

## Reader Response: Burden of Chronic and Acute Conditions and Symptoms in People With Epilepsy

Divyani Garg (New Delhi)
*Neurology*® 2022;98:340–341. doi:10.1212/WNL.0000000000013284

I read with great interest the article by Bensken et al.[1] Although the burden of epilepsy is all-pervasive, an important facet is missing in nearly all outcome-based data—the effect of epilepsy on sleep parameters. Seizure outcomes infrequently assess subjective and objective sleep measures. The limited data that exist suggest that there is widespread disruption of both self-reported and polysomnography-derived sleep parameters among persons with refractory epilepsy,[2] and there is suggestion that this improves with successful epilepsy surgery.[3]

The influence of epilepsy on sleep architecture has also been investigated and may be more important for temporal lobe epilepsies.[4] Considering this reciprocal relationship between sleep and epilepsy, it is surprising that there is limited focus on this relationship, especially in burden-of-disease measurements. Although there is no doubt about the omnipresent influence of epilepsy burden in physical and psychosocial terms, let us not ignore the effects related to sleep.

1. Bensken WP, Fernandez-Baca Vaca G, Jobst BC, et al. Burden of chronic and acute conditions and symptoms in people with epilepsy. *Neurology.* 2021;97(24):e2368-e2380.
2. Zanzmera P, Shukla G, Gupta A, et al. Markedly disturbed sleep in medically refractory compared to controlled epilepsy—a clinical and polysomnography study. *Seizure.* 2012;21(7):487-490.
3. Zanzmera P, Shukla G, Gupta A, et al. Effect of successful epilepsy surgery on subjective and objective sleep parameters—a prospective study. *Sleep Med.* 2013;14(4):333-338.

Author disclosures are available upon request (journal@neurology.org).

4. Sudbrack-Oliveira P, Lima Najar L, Foldvary-Schaefer N, da Mota Gomes M. Sleep architecture in adults with epilepsy: a systematic review. *Sleep Med.* 2019;53:22-27.



## Author Response: Burden of Chronic and Acute Conditions and Symptoms in People with Epilepsy

Wyatt P. Bensken (Cleveland)
*Neurology*® 2022;98:341. doi:10.1212/WNL.0000000000013285

Thank you for your thoughtful comment on our article.[1] We agree that there is an important relationship between epilepsy and sleep. Sleep quality may even affect some of the conditions we examined, such as anxiety and mood disorders. Unfortunately, large health care data, which were used in this study, often does not prioritize these important aspects of health. The points raised here are certainly an important direction for future work and highlight the multifaceted health needs and priorities for people with epilepsy.

1. Bensken WP, Fernandez-Baca Vaca G, Jobst BC, et al. Burden of chronic and acute conditions and symptoms in people with epilepsy. *Neurology*. 2021;97(24):e2368-e2380.



**CORRECTIONS**

## Recovery and Prediction of Bimanual Hand Use After Stroke

*Neurology*® 2022;98:341. doi:10.1212/WNL.0000000000012717

In the Research Article "Recovery and Prediction of Bimanual Hand Use After Stroke" by Plantin et al.,[1] the Outcome–Ad-AHA–R2 column of eTable 1 contained incorrect values. A corrected version is available at doi.org/10.5281/zenodo.5054068 as Version 2. The authors regret the error.

### Reference

1. Plantin J, Verneau M, Godbolt AK, et al. Recovery and prediction of bimanual hand use after stroke. *Neurology*. 2021;97(7):e706-e719.

## High Prevalence of Neutralizing Antibodies After Long-term Botulinum Neurotoxin Therapy

*Neurology*® 2022;98:341. doi:10.1212/WNL.0000000000013258

In the article "High Prevalence of Neutralizing Antibodies After Long-term Botulinum Neurotoxin Therapy" by Albrecht et al.,[1] the third sentence of the Conclusions paragraph in the Abstract should read: "However, in addition to avoiding booster injections and extending the interval between injections, reducing the individual injected doses may diminish the risk of NAb induction independently of the indication for which BoNT/A is used." The authors regret the error.

### Reference

1. Albrecht P, Jansen A, Lee JI, et al. High prevalence of neutralizing antibodies after long-term botulinum neurotoxin therapy. *Neurology*. 2018;92(1):e48-e54.

Author disclosures are available upon request (journal@neurology.org).