Recovery and Prediction of Bimanual Hand Use After Stroke

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Neurology® 2021;97:e706-e719. doi:10.1212/WNL.0000000000012366

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.
Stroke survivors with arm and hand motor impairment often experience reduced daily life activities and participation. 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. Impaired interlimb coordination and grip force matching between hands 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. 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 abstraction 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. Furthermore, given the importance of somatosensory and cognitive impairment 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 was used to evaluate how effectively the patients used their contralateral 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. 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 with good to excellent interrater and intrarater reliability for patients with subacute stroke. 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.
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, 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, categorized as normal–near normal/impaired/absent.
3. Pain: FMA subdomain for pain during passive movement. A score of ≤23 of 24 indicated pain.
4. Discriminative sensation (2-point discrimination [2pD]): index and thumb finger pads were tested with a Discriminator (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 metacarpalphalangeal 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 (range 0–5).
8. Cognitive status: determined with the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) (range 0–50).
9. Anxiety/depression: Hospital Anxiety and Depression Scale (range 0–21 for the respective domain).
10. Neglect: baking tray task (yes/no).
11. Neural resistance, indicating spasticity, of wrist and finger flexor muscles: the NeuroFlexor method.
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; filion.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/orden/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 (filion.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 sources28 that takes into account the non-homogeneous 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).

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

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 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, $p ≥ 0.027$, 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 ± 36 points [mean ± SD]) at 3 weeks were not included in the prediction analysis, yielding a sample of n = 66. Univariate associations are shown in table 1 (available from Zenodo: 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 FCPCG, together explaining 87% of the variance, of which FCPCG 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 prediction 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 FCPCG (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 cm³, 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 cm³ 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 cm³ (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 cm³ and more variable in patients with wCST-LL <5.5 cm³, with no patient with wCST-LL >5.5 cm³ having Ad-AHA score increase above ≥20. Conversely, Ad-AHA recovery was highly variable in patients with wCST-LL <5.5 cm³ (figure
| Variables                                    | All (n = 89) | Mild (n = 23) | Moderate (n = 19) | Severe (n = 47) | Group Difference (Significance) |
|---------------------------------------------|--------------|--------------|------------------|----------------|-------------------------------|
| 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, cm³                                | 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*                       | 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 (%)         | 39 (44)      | 3 (13)       | 5 (26)           | 31 (66)        | 0.281 <0.0001 0.0036          |
| 2-Point discrimination (absent), n (%)a     | 48 (54)      | 4 (17)       | 4 (21)           | 40 (85)        | 0.766 <0.0001 <0.0001         |
| Vibration (absent), n (%)d                  | 24 (29)      | 1 (4)*       | 3 (16)           | 20 (48)        | 0.214 0.0004 0.185            |
| Touch (impaired or absent), n (%)b          | 60 (67)      | 7 (30)       | 10 (53)          | 43 (92)        | 0.242 <0.0001 <0.0001         |
| Proprrioception (impaired or absent), n (%)c| 51 (58)      | 4 (17)       | 9 (47)           | 38 (83)        | 0.032 <0.0001 0.001           |
| FMA-SAFE score (0–4 points)                | 3 (1–4)      | 4 (4–5)      | 3 (3–4)          | 1 (0–2)        | <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 χ² tests.
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 cm³ (figure 4B).

Outcome and Recovery in Patients With wCST-LL <5.5 cm³
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, FCPCG, 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 cm³ 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 FCPCG 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
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 ($R = 0.50$, $p = 0.028$ 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).)

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. 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. FMA-SAFE assesses shoulder abduction, which is involved in arm transport, and finger extension, which is necessary for opening fingers before grasping. 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<sup>a</sup> of Outcome and Recovery

| Dependent Variables | Model<sup>a</sup> Independent Variables | Unstandardized Coefficients | 95% Confidence Interval for B | Change Statistics |
|---------------------|-----------------------------------------|-----------------------------|------------------------------|------------------|
|                     |                                         | B   | SE  | Significance | 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     | 0.088             | 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             | 0.049         | 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<sub>PCG</sub>                      | 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<sub>PCG</sub>                      | 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<sub>PCG</sub>                      | 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           |

<sup>a</sup>Significance levels: *<sup>p</sup> < 0.05, **<sup>p</sup> < 0.01, ***<sup>p</sup> < 0.001.
(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 (Table 1 available from Zenodo: 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 findings38,39 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 cm³ was highly predictive of both poor bimanual and unimanual recovery (Figure 4). Feng et al.38 also reported that a wCST-LL >5.5 cm³ in the acute phase was a strong predictor of unimanual motor recovery (FMA-UE outcome score >25) at 6 months after stroke.

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

| Dependent Variables | Model* | Independent Variables | Unstandardized Coefficients | 95% Confidence Interval for B | Change Statistics |
|---------------------|--------|-----------------------|----------------------------|------------------------------|------------------|
|                     |        |                       | B   | SE  | Significance | Lower Bound | Upper Bound | R² Accumulated | R² 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 | -0.004 | 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.

* 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.

**Figure 4 Predictive Threshold of CST Injury (wCST-LL) of 5.5 cm³ 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 cm³ 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 cm³. 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 cm³ and high interindividual variance in patients with a wCST-LL <5.5 cm³ (C).
### Table 3: Multivariable Linear Regression Prediction Models of Outcome and Recovery in 38 Patients With wCST-LL < 5.5 cm³

| Dependent Variables | Model | Predictor Variables | Unstandardized Coefficients | Significance | 95% Confidence Interval for B | Change Statistics | Accumulated R² | R² Change | Significant F Change |
|---------------------|-------|---------------------|-----------------------------|-------------|-----------------------------|------------------|--------------|-----------|----------------------|
|                     |       |                     | B   | SE  | Significance | Lower Bound | Upper Bound |          |          |                      |
| 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 |
| 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 |
|                     | 2     | 2pD                 | 0.343 | 0.089 | 0.000 | 0.163      | 0.524 | 0.254 | 0.254 | 0.001 |
| FMA-UE outcome      | (Constant) |                     | 0.859 | 4.629 | 0.854 | −6.609     | 10.328 |          |          |                      |
|                     | 1     | FMA-SAFE score      | 12.788 | 1.294 | 0.000 | 10.142     | 15.434 | 0.739 | 0.739 | 0.000 |
|                     | 2     | FPCG                | 10.259 | 4.719 | 0.038 | 0.607      | 19.911 | 0.776 | 0.037 | 0.038 |
| FMA-Hand outcome    | (Constant) |                     | 0.509 | 0.127 | 0.403 | −0.891     | 2.122 |          |          |                      |
|                     | 1     | FMA-SAFE score      | 3.381 | 0.407 | 0.000 | 2.546      | 4.215 | 0.661 | 0.661 | 0.000 |
|                     | 2     | FPCG                | 3.731 | 1.486 | 0.018 | 0.688      | 6.774 | 0.723 | 0.062 | 0.018 |
| FMA-Hand recovery   | (Constant) |                     | −0.255 | 0.104 | 0.200 | −0.466     | 0.485 |          |          |                      |
|                     | 1     | FMA-SAFE score      | 0.218 | 0.035 | 0.000 | 0.146      | 0.291 | 0.500 | 0.500 | 0.000 |
|                     | 2     | FPCG                | 0.349 | 0.129 | 0.011 | 0.085      | 0.613 | 0.600 | 0.101 | 0.011 |
| 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. 

*Stroke type refers to ischemic or hemorrhagic stroke. The effect of stroke type was in favor of patients with hemorrhagic stroke.*
In patients with CST lesion load <5.5 cm³, the predictors of bimanual recovery showed that CST integrity is important for bimanual recovery. Agreement with some other studies.45-47 Notably, the greatest recovery, in addition to FMA-SAFE score (table 2), in explaining some additional variance in unimanual outcome and 25% of recovery, particularly in patients with relatively spared CST.44,45 The present findings show that CST integrity is important for bimanual recovery.

In patients with CST lesion load <5.5 cm³, 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 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 cm³ (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 cm³), 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 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 cm³ 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.

Study Funding
Funding provided by the Promobilia Foundation, STROKEFörsbundet, NEURO Sweden, Lars Hedlund (Karolinska Institutet Dnr 2-1582/2016).

Disclosure
J. Plantin, M. Verneau, A.K. Godbolt, G.V. Pennati, E. Laurencikas, B. Johansson, L. Krumlinde-Sundholm, J.-C. Baron, and J. Borg report no disclosures. P.G. Lindberg is a shareholder in the company Aggero MedTech AB, manufacturing a measurement instrument for spasticity, and has patented a holder in the company Aggero MedTech AB, manufacturing a measurement instrument for spasticity, and has patented a holder in the company Aggero MedTech AB. The other authors report no disclosures.

Publication History
Received by Neurology August 9, 2020. Accepted in final form May 20, 2021.

Appendix

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 |

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