Distinct Constructs Underlie Patient-Reported and Performance-Rated Outcomes after Stroke

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Objective: Patient-reported outcome measures (PROMs), which capture patients' perspectives on the consequences of health and disease, are widely used in neurological care and research. However, it is unclear how PROMs relate to performance-rated impairments. Sociodemographic factors are known to affect PROMs. Direct damage to brain regions critical for self-awareness (i.e., parietal regions and the salience/ventral-attention network) may also impair self-report outcomes. This study examined the relationship between PROMs and performance-based measures in stroke survivors with arm motor impairments. We hypothesized that PROMs would be distinct from performance-based outcomes, influenced by sociodemographic factors, and linked to damage in brain circuits involved in self-perception.
Methods: We longitudinally assessed 54 stroke survivors using patient-reported and performance-rated measures at 4 timepoints. We used factor analysis to reveal the outcome battery's factorial structure. Linear regression examined the association between classes of measures and sociodemographics. Voxel-lesion-symptom-mapping, region-of-interest-based analysis, and voxel-lesion-network-mapping investigated the relationship between classes of outcomes and stroke-related injury.
Results: Performance-based and patient-reported measures formed distinct factors, consistent across recovery phases. Higher education ($\beta 1 = 0.36$, $p = 0.02$) and income adequacy ($\beta 2 = 0.48$, $p = 0.05$) were associated with patient-reported, but not performance-rated outcomes. Greater parietal lobe injury, irrespective of hemisphere, was associated with worse patient-reported outcomes; greater corticospinal tract injury related to worse performance-rated outcomes. Lesions with greater functional connectivity to the salience/ventral-attention network were associated with worse patient-reported outcomes ($r = -0.35$, $p = 0.009$).
Interpretation: Our findings reveal important differences between performance-rated and patient-reported outcomes, each with specific associated factors and anatomy post-stroke. Incorporating sociodemographic and neuroanatomic characteristics into neurorehabilitation strategies may inform and optimize patient outcomes.

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Patient-reported outcome measures (PROMs) have become widely adopted in neurological research and clinical practice and are advocated for by the National Institutes of Health (NIH)[1,2] and Food and Drug Administration (FDA), and are a cornerstone of value-based health care.[3–11] In neurology, PROMs are designed to

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capture patient's perceptions of the real-life consequences of primary neurological impairments, such as arm motor deficits after stroke.[7,12–14] The essential feature of PROMs is that they are directly reported by patients themselves, without rating or interpretation by others, including clinicians. The Patient Reported Outcomes Measurement Information System (PROMIS) Global-10, for example, one of the most extensively used PROMs, consists of 10 items for which patients report on their physical health, physical functioning, general mental health, emotional distress, satisfaction with social activities and relationships, ability to carry out usual social activities and roles, pain, fatigue, and overall quality of life.[15] In stroke, lesions lead to primary neurologic impairments in motor, speech, and/or cognitive function, which are traditionally assessed by domain-specific outcomes measures (clinicians rate performance on a motor, speech, or cognitive task, performance-rated assessment).[16,17] PROMs in stroke are thought to provide patient perspectives on the impact of these domain-specific, performance-rated deficits on overall health. In patients with motor dysfunction after stroke, PROMs have been shown to be concordant with the severity of motor deficits[1] and provide an even more sensitive assay of motor impairments[18] as compared to traditional, clinician, performance-rated assessments.

Questions, however, have emerged regarding the interpretation of PROMs, especially their concordance with objective measures of physical function.[19,20] Factors such as sociodemographics,[21] cultural influences, and personality[22] are known to influence patient self-report. Baseline cognition and mood may also impact PROMs.[23] Given that PROMs are uniquely associated with these baseline psychosocial features, they may represent an altogether distinct construct of outcome measure[24] from performance-rated assessments. In patients with stroke, these findings call into question the model of PROMs reflecting the impact of domain-specific deficits on overall health.

The ability to accurately self-report symptoms by patients with stroke can be directly compromised by the pattern of stroke-induced neuroanatomic injury itself. In particular, parietal areas, important for attention and awareness (ie, right parietal injury commonly results in spatial neglect or anosognosia), are also known to be critical for general self-representation and interpretation of sensory information, regardless of cortical side (ie, right or left hemisphere).[25–28] The parietal lobe is a primary input to the salience/ventral-attention network, which integrates sensory percepts with emotional and cognitive context,[29,30] altogether influencing self-perception of real-world experiences including health. Direct damage to these areas can impair the processing and integration of sensory information, thereby potentially affecting self-report. Damage to parietal areas and its connections could, therefore, directly impact PROMs.

Given the above considerations, this study aimed to test whether PROMs represent the health-related consequences of primary neurological impairments after stroke or a different construct of outcome altogether. We investigated the relationship between PROMs and performance-rated outcome measures in a longitudinal cohort of patients with upper extremity (UE) motor deficits after stroke. Our primary hypotheses were that PROMs would be a distinct outcome measure construct from performance-rated assessments, influenced by sociodemographic features, and associated with damage to parietal networks.

Materials and Methods

Participants

Participants were enrolled as part of a prospective, single-center natural history study of stroke motor recovery (Stroke Motor Rehabilitation and Recovery Study, clinicaltrials.gov NCT03485040) during their acute stroke hospitalization. Adults, age 18 to 90, within 2 weeks of a new stroke resulting in unilateral UE motor weakness (defined by National Institute of Health Stroke Scale [NIHSS] arm motor drift questions 5a or 5b ≥1), who could follow simple commands in English and were admitted to the Massachusetts General Hospital Stroke Service, were eligible. We excluded individuals with a history of a major psychiatric, developmental, or neurological disorder causing functional disability limiting their testing participation. At enrollment, we recorded baseline clinical and demographic information, including age, sex, handedness, paretic side, stroke risk factors, treatment status with respect to tissue-type plasminogen activator (tPA) or endovascular therapy (EVT), infarct location, and initial NIHSS score. Sociodemographic characteristics, which included marital status, education level (dichotomized as high school or less vs greater than high school), and perceived income adequacy (as defined by how difficult it is to meet basic needs; categorized as 0-not difficult, 1-not very difficult, 2-somewhat difficult, or 3-very difficult to meet basic needs)[31] were also gathered at the time of enrollment. Participants were assessed using an outcome measure battery (detailed below) acutely (0–14 days) (T_1) and returned for research follow-up during the sub-acute (15 days–3.5 months) (T_2), early-chronic (3.5 months–6 months) (T_3), and late-chronic (>6 months) (T_4) phases of stroke.[32,33] Subjects who did not participate in all 4 study visits were excluded.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Mass General Brigham Institutional Review Board, and all participants provided written informed consent.

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Outcome Measure Battery

We administered a battery of standardized stroke rehabilitation outcome measures including performance-rated (ie, activity-based, clinician-observed) and PROMs (Table S1). Performance-rated outcome measures included the UE Fugl-Meyer assessment (UE-FMA) (maximum score 66, higher scores are better), grip strength assessed by dynamometry (higher values are better), modified Rankin Scale (mRS) (maximum score 6, lower scores are better), Barthel Index (BI) (maximum score 100, higher scores are better), Box and Blocks Test (B&B) (higher scores are better), and 9-Hole Peg Test (9-HP) (time to complete the task, lower scores are better). For performance-rated outcomes, a core group of assessment administrators (occupational therapists and research staff) underwent annual assessment training on the BlueCloud platform for those available with bi-annual inter-rater reliability meetings to ensure assessment protocol consistency.

PROMs included the PROMIS Global-10 Questionnaire and the Patient Health Questionnaire-9 (PHQ-9) (measures depression, maximum score 27, lower scores are better). Global Physical Health (GPH) (maximum raw score 20, higher scores are better), Global Mental Health scores (GMH) (maximum raw score 20, higher scores are better), and Global Social Health (GSH) (maximum raw score 5, higher scores are better) scores were derived from the PROMIS Global-10 questions and used in subsequent analyses.[34] The PROMIS Global-10 includes 10 items that assess physical (GPH), mental (GMH), and social health (GSH) (and together comprising overall health). Each item is scored on a 1 to 5 scale, with higher scores indicating better health. Specifically, the GPH is derived from items that ask patients to rate their general physical health, pain, fatigue, and physical functioning. The GMH is derived from items that ask patients to rate their quality of life, emotional problems, and social roles. The GSH score provides insight into social health by summarizing responses to items on social roles and relationships. Together, these measures, comprising the PROMS-10, were designed to capture a holistic view of a patient's health status by assessing multiple domains that contribute to overall well-being, making them particularly useful in our study to evaluate the broader impact of stroke on patients' lives[35]. PROMIS-Global Health measures were not collected during the acute timepoint because we reasoned hospitalization may compromise the validity of the scale. Scores on all outcome measures were normalized with 1 representing best and 0 representing worst possible scores.

Neuroimage Processing

Stroke lesion topography was determined using magnetic resonance (MR) diffusion-weighted images from acute stroke standard-of-care clinical workup. MR imaging was clinically contraindicated for 2 participants, in whom a computed tomography (CT) scan was used instead. Research staff manually outlined stroke lesions on the diffusion-weighted image/apparent diffusion coefficient volumes with the use of FSL (fsl.fmrib.ox.ac.uk/fsl/fslwiki). Tracings were independently verified by 2 board-certified neurologists (D.J.L. and S.B.S) who were blinded to the clinical status of the patient. Lesions were spatially normalized to the Montreal Neurological Institute (MNI) brain template using established methods.[36] In sum, diffusion images were extracted from the skull using Brain Extraction Tool (BET) on FSL and spatially normalized to the 2-mm T1-weighted MNI brain template using Advanced Normalization Tools (Philadelphia, PA). For scans with stroke lesions above the brainstem, co-registration included the center of mass alignment, rigid, similarity, and fully affine linear transformations. For scans with lesions within the brainstem, an additional nonlinear (symmetric diffeomorphic) transformation was performed to ensure accurate coregistration in this region. Resultant transformation matrices were then applied to the stroke masks using Advanced Normalization Tools, bringing each into MNI standard stereotaxic space. The anatomic accuracy of the stroke masks in standard space was then verified by a board-certified neurologist (D.J.L).

Participants had a unilateral lesion, except for 3 individuals who had a punctate area of infarction in the contralateral hemisphere, which did not cause motor deficits. To allow for group comparisons, left-sided stroke lesions were flipped along the midline to the right hemisphere for subsequent imaging analyses. Lesion side was considered as a covariate in subsequent analyses.

Statistical Analysis

Descriptive statistics were calculated, and independent sample *t* tests and chi-squared tests were performed to compare demographic characteristics between those included and those excluded in this analysis.

We conducted Bartlett's test of sphericity, which indicated there was redundancy within the measures in the outcome battery and that it was appropriate to perform factor analysis. Next, we conducted exploratory factor analysis (EFA) on the outcome measures in the battery using the restricted maximum likelihood (REML) estimation method with the oblimin rotation, separately at each timepoint (T_1-T_4). To decide on the number of factors to retain, we used Kaiser's eigenvalue-greater-than-1 rule (Kaiser criterion) and evaluated the scree plots. The loadings of individual indicators on the extracted factors were consistent across analyses at all 4 timepoints (T_1, T_2, T_3, and T_4), so we proceeded by using the results obtained at T_4 and conducted confirmatory factor analysis (CFA) with the maximum likelihood estimator. We assumed a simple structure, namely 1 non-0 loading on each factor. We evaluated the findings based on the standardized results (ie, standardized loadings of the indicators on their respective factors). For each patient, we also estimated their factors scores. To assess the scores' internal consistency, we obtained the Cronbach's alpha for each factor score. Based on the emergent factor structure from the EFA, factor 1 represented performance-rated outcome measures, whereas factor 2 represented PROMs.

To investigate the impact of dominant arm impairment (ie, the dominant UE being the one primarily affected by the stroke) on outcome measures, we divided the study population into 2 groups: those with dominant arm affected ($n = 25$, 46.3%) and non-dominant arm affected ($n = 29$, 53.7%), and compared scores on self-report between groups on patient-reported outcomes.

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Linear regression modeling was used to assess the association between factor scores and sociodemographic characteristics. Statistical significance was set at $p < 0.05$ level.

Neuroimaging Statistical Analysis

Voxel-Based Symptom Lesion Mapping. To identify brain voxels significantly associated with differences in factor 1 (performance-rated outcome measures) and factor 2 (PROMs), voxel-based lesion symptom mapping (VLSM) was performed using canonical methods.[37] A voxel would be tested only if at least 5 (9.3%) patients exhibited a lesion there. For each voxel, participants were divided into 2 groups according to whether they did or did not have a lesion affecting that voxel. Factor 1 and factor 2 scores were then compared for these 2 groups, yielding a t-statistic for each voxel. Voxels were further considered if the t-statistic met a threshold value of $p < 0.001$. Correction for multiple comparisons was achieved by permutation analysis (1,000 permutations). Significant clusters of voxels were identified by size and location in MNI space by overlay with the Automated Anatomical Labeling Atlas 3.0.[38]

Region-of-Interest Analysis. Structural regions of interest (ROIs) were identified as the corticospinal tract (CST) and the parietal lobe[39] given their known role in motor performance and self-perception, respectively. Voxels significantly associated with worse patient-reported and performance-rated outcomes were identified, and percent of overlap with the ROIs were calculated. Fisher's exact test was used to compare the proportion of overlap between patient-reported and performance-rated outcomes for each ROI (ie, the CST and parietal lobe).

For each participant, lesion volume, CST-weighted lesion load, and extent of parietal injury were calculated. CST-weighted lesion load calculation was performed in line with previously validated methods.[40,41] Parietal lobe injury was calculated by quantifying the percent of parietal lobe voxels overlapping each individual stroke mask. CST-weighted lesion load, parietal injury, and lesion volume underwent log transformation to reduce the skewness of the variables. Linear regression modeling was used to assess the association between factor scores and CST or parietal lobe damage while also controlling for lesion volume and stroke lesion side. Statistical significance was set at $p < 0.05$.

Salience/Ventral-Attention Network Disconnection (Voxel-Based Lesion Network Mapping). The functional connection of each lesion to the salience/ventral-attention network was estimated based on previously validated methods.[42–44] Each participant's lesion was used as a seed region to compute the functional connectivity to all voxels in the brain. We relied on a functional connectome comprising resting-state data from 1,000 healthy, right-handed subjects (mean age, 21.3 [range 18–35] years, 43% men, preprocessed in accordance with Fox et al.)[45] Subsequently, we averaged the Fisher z-transformed voxel-wise lesion connectivity (positive and negative values) within 100 Yeo-Schaefer atlas-defined cortical parcels.[46,47] Last, we summarized the parcel-wise lesion absolute connectivity within the atlas-defined salience/ventral-attention network. Variables were tested for normal distribution using the Shapiro Wilk test. We then obtained bivariate, Spearman's rho (for non-normally distributed variables, factor 1), and Pearson's r (for normally distributed variables, factor 2) correlation statistics to examine the association between patient-reported versus performance-rated outcome measures and each participants lesion's functional connection to the salience/ventral-attention network.

All analyses were carried out in RStudio (version 2022.07.2) (Boston, MA) and MATLAB (version R2019B) (The MathWorks, Natick, MA).

Results

Study Cohort

A total of 94 patients met study inclusion criteria and consented to participate. Subjects who passed away (n = 7), withdrew (n = 11), or were unable to complete all 4 study visits (n = 22) were excluded from this analysis. There were no statistically significant differences between those included and those excluded on age ($p = 0.88$), gender ($p = 0.17$), or initial stroke severity ($p = 0.54$). In the included sample of 54 participants, age was 62.0 ± 13.4 (mean ± standard deviation) years, and there was an even distribution of sex (48.1% male). Participants' initial UE motor impairment ranged from a score of 4 to 65 on the UE-FMA, with a median of 28 (5–53.3). The actual time post-stroke for each visit was 3.3 ± 2.5 (T_1, acute), 46.6 ± 4.4 (T_2, subacute), 92.2 ± 8.8 (T_3, early-chronic), and 344.7 ± 63.2 (T_4, late-chronic) days. Additional baseline demographic, clinical and stroke characteristics are summarized in Table 1. Outcome measure scores across time are summarized in Table S2.

PROMs Are Distinct from Performance-Rated Outcome Measures. Of the 10 outcome measures collected, 6 measures were obtained by performance-rating (either via direct observation of performance or by clinician-directed interview) and the other 4 by patient-report (on mental, social, and physical health). As shown in Figure 1, participant A self-reported good physical, social, and mental health, but exhibited substantial and sustained deficits

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TABLE 1. Baseline demographic and clinical characteristics of cohorts

N	54
Age, yr	62 ± 13.4
Sex (males)	26 (48.1)
Dominant hand (right)	45 (83.3)
Affected extremity (right)	28 (51.9)
Dominant side, affected	25 (46.3)
Married	29 (53.7)
>HS diploma	34 (63.0)
Income adequacy	2 [2]
Pre-stroke vascular risk factors	
Hypertension	34 (63.0)
Hyperlipidemia	33 (61.1)
Diabetes	16 (29.6)
Current smoker	10 (18.5)
Atrial fibrillation	8 (14.8)
Acute stroke therapy	
IV tPA	14 (25.9)
EVT	11 (20.4)
Stroke etiology	
Large artery	17 (31.5)
Cardio embolic	9 (16.7)
Small vessel	10 (18.5)
Other determined	2 (3.7)
Undetermined	16 (29.6)
Infarct hemisphere (left)	27 (50.0)
Infarct territory	
MCA	38 (70.4)
PCA	2 (3.7)
Brainstem	5 (9.3)
Multi-territory	8 (14.8)
Lesion volume (raw)	11,260 [62030]
CST-wLL (log-transformed)	1.86 [0.97]
Parietal injury (log-transformed)	2.37 [1.40]
Acute NIHSS	7 [4–10]
Acute UE-FMA	28 [5–53.3]

Statistics are presented as mean ± SE, n (%) and median [interquartile range].
CST-wLL = corticospinal tract-weighted lesion load; EVT = endovascular therapy; HS = high school; MCA = middle cerebral artery; NIHSS = National Institute of Health Stroke Scale; PCA = posterior cerebral artery; tPA = tissue-type plasminogen activator; UE-FMA = upper extremity Fugl-Meyer assessment.

measured by performance-rated outcome measures at all timepoints (limited arm and hand function and poor recovery). In contrast, participant B self-reported poor physical, social, and mental health at all timepoints, but only had modest performance-rated deficits, which recovered near fully. These cases illustrate distinct patterns of patient-reported and performance-rated outcomes measures of health among different patients.

To systematically examine underlying constructs associated with patient-reported versus performance-rated outcome measures, 2-stage factor analysis was applied to the cohort's outcome measure battery. First, exploratory factor analysis identified 2 main and significantly different factors (Bartlett's test of sphericity, $p < 0.001$), which together explained approximately 80% of variance at each timepoint ($T_1 = 81.4\%$, $T_2 = 79.5\%$, $T_3 = 82.5\%$, $T_4 = 78.4\%$) (Fig S1). Performance-rated outcome measures (UE-FMA, grip strength, B&B, 9-HP, BI, and mRS) loaded onto factor 1, whereas PROMs (PROMIS-physical, mental, and social health, PHQ-9) loaded onto factor 2. Second, confirmatory factor analysis confirmed the significance of the 2-factor model and consistency of factor-loadings (Fig 2). The correlation in the 2-factor model ($R = 0.224$, Standard Error, SE $= 0.140$, 95% confidence intervals: [−0.050, 0.498]) was weakest at T_4 (late chronic recovery, approximately 1 year after stroke), indicating the greatest separation of the 2-factor model at this timepoint (Fig S1). Both factor 1 and 2 had good internal consistency, with Cronbach's alphas estimated at 0.81 and 0.80, respectively, at T_4. Taken together, factor analysis applied to a battery of commonly used outcome measures—collected on a cohort of participants recovering over the first year after stroke—revealed a clear separation of patient-reported from performance-rated outcomes.

To assess the impact of the dominant arm being the more affected side on performance-based and self-reported scores, we compared factor scores between individuals with affected dominant arms and those with affected non-dominant arms. We did not observe significant differences on factor 1 (performance-based abilities) (U-statistic $= 318$, $p = 0.45$) or factor 2 (self-reported abilities) ($U = 354$, $p = 0.891$) between groups.

Sociodemographic Characteristics Are Associated with Patient-Reported but Not Performance-Rated Outcomes. To examine the hypothesis that baseline sociodemographic characteristics are associated with patient-reported health, multiple linear regression was performed with the factor 2 score (representing aggregated patient-reported health outcomes) as the dependent variable and age, sex, education level, marital status, and income. Sociodemographic variables explained over 37% of variance in patient-

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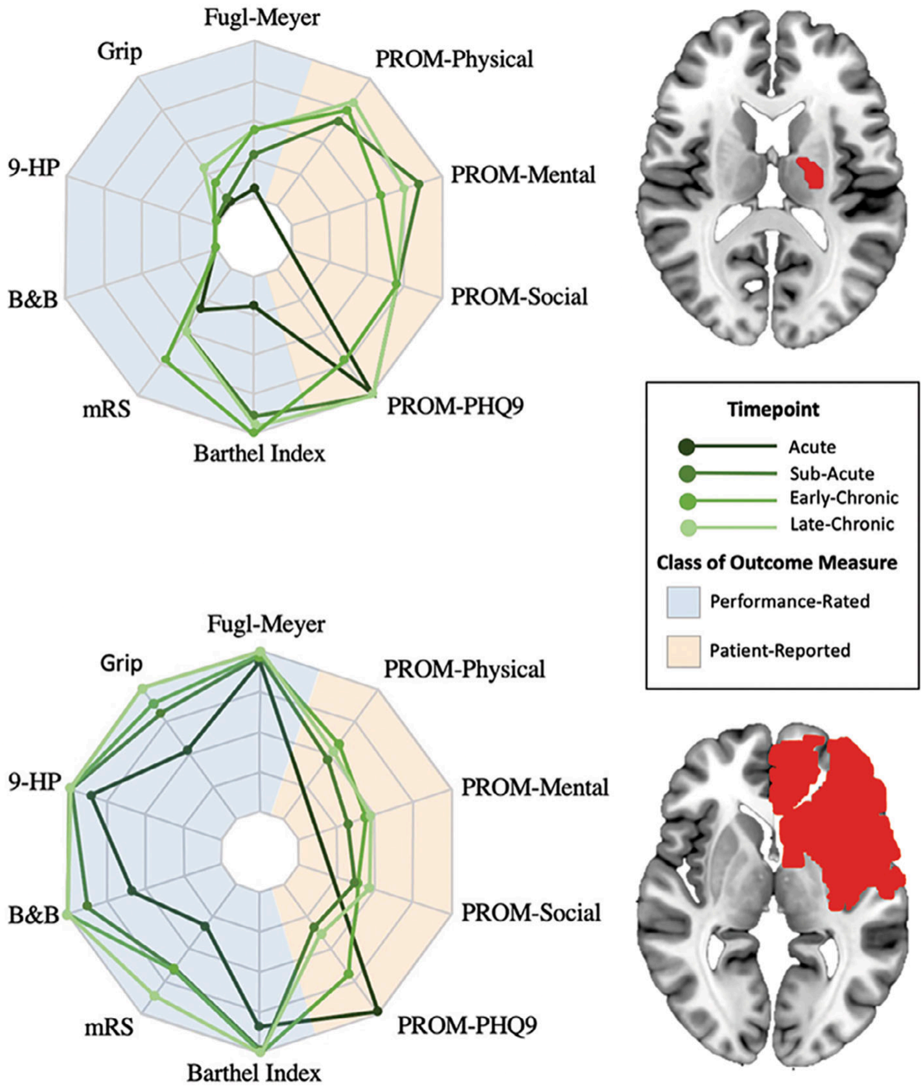

FIGURE 1: Radar plots of outcome measures for 2 patients across time. Radar plots (left) are shown, denoting performance across measures (maximum scores around outside of radar plot) and time (*green shades*) after stroke are shown for 2 unique patients (top and bottom). Outcome measures and scores are normalized on a common scale. Points further away from the center represent better performance. Performance-rated outcomes are shown in light blue and patient-reported in light orange. Top patient has a subcortical lesion overlapping the corticospinal tract and significant impairments in performance-rated outcomes with relative preservation of patient-reported outcomes. Bottom patient has a cortical lesion in the parietal/temporal regions and self-reports significant difficulties with relative preservation of performance.

reported health outcomes ($R^2 = 0.37$, $F [5, 48] = 5.52$, $p = <0.001$) (Table 2). Controlling for other variables in the model, higher education level ($\beta_1 = 0.36$, $p = 0.02$), and better income adequacy ($\beta_2 = 0.48$, $p = 0.05$) were found to be statistically significant independent predictors of better patient-reported health. Marital status (married) trended toward significance ($\beta_3 = 1.05$, $p = 0.06$). In contrast, sociodemographic characteristics did not significantly predict factor 1 (representing aggregated performance-rated health outcomes) score, ($R^2 = 0.03$, $F [5, 48] = 0.33$, $p = 0.89$) (Table 2). Taken together, baseline sociodemographic characteristics predicted patient-reported, but not performance-rated health outcomes after stroke.

Patient-Reported and Performance-Rated Outcomes Are Related to Distinct Patterns of Brain Injury. To test the hypothesis that injury to parietal areas and the associated salience/ventral-attention network would relate to worse patient-reported health outcomes, we performed VLSM, region-of-interest-based lesion analysis, and voxel-lesion network mapping (VLNM). Stroke lesion overlap of the 54 participants in the study is shown in Figure 3. VLSM revealed that voxels where injury was significantly associated with worse patient-reported outcomes were

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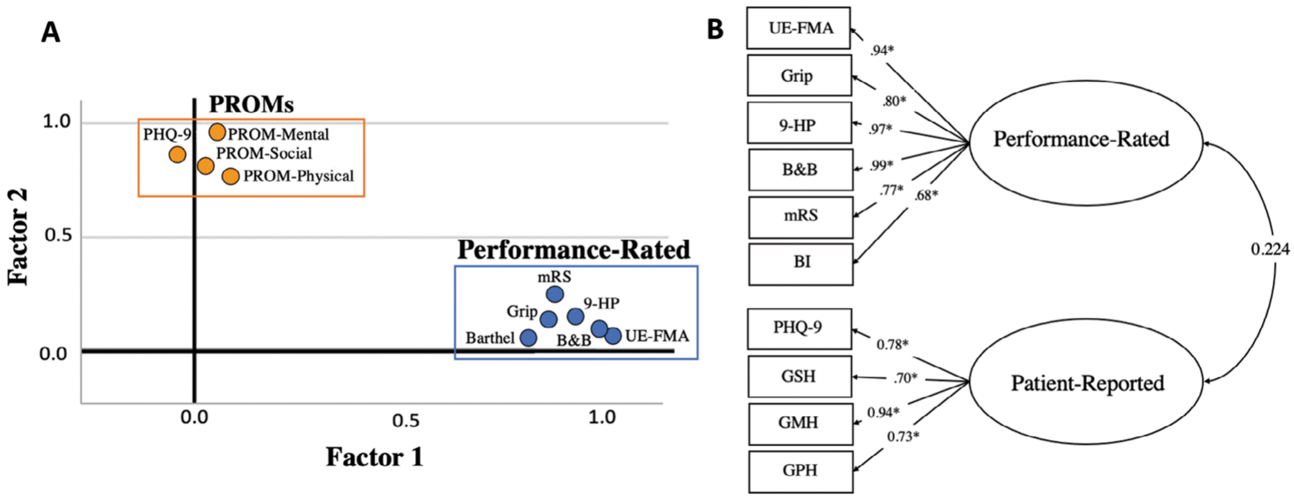

FIGURE 2: Exploratory and confirmatory factor analysis clustering and loadings performed at T_4. (A) Exploratory factor analysis identified the underlying factorial structure of the outcome battery; performance-rated outcome measures and patient-reported outcome measures separately independently into 2 factors. (B) Confirmatory factor analysis proved the 2-factor model was significant while providing factors loadings for the 10 individual outcome measures at T_4. [Color figure can be viewed at www.annalsofneurology.org]

TABLE 2. Linear regression models.

Variables	Performance-rated health (factor 1)					Patient-reported health (factor 2)				
	B	Co SE	β	*t*	*p*	B	Co SE	β	*t*	*p*
Model A										
Age	−0.03	0.23	−0.02	−0.14	0.89	0.04	0.02	0.22	1.78	0.08
Female	−4.71	6.04	−0.12	−0.78	0.44	−0.11	0.53	−0.03	−0.20	0.84
Married	−0.09	6.06	−0.00	−0.02	0.99	1.05	0.54	0.25	1.05	0.06
>HS diploma	1.02	1.66	0.09	0.61	0.54	0.36	0.15	0.29	2.47	**0.02***
Income	1.08	2.69	0.06	0.40	0.69	0.48	0.24	0.25	2.00	**0.05***
R^2	0.033					0.365				
p	0.89					**<0.001***				
Model B										
Lesion volume	−4.42	3.83	−0.19	−1.15	0.26	−0.22	0.43	−0.09	−0.51	0.61
Lesion side	−5.05	5.18	−0.13	−0.97	0.34	0.26	0.58	0.061	0.45	0.66
CST-wLL	−6.21	3.01	−0.31	−2.06	**0.05***	−0.21	0.34	−0.10	−0.63	0.53
Parietal injury	0.07	5.10	0.002	0.014	0.99	−1.25	0.57	−0.33	−2.20	**0.03***
R^2	0.214					0.180				
p	**0.017***					**0.041***				

Note: Bold and asterisk indicate significance at $p < 0.05$.
Model A: Linear regression was performed with factor 1 (representing aggregated performance-rated health outcomes) and factor 2 score (representing aggregated patient-reported health outcomes) as the dependent variable and age, sex, education level, marital status, and income adequacy as independent variables. The analysis was performed at T_4 because the internal consistency of the factors was the highest (Cronbach's α estimated at 0.81 and 0.80, respectively). Model B: Linear regression was performed with factor 1 and factor 2 scores as the dependent variable and CST-wLL, parietal lobe injury, lesion volume, and lesion side as independent variables. The analysis was also performed at T_4.
CST-wLL = corticospinal tract-weighted lesion load; HS = high school.

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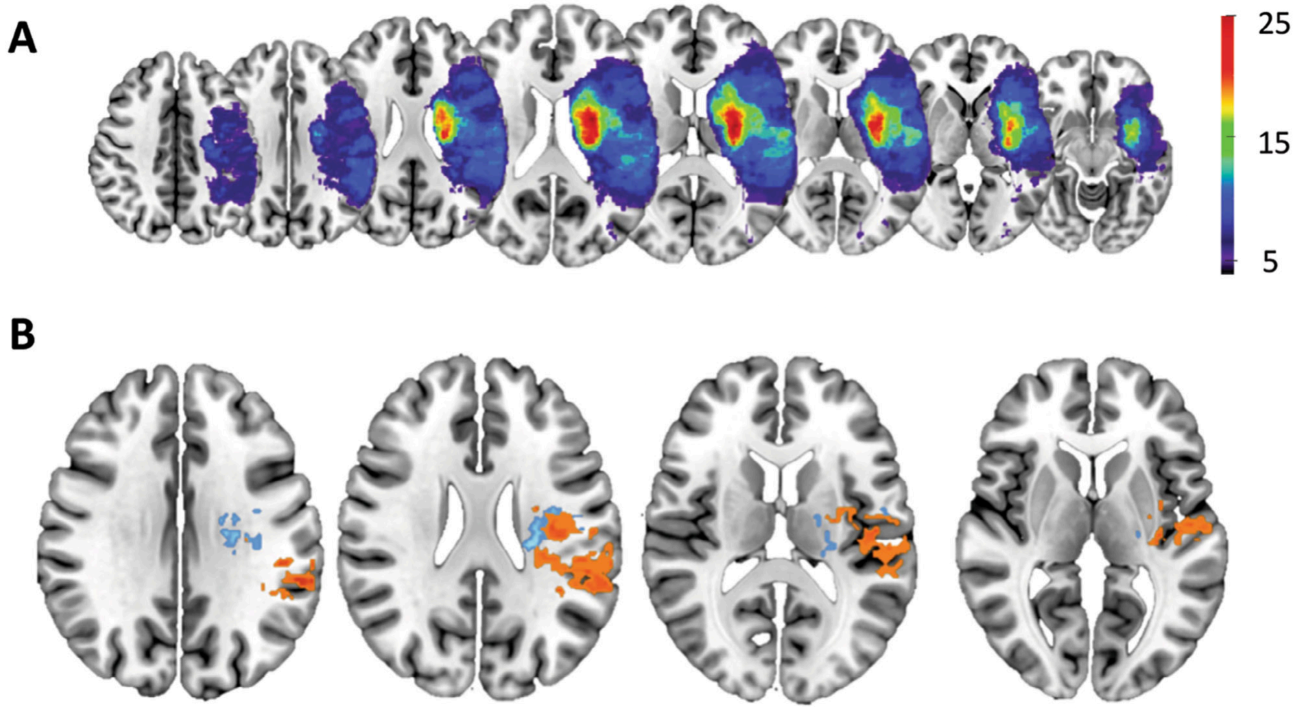

FIGURE 3: Voxel-based lesion symptom mapping (VLSM) of performance-rated and patient-reported health. (A) Stroke lesion overlap map for n = 54 study participants. All lesions were flipped onto the right hemisphere for display. The color bar (right) indicates the number of lesions over-lapped with dark blue to red showing increasing overlap from z = −10 to z = 25 by 5mm slice. (B) Separate VLSM t-maps were generated for factor 1 (representing aggregated performance-rated health outcomes) and factor 2 (representing aggregated patient-reported health outcomes) at 0.001 threshold shown in blue and orange, respectively.

concentrated in the inferior parietal lobule, supramarginal gyrus, angular gyrus, Rolandic operculum, and precuneus, extending up to the postcentral gyrus, down to the superior temporal gyrus, and involving the ventral posterior insula (Fig 3).

Significant voxels were predominantly cortical with little involvement of subcortical white matter and CST. In contrast, voxels significantly associated with worse performance-rated outcome measures clustered in subcortical white matter and specifically concentrated in the posterior limb of the internal capsule. A total of 35.3% (481/1364) of significant voxels for patient-reported outcomes were within the parietal lobe as compared to 11.4% (58/508) for performance-rated ($p < 0.001$). A total of 27% (138/508) of the significant voxels for performance-rated outcomes were contained within the CST as compared to only 2% (36/1364) for patient-reported outcomes ($p < 0.001$).

After controlling for overall lesion volume and hemisphere side, CST-weighted lesion load was significantly related to performance-rated health (factor 1, $\beta = -0.31$, $p = 0.02$), but not patient-reported health (factor 2, $\beta = -0.10$, 0.53) (Table 2). In contrast, parietal injury significantly explained variance in patient-reported (factor 2, $\beta = -0.33$, $p = 0.03$), but not performance-rated outcomes measures (factor 1, $\beta = 0.002$, $p = 0.99$) (Table 2). Notably, stroke side was not significant in either of these models.

To examine the hypothesis that worse PROMs are associated with lesions with greater functional connectivity to the salience/ventral-attention network, resting-state functional connection to this network was estimated for each participant's lesion and related to patient-reported and performance-rated outcomes (Fig 4). Participants with worse scores on patient-reported outcomes had lesions that showed greater connection with the salience/ventral-attention network ($r = -0.35$, $p = 0.009$); this was not true for performance-rated outcomes ($r = -0.21$, $p = 0.13$).

In sum, performance-rated and patient-reported outcomes after stroke were related to distinct patterns of neuroanatomical injury and network functional connectivity. Performance-rated measures mapped to stroke-related injury to a subcortical brain pathway important for UE motor control, specifically the CST. Patient-reported outcomes were related to injury to cortical areas centered in the inferior parietal lobule and, furthermore, were significantly associated with estimated functional connectivity to the salience/ventral-attention network.

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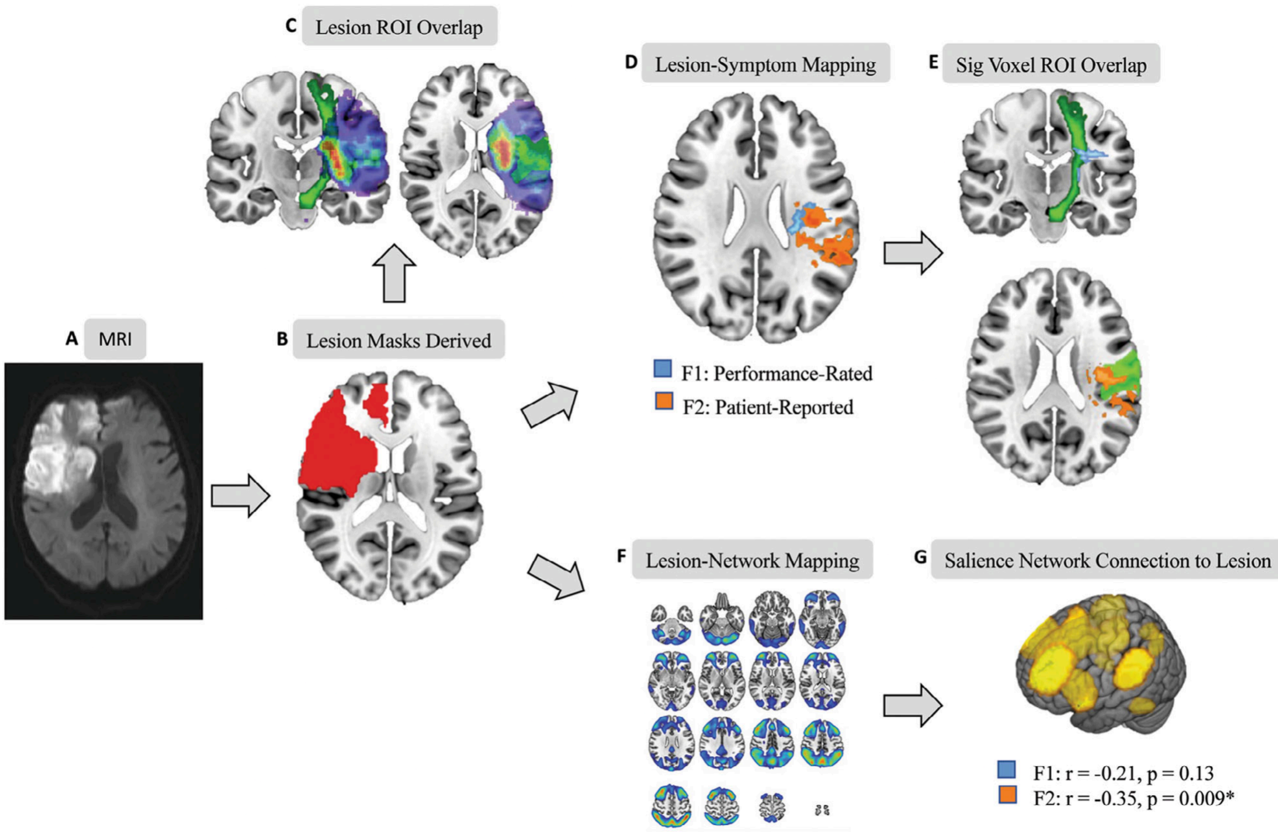

FIGURE 4: Regions-of-interest and voxel-based lesion mapping analyses. Individual stroke lesion masks (A) were derived from diffusion-weighted scans, and (B) transformed to standard space (Montreal Neurological Institute). Right-sided lesions were flipped at the midline on to the left hemisphere for group comparison. Region of interest (ROI) analyses (C) were performed to calculate lesion overlap with the parietal lobe and corticospinal tract (Table 1). Voxel-based lesion symptom mapping (VLSM) (D) was performed to confirm the patterns of neuroanatomical injury associated with factor 1 (representing aggregated performance-rated health outcomes) and factor 2 (representing aggregated patient-reported health outcomes) scores at the group level. The relationship with VLSM results and ROIs (CST and parietal) was calculated (E). Finally, voxel-based lesion network mapping (VLNM) (F) was performed to estimate the functional connectivity of each individual's stroke lesion to the salience/ventral-attention network. Individual patient's lesion connectivity to the salience/ventral-attention network was related to their performance on factor 1 and factor 2 (G).

Discussion

This study aimed to investigate the relationship between PROMs and performance-rated outcomes in a longitudinal cohort of stroke survivors with arm motor weakness and examined associations between classes of outcomes, sociodemographic factors, and patterns of neuroanatomic injury. Our findings demonstrate dissociation between PROMs and performance-rated outcomes throughout stroke recovery stages. Sociodemographic factors (education and income adequacy) predicted PROMs, but not performance-rated outcomes. Performance-rated outcomes were related to degree of injury to the corticospinal tract, whereas PROMs were associated with injury to the parietal lobe and the associated ventral attention/salience network.

The study underscores that PROMs measure different domains of self-perception of health and disease that are not captured by performance-rated outcomes.[6] Notably, even in the absence of significant performance-rated impairments (ie, motor weakness), stroke patients may report considerable impacts on their quality of life.[18] The decision to focus on PROMs reporting on general health status (ie, PROMIS-10) rather than self-reported perspectives on UE motor function (ie, Stroke Impact Scale) was intentional. The PROMIS-10 is the specific PROM widely accepted in stroke and neurology clinical trials. A predominant model in stroke rehabilitation is that stroke leads to domain-specific impairments (ie, motor, language, or cognitive), which lead to worse overall patient report on health.[48] Our study calls this model into question and highlights that factors beyond primary neurologic impairments (ie, motor dysfunction in this case) are the primary drivers of self-report after stroke. We also found that the distinction between performance-based function and self-reported health was not influenced by whether the dominant or non-dominant arm was affected in our

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cohort. In other words, having the dominant arm primarily affected by stroke does not lead to worse self-reported outcomes compared to if the non-dominant arm was affected, further highlighting the distinction between classes of outcome measures, which in the model of PROMs primarily reflecting the impact of domain-specific impairments, one might hypothesize that stroke affecting motor function of the dominant arm would lead to worse self-report on health (given baseline increased reliance on the dominant UE). Taken together, our findings further strengthen the importance of PROMs as outcome measures to complement, but not substitute for domain-specific, performance-rated measures in stroke recovery studies. Our study emphasizes that outcome measure selection should be aligned with specific research and clinical, hypotheses, and goals.[16]

Sociodemographic factors, specifically education and income, significantly predicted PROMs, but not performance-rated outcomes. Our findings build on previous research[49] emphasizing the importance of considering sociodemographic characteristics when interpreting patient-reported outcomes. Developing systematic approaches to identify sociodemographic risk factors predictive of PROMs could help to stratify patients most appropriate for psychosocial support programs post-stroke (ie, those part of organized rehabilitation). Performance-rated outcomes were not associated with sociodemographic characteristics in this study. Taken together, our results highlight the utility of personalized approaches to stroke rehabilitation assessment and planning.

We found an association between worse patient-reported outcomes and greater stroke-induced injury to key parietal lobe regions such as the supramarginal gyrus, angular gyrus, Rolandic operculum, and precuneus. These areas play critical roles in body-related perception,[50–52] sensory processing,[53–55] and self-referential[56] processing, functions that are critical to self-report. The insula, which is interconnected with these regions, is vital for awareness,[57–59] interpretation of limb ownership and actions,[60] and sensory information processing from the motor cortex.[61] These circuit functions are necessary for overall the perception of overall health, physical sensation, and emotional well-being, which are measured by the PROMIS Global Health, used in this study. Stroke-induced damage to the parietal cortex and insula can impair these functions, leading to altered self-perception and contributing to negative responses on health-related questionnaires. The current findings highlight how focal brain injury disrupts normal parietal circuit functions after stroke.[25–28] Moreover, these brain areas are interconnected with the ventral-attention/salience network, which influences perceptual processing and attention control.[62] Quantifying lesion connectivity to this network and its association with PROMs confirmed our hypotheses that stroke-induced damage to parietal cortex and associated networks correlated with lower PROMIS Global Health scores and a diminished self-reported health status.

Our study has notable limitations. We focused on the relationship between PROMs and performance-rated outcomes in a cohort of participants with UE motor weakness after stroke. Future studies should investigate these relationships in other stroke-related deficits (ie, gait, aphasia, and neglect) and even different neurological conditions to determine the generalizability of our findings. Our study was conducted at a single academic medical center with a predominantly English-speaking, Caucasian population. Especially given the sociodemographic findings here, future studies should investigate these hypotheses in more diverse populations, potentially in different geographic regions. Finally, incorporating more detailed structural neuroimaging (ie, diffusion tensor imaging) or real-time functional neuroimaging to probe circuits underlying patient-reported versus performance-rated outcomes was not performed in this study, but is ripe for future study.

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Author Contributions

J.A.D. and D.J.L. have contributed to conception and design of the study; J.A.D., P.G., A.K.B., and D.J.L. have contributed to acquisition and analysis of data; J.A.D., A.J., P.G., A.K.B., R.H., K.S.E., J.R., A.C., N.W., K.L.S., L.H.S., S.C.C., and D.J.L. have contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report

Data Availability

To protect the data used in this study, data may be available from the corresponding author on reasonable request.

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