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ARTICLE

Cognitive Demands Influence Upper Extremity Motor Performance During Recovery From Acute Stroke

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Abstract

Objective

To test the hypothesis that cognitive demands influence motor performance during recovery from acute stroke, we tested patients with acute stroke on 2 motor tasks with different cognitive demands and related task performance to cognitive impairment and neuroanatomic injury.

Methods

We assessed the contralesional and ipsilesional upper extremities of a cohort of 50 patients with weakness after unilateral acute ischemic stroke at 3 time points with 2 tasks: the Box & Blocks Test, a task with greater cognitive demand, and Grip Strength, a simple and ballistic motor task. We compared performance on the 2 tasks, related motor performance to cognitive dysfunction, and used voxel-based lesion symptom mapping to determine neuroanatomic sites associated with motor performance.

Results

Consistent across contralesional and ipsilesional upper extremities and most pronounced immediately after stroke, Box & Blocks scores were significantly more impaired than Grip Strength scores. The presence of cognitive dysfunction significantly explained up to 33% of variance in Box & Blocks performance but was not associated with Grip Strength performance. While Grip Strength performance was associated with injury largely restricted to sensorimotor regions, Box & Blocks performance was associated with broad injury outside sensorimotor structures, particularly the dorsal anterior insula, a region known to be important for complex cognitive function.

Conclusions

Together, these results suggest that cognitive demands influence upper extremity motor performance during recovery from acute stroke. Our findings emphasize the integrated nature of motor and cognitive systems and suggest that it is critical to consider cognitive demands during motor testing and neurorehabilitation after stroke.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BBT = Box & Blocks Test; **dAI** = dorsal anterior aspect of the insula; **MNI** = Montreal Neurological Institute; **NIHSS** = NIH Stroke Scale; **SMaHRT** = Stroke Motor Rehabilitation and Recovery Study; **VLSM** = voxel lesion symptom mapping.

Upper extremity motor impairment, which occurs in up to 85% of stroke survivors,[1] is a key contributor to poststroke disability.[2,3] Cognitive impairments, including deficits in attention, executive function, visuospatial ability, and language, are also common after stroke,[4-6] are most prevalent during the early postacute stroke period,[7,8] and negatively affect long-term functional outcomes.[9,10]

Here, we asked whether cognition influences upper extremity motor performance during recovery from stroke. We serially assessed a cohort of patients with acute stroke on 2 common tests of upper extremity motor performance with inherently varying cognitive demands, the Box & Blocks Test (BBT), a motor task with relatively higher cognitive demands, and Grip Strength, a simple, ballistic motor task.[11] We assessed both the more affected (i.e., contralesional) and less affected (i.e., ipsilesional) upper extremities because cognitive demands on motor performance should extend to the ipsilesional upper extremity where direct injury to the motor system is absent.

We specifically investigated (1) whether the cognitive demands of a test influence poststroke motor performance, hypothesizing that BBT, given its higher cognitive demands, would show relatively greater deficits than Grip Strength; (2) whether cognitive dysfunction after stroke explains motor performance, hypothesizing that the presence of cognitive impairment would be associated with reduced BBT but not Grip Strength performance; and (3) whether motor performance on tests with varying cognitive demands is associated with different patterns of neuroanatomic injury, hypothesizing that BBT performance would be associated with greater injury to cortical structures that support cognitive more than sensorimotor function.

Methods

Participants

Patients were recruited from an ongoing, prospective, single-center natural history study of recovery of upper extremity weakness after stroke, Stroke Motor Rehabilitation and Recovery Study (SMaHRT). From June 2017 to December 2019, eligible patients with stroke between age 18 and 90 years of age with unilateral upper extremity weakness (defined by NIH Stroke Scale [NIHSS] Q5a or Q5b≥1) and the ability to follow simple commands in English were screened from the Massachusetts General Hospital inpatient stroke service. Patients with a history of developmental, neurologic, or major psychiatric disorders resulting in functional disability and those with visual or auditory disorders limiting their ability to participate in testing procedures were excluded.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants in the study provided written informed consent. The Institutional Review Board at Mass General Brigham (Partners Healthcare) approved the study. The parent study was registered on ClinicalTrials.gov (NCT03485040).

Research Assessments

Baseline information on age, sex, handedness, affected arm, stroke hemisphere, stroke risk factors, treatment status with respect to tissue plasminogen activator or endovascular therapy, and infarct location was recorded for all participants at the time of enrollment.

Participants underwent initial evaluation within 1 week of stroke (T_1). They returned for research follow-up 6 weeks (T_2) and 3 months (T_3) after stroke. At each time point, the NIHSS and modified Rankin Scale were performed.[12] Total hours of standard occupational, physical, and speech therapies received between study visits were estimated by direct interview.

Cognitive impairment was measured with a validated composite score (Cog-4) based on the sum of 4 NIHSS subscale items corresponding to orientation (NIHSS_1b), executive function (NIHSS_1c), language (NIHSS_9), and inattention (NIHSS_11).[13] Cognitive impairment was treated as present (i.e., NIHSSCog-4 > 0) vs absent.

Motor Evaluation of Contralesional and Ipsilesional Upper Extremities

At each assessment time point, participants underwent BBT and Grip Strength testing, separately, for both the contralesional and ipsilesional upper extremities. A core group of 4 trained assessors administered motor performance testing; biannual meetings were held to maintain maximal adherence to study-related training and protocol administration.

In BBT, participants were instructed to move as many blocks as possible, 1 at a time, from 1 compartment to another for a period of 60 seconds. The BBT score was the number of blocks transferred during the 60-second period. After the start of the task, assessors were instructed not to provide encouragement to participants. Grip Strength was measured with a handheld dynamometer (Lafayette Instrument, Lafayette, IN). Maximum force was averaged across 3 trials separated by short rest periods. Raw scores for BBT and Grip Strength were converted to z scores based on age-, sex-, and hand-matched normative values.[14,15]

Image Processing and Voxel Lesion Symptom Mapping

Stroke topography was determined with magnetic resonance diffusion-weighted images obtained as part of the standard-of-care acute stroke inpatient workup. In 2 cases, MRI was clinically contraindicated, and the patient's CT scan was used instead. Lesions were manually traced on diffusion-weighted image/apparent diffusion coefficient volumes with the use of FSL (fsl.fmrib.ox.ac.uk/fsl/fsl-wiki) by research staff (J.A.D. and N.L.) and 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 well established methods.[16,17] Briefly, diffusion images were skull-stripped using BET (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 level of the brainstem, coregistration included center of mass alignment, rigid, similarity, and fully affine linear transformations. For scans with stroke lesions within the brainstem, an additional nonlinear (symmetric diffeomorphic) transformation was added to ensure accurate coregistration in this region. The resulting transformation matrices were applied to the stroke masks using Advanced Normalization Tools to bring them into the MNI space. The anatomic accuracy of each stroke mask in template space was visually verified by 2 board-certified neurologists (D.J.L. and S.B.S.).

Participants had unilateral lesions, except 2 individuals who had a punctate degree of injury in the other hemisphere that was not felt to be exclusionary and thus not further considered. Right-sided stroke lesions were flipped onto the left hemisphere for subsequent imaging analyses.

To identify brain voxels significantly associated with differences in BBT and Grip Strength motor evaluations, voxel lesion symptom mapping (VLSM) was performed.[18,19] A voxel would be tested only if at least 5 patients exhibited a lesion at this location. For each voxel, participants were divided into 2 groups according to whether they did or did not have a lesion affecting that voxel. BBT and Grip Strength z scores were then compared for these 2 groups, yielding a t statistic for each voxel. Voxels were considered if the t statistic met a threshold value of $p < 0.01$. 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 Harvard-Oxford cortical/subcortical atlas.[20] Voxels were considered to be within motor areas if they overlapped perirolandic cortical Brodmann areas 1/2/3a/3p/4a/4p (from the Julich histologic atlas[21]) or the corticospinal tract. The corticospinal tract used in this study was generated at the University of California, Irvine from 17 healthy, right-handed individuals using diffusion-weighted images obtained at 3T as described previously.[17]

Statistical Analysis

To determine whether motor z scores for BBT and Grip Strength were significantly different from age-, sex-, and hand-matched normative values at each assessment time point, median z score values were compared to ±1.96 SDs, corresponding to the 95% confidence interval of population-based normative values. To assess recovery of BBT and Grip Strength z scores across the 3 assessment time points, 4 separate repeated-measures analyses of variance with post hoc pairwise comparisons between assessment time points were performed, 1 for each test, separately for contralesional and ipsilesional upper extremities. To compare performance of the contralesional and ipsilesional upper extremities on each test, paired t tests (2 tailed) between BBT and Grip Strength z scores were performed at each assessment time point.

The proportion of patients with cognitive impairment in the cohort was compared across the 3 time points with the Cochran Q test. To determine whether cognitive impairment had an effect on motor performance at different time points, separate independent 2-tailed t tests were performed on BBT and Grip Strength z scores between patients with and without cognitive dysfunction. To determine the variance in motor performance explained by cognitive dysfunction, multivariate linear regressions on z scores for BBT and Grip Strength were performed, with each arm and at each time point as the dependent measure and cognitive impairment, treated as a categorical variable with 2 levels (present vs absent) as the independent measure (12 separate regressions were performed). Lesion volume was transformed with the boxcox transform and included in each model. An adjusted test and model significance level of $p < 0.005$ was used to compensate for the multiple comparisons. Infarct hemisphere was explored as an additional covariate in significant models. Additional post hoc analyses at follow-up time points were performed in which models included the hours of therapy received between study visits.

Percents of statistically significant sensorimotor vs non-sensorimotor voxels resulting from VLSM analyses of BBT and Grip Strength scores were compared with χ^2 tests. All data were normally distributed or could be transformed to be, and all analyses used parametric statistics, except for the Cochran Q test. Unless otherwise specified, $p < 0.05$ was used to determine statistical significance. All imaging and statistical analyses were performed in MATLAB (MathWorks, Natick, MA).

Data Availability

The data and analysis code that support the findings from this study are available from the corresponding author on reasonable request.

Results

Study Subjects

A total of 75 patients with documented unilateral upper extremity weakness after ischemic stroke consented for this

study and had research measures collected within the first week after stroke. Of these, 25 patients were not available for subsequent research follow-up because of the following reasons: deceased (3), medical complication (5), lost to follow-up (7), and study withdrawal (10). These patients did not differ in age ($p = 0.10$), sex ($p = 1.0$), or initial stroke severity ($p = 0.1$) from those included in the analysis.

Fifty participants completed both initial assessments and 90-day research follow-up and were included in the final analysis; 45 participants were also available for the interim research assessment at 6 weeks. Participants were assessed at 3.0 ± 1.8 (T_1, mean ± SD), 46.8 ± 5.7 (T_2), and 92.1 ± 10.5 (T_3) days after stroke. The initial median NIHSS score for the cohort was 6 (interquartile range 4–9). Demographic and clinical characteristics of the cohort are summarized in table 1. Key clinical outcomes and motor scores for both contralesional and ipsilesional upper extremities are summarized in table 2.

Motor Performance Early After Stroke Is Associated With Cognitive Demand of the Test

In the first week after stroke, BBT scores for both upper extremities were significantly different from normative values, indicating bilaterally impaired motor performance (red boxplots, figure 1). Grip Strength scores for the more affected (contralesional) upper extremity were initially also significantly different from normative values (black boxplots, figure 1). Grip Strength scores for the less affected (ipsilesional) upper extremity were within normative range (yellow zone, figure 1).

BBT performance for both upper extremities showed significant recovery at 6 weeks and 3 months but remained outside the normative range even at follow-up time points. Contralesional Grip Strength performance recovered to within normative range by 6 weeks after stroke (red and black bars with asterisks below boxplots, figure 1).

At all time points tested and for both upper extremities, BBT scores, compared to Grip Strength scores, were significantly further from normative values indicating greater impairment in motor performance (gray asterisks over boxplots, figure 1). This was particularly true in the first week after stroke during which differences in BBT and Grip Strength in each upper extremity were most apparent.

Early After Stroke, Cognitive Impairment Explains Significant Variance in Motor Performance on Test With Greater Cognitive Demand

Cognitive impairment in our cohort was most prevalent during the acute stroke period (48% at T_1) and decreased at follow-up time points (42% at 6 weeks and 34% at 3 months) (Cochran Q test, χ^2 [2] = 7.1, $p = 0.29$). Compared to patients without cognitive impairment, patients with cognitive impairment performed significantly worse on both more affected (contralesional) and less affected (ipsilesional) extremity BBT in the first week after stroke (contralesional BBT $p = 0.002$, ipsilesional BBT $p = < 0.001$) but not at follow-up time points. Groups did not differ on Grip Strength for either upper extremity at any time point tested. Table 3 shows the results of multivariate linear regression analyses investigating the variance of motor performance at each time point explained by cognitive impairment. The presence of cognitive impairment, independently of lesion volume, significantly explained variance in ipsilesional BBT performance in the first week after stroke (β = −1.2, t [47] = −2.2, $p = 0.034$). The overall model including lesion volume as a covariate explained 33% of the variance in ipsilesional extremity BBT performance ($F_{47} = 11.4$, $p < 0.001$). There was also a trend toward significance for the independent effect of cognitive impairment on contralesional BBT performance at T_1 (β = −1.5, t [47] = −1.9, $p = 0.061$), and the overall model with lesion volume as a covariate explained 22% of the variance ($F_{47} = 6.6$, $p = 0.0031$) in contralesional BBT performance. Adding infarct hemisphere (i.e., right or left) as an additional covariate into the models did not significantly change these results.

Table 1 Demographic and Clinical Characteristics of Cohort

No.	50
Age, mean ± SD, y	60.9 ± 12.3
Male, n (%)	28 (56)
Right-hand dominant, n (%)	44 (88)
Infarct hemisphere, n (%)	
Right	29 (58)
Left	21 (42)
Stroke risk factors, n (%)	
Hypertension	27 (54)
Diabetes	13 (26)
Hyperlipidemia	28 (56)
Current smoker	11 (22)
Atrial fibrillation	6 (12)
Acute stroke therapy, n (%)	
IV tPA	13 (26)
EVT	13 (26)
Infarct territory, n (%)	
MCA	39 (78)
PCA	2 (4)
Brainstem	5 (10)
Multiterritory	4 (8)

Abbreviations: EVT = endovascular therapy; MCA = middle cerebral artery; PCA = posterior cerebral artery; tPA = tissue plasminogen activator.

Table 2 Assessment Time Points, Outcome Measures, and Results of Motor Testing

Assessment Time Point	T_1 (Acute)		T_2 (Interim)		T_3 (90 d)	
Days after stroke	3.0 ± 1.8		46.8 ± 5.7		92.1 ± 10.5	
NIHSS score	6 (4–9)		3 (1–4)		2 (1–4)	
mRS score	4 (3–4)		2.5 (2–3)		2 (1–3)	
Cognitive dysfunction, %	48		42		34	
Therapy time, h			40.3 ± 31.9		19.9 ± 30.2	
	C	**I**	**C**	**I**	**C**	**I**
BBT score, n blocks transferred	7.5 (0–32)	34.5 (23–47)	38 (21–48)	48 (39–56)	42 (25–51)	49 (40–56)
Grip Strength score, kg	7.2 (0–27)	28.5 (17.3–36.7)	17.0 (7.3–30.7)	29.7 (19.7–37.3)	18.2 (9.7–34.7)	30.7 (21.7–38.7)

Abbreviations: BBT = Box & Blocks Test; C = contralesional; I = ipsilesional; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.
Participants were assessed within 1 week of stroke and then again at 6 weeks and 3 month after stroke. At these time points, global stroke severity via the NIHSS and disability via the mRS were obtained. Total hours of occupational, physical, and speech therapy that participants received between study visits was estimated by directed interview. In addition, at each time point, participants underwent BBT and Grip Strength testing for both the contralesional and ipsilesional upper extremities. Data are presented as mean ± SD, median (interquartile range), or percent (percent of cohort with any cognitive dysfunction present as indexed by NIHSSCog-4 > 0).

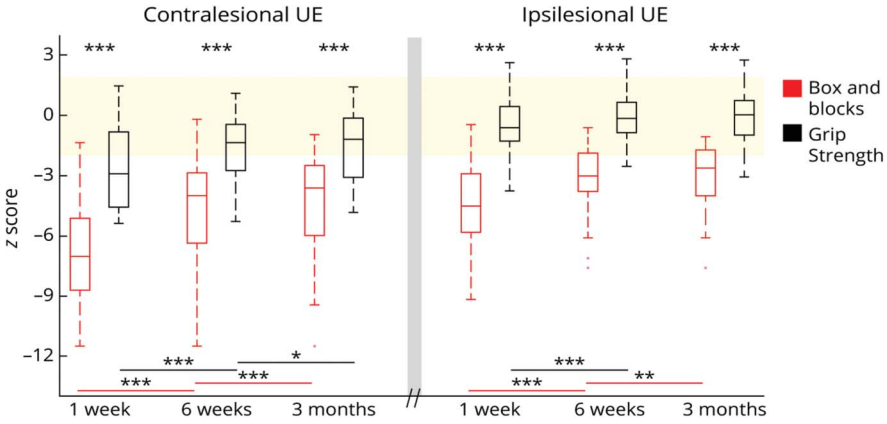
Number of therapy hours, independently of lesion volume and cognitive impairment, was inversely related to contralesional BBT and Grip Strength motor performance at T_2 (BBT: $\beta = -0.032 \pm 0.010$, $p = 0.0034$; Grip Strength: $\beta = -0.022 \pm 0.0078$, $p = 0.0074$) and T_3 (BBT: $\beta = -0.033 \pm 0.0097$, $p = 0.014$; Grip Strength: $\beta = -0.029 \pm 0.0077$, $p < 0.001$). There was no independent effect of therapy hours on ipsilesional motor performance.

At 6 weeks and 3 months after stroke, cognitive impairment did not explain significant variance in contralesional or ipsilesional BBT motor performance. Cognitive impairment also did not explain significant variance in contralesional or ipsilesional Grip Strength performance at any time point because the models that included cognitive impairment and lesion volume to explain Grip Strength performance were not significant.

Performance on a Motor Test With Greater Cognitive Demand Is Associated With Broad Injury Outside Sensorimotor Structures, Particularly the Dorsal Anterior Insula

Figure 2 shows the lesion overlap map for the 50 patients in the cohort. Voxels where injury was associated with more affected (contralesional) upper extremity BBT performance in the first week after stroke were centered in the dorsal anterior aspect of the insula (dAI), extending along the inferior frontal gyrus and to the posterior orbitofrontal cortex with only a small amount of perirolandic injury (figure 3A). For less affected (ipsilesional) BBT performance in the first week after stroke, the pattern of

Figure 1 Upper Extremity Motor Performance on BBT and Grip Strength After Acute Stroke



Boxplots for Box & Blocks Test (BBT; red) and Grip Strength (black) motor performance scores (*z* scores) of the more affected (contralesional) and less affected (ipsilesional) upper extremities (UEs) performed within 1 week and repeated at 6 weeks and 3 months after stroke. Yellow zone indicates normative performance (1.96 SDs). Gray asterisks above boxplots indicate significant differences between BBT and Grip Strength scores at each time point (paired *t* test). Red and black bars below boxplots show results of repeated-measures analysis of variance with post hoc pairwise comparisons used to compare results for each test within participant over time (i.e., to assess recovery of test performance between assessment time points). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table 3 Effect of Cognitive Dysfunction on BBT vs Grip Strength Motor Performance

	BBT Score					
	Contralesional UE			Ipsilesional UE		
	T_1	T_2	T_3	T_1	T_2	T_3
Intercept	−3.8 ± 1.4 (0.0098)[a]	−1.2 ± 1.5 (0.44)	−0.95 ± 1.34 (0.48)	−1.2 ± 1.0 (0.24)	−1.08 ± 0.97 (0.27)	−0.95 ± 0.86 (0.28)
Lesion volume	−0.17 ± 0.12 (0.15)	−0.24 ± 0.13 (0.062)	−0.22 ± 0.10 (0.041)	−0.2 ± 0.086 (0.025)	−0.14 ± 0.079 (0.076)	−0.14 ± 0.067 (0.04)[a]
Cognitive dysfunction	−1.5 ± 0.77 (0.061)	−0.50 ± 0.81 (0.56)	−1.2 ± 0.73 (0.11)	−1.20 ± 0.57 (0.034)[a]	−0.31 ± 0.53 (0.57)	−0.38 ± 0.47 (0.43)
R^2 value	0.22	0.16	0.21	0.33	0.14	0.14
***p* Value**	0.0031[b]	0.029	0.0042	<0.001[b]	0.040	0.027
	Grip Strength Score					
	Contralesional UE			**Ipsilesional UE**		
	T_1	T_2	T_3	T_1	T_2	T_3
Intercept	−0.34 ± 1.1 (0.75)	0.18 ± 1.1 (0.88)	0.35 ± 1.1 (0.78)	1.1 ± 0.80 (0.17)	1.0 ± 0.72 (0.045)	1.0 ± 0.69 (0.15)
Lesion volume	−0.15 ± 0.088 (0.10)	−0.12 ± 0.093 (0.19)	−0.12 ± 0.085 (0.16)	−0.11 ± 0.066 (0.11)	−0.09 ± 0.059 (0.14)	−0.060 ± 0.054 (0.27)
Cognitive dysfunction	−0.70 ± 0.59 (0.24)	−0.60 ± 0.62 (0.34)	−0.82 ± 0.59 (0.17)	−0.24 ± 0.44 (0.59)	−0.61 ± 0.39 (0.13)	−0.60 ± 0.38 (0.12)
R^2 value	0.17	0.12	0.13	0.11	0.20	0.12
***p* Value**	0.013	0.067	0.041	0.070	0.0089	0.050

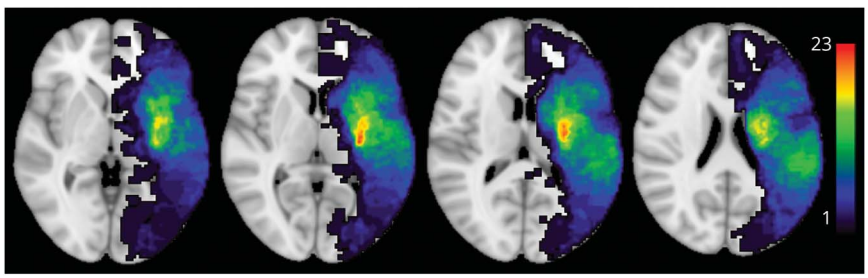
Abbreviations: BBT = Box & Blocks Test; UE = upper extremity.
Normalized motor *z* scores for BBT and Grip Strength for the contralesional and ipsilesional UEs were modeled as a linear combination of cognitive dysfunction (present/absent) and lesion volume. Cell values are presented as [β (estimated regression coefficient) ± SE (standard error)]/*p* value. $\frac{\beta(\text{estimated regression coefficient} \pm \text{SE(standard error)})}{(\text{p-value})}$ Lesion volume values were normalized with boxcox transform. T_1 = 1 week, T_2 = 6 weeks, T_3 = 3 months after stroke.
β Values were considered significant if [a]$p < 0.05$. Overall models were considered significant only if [b]$p < 0.0042$ to correct for multiple comparisons.

injury was nearly identical, with associations that were substantial in the dAI and small in perirolandic areas (figure 3B).

Voxels significantly associated with contralesional Grip Strength performance in the first week after stroke involved predominantly perirolandic gyri and subjacent white matter, extending down to secondary somatosensory area (S2), tapering at the posterior insula (figure 3C). Ipsilesional Grip Strength performance in the first week after stroke was associated with a similar pattern of injury although more restricted to perirolandic gyri and somewhat more posteriorly translocated (figure 3D).

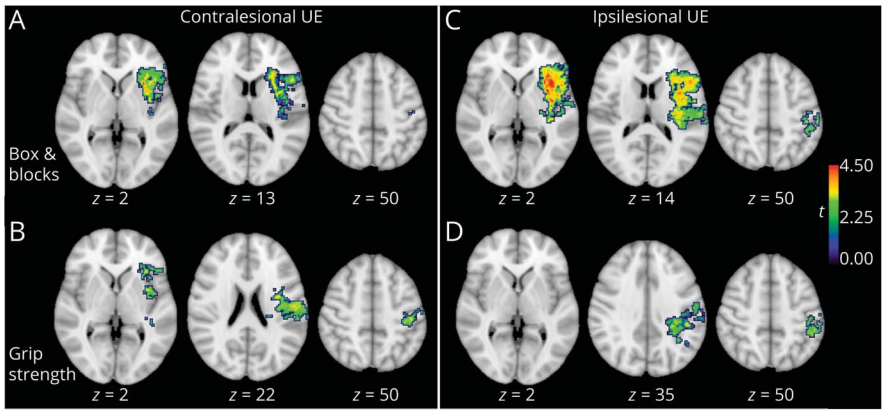
We quantified the number of significant voxels identified by VLSM analyses that were sensorimotor (light gray boxes), i.e., located within these structures, vs nonsensorimotor

Figure 2 Stroke Lesion Overlap Map for Study Participants



Total number of lesions included, n = 50. Color bar (right) shows the number of lesions overlapped with dark blue to red showing increasing overlap.

Figure 3 Patterns of Neuroanatomic Injury Associated With BBT vs Grip Strength Performance



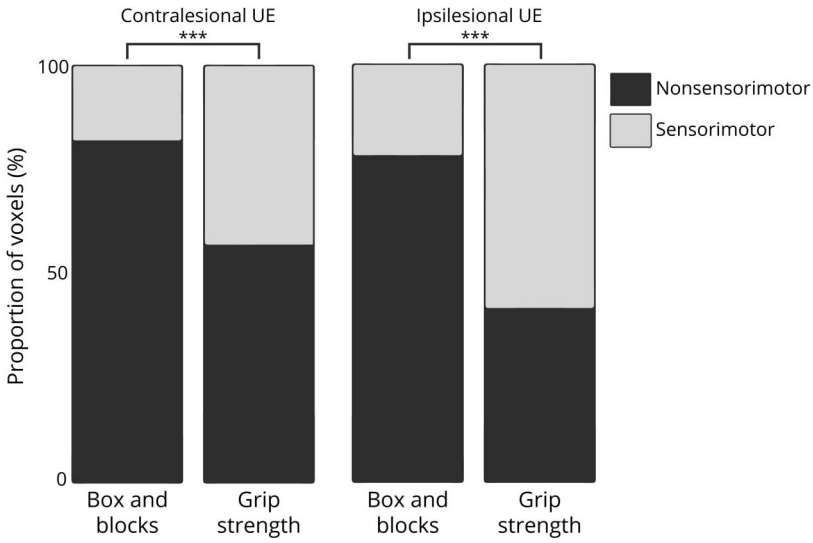
Representative slices from voxel lesion symptom mapping maps computed for Box & Blocks Test (BBT) (A and C) and Grip Strength (B and D) *z* scores, obtained within 1 week of stroke, on both contralesional (A and B) and ipsilesional (C and D) upper extremities. Maps are colorized to depict *t* test results evaluating upper extremity performance on a voxel-by-voxel basis. Color bar on the right show *t* values. Only voxels that are significant at $p < 0.01$ are shown. Cluster analysis revealed 1 significant cluster after controlling for multiple comparisons with 1,000 permutations, for each upper extremity and each motor test. For each panel, 3 representative axial slices are shown: left and right show z slices at basal ganglia and perirolandic cortices respectively, and middle panel shows z slice at the centroid of the statistically significant cluster for each analysis. Clusters identified were as follows: (cluster centroid Montreal Neurological Institute coordinates [x, y, z], volume): contralesional BBT score ([−37, 8, 13], 3,164 mm^3), ipsilesional BBT score ([−42, 0, 14], 7,470 mm^3), contralesional Grip Strength score ([−44, −13, 22], 3,086 mm^3), and ipsilesional Grip Strength score ([−44, −34, 35], 1,423 mm^3).

(dark gray boxes, figure 4), i.e., outside the perirolandic cortices or corticospinal tract. A total of 82% and 78% of voxels significantly associated with contralesional and ipsilesional BBT performance during VLSM analyses, respectively, were nonsensorimotor. In contrast, for Grip Strength, 57% and 42% of the voxels identified as associated with contralesional and ipsilesional upper extremities during VLSM analysis, respectively, were nonsensorimotor, significantly less than BBT for both contralesional ($\chi^2[1] = 464$, $p < 0.001$) and ipsilesional ($\chi^2[1] = 795$, $p < 0.001$) upper extremities.

Discussion

We used 2 common clinical assessments of upper extremity motor performance with inherently varying cognitive demands, BBT vs Grip Strength, to test the more affected (contralesional) and less affected (ipsilesional) upper extremities of 50 patients with stroke at 3 time points over the first 3 months after stroke. Our main findings were that BBT, the test with greater cognitive demand, (1) had significantly worse upper extremity motor performance in each arm compared to Grip Strength, particularly in the first week after stroke; (2) had

Figure 4 Sensorimotor and Nonsensorimotor Voxels Associated With UE Motor Performance



Bar plots showing proportion (percent) of statistically significant voxels identified during voxel lesion symptom mapping analyses within sensorimotor (light) and nonsensorimotor (dark) brain regions, for more affected (contralesional) and less effected (ipsilesional) Box & Blocks and Grip Strength testing. UE = upper extremity. ***$p < 0.001$ on χ^2 analysis.

significant variance explained by cognitive impairment, which was most prevalent during the acute stroke setting; and (3) was associated with structural injury to broad cortical regions outside sensorimotor areas, particularly the dAI. These findings stood in contrast to Grip Strength, the cognitively simpler and ballistic motor test, in which motor performance for both upper extremities was less impaired, not explained by cognitive impairment, and associated with injury largely restricted to sensorimotor cortical and subcortical structures. Together, these findings suggest that cognitive demands influence upper extremity motor performance during recovery from acute stroke.

BBT and Grip Strength are 2 commonly used motor performance-based outcome measures that have different task characteristics and requirements. BBT requires sustained attention over a full minute, adequate comprehension of testing instructions, and visuomotor planning to execute goal-directed, multijoint arm movements. Proprioception and multisensory integration to coordinate object grasp and release are also likely important for successful BBT performance.[22,23] In contrast, Grip Strength is a force generation task that involves the abrupt (i.e., ballistic) onset and offset of hand and forearm force.[24] A prior study showed that, compared to Grip Strength, BBT had a higher dual-task cost during simultaneous motor performance with cognitive testing.[11] Moreover, one of the core features that vary between BBT and Grip Strength, among others, is cognitive demand: BBT is a complex and cognitively demanding motor task, while Grip Strength is relatively simple and less cognitively demanding. Transforming BBT and Grip Strength scores to *z* scores based on age-, sex-, and hand-matched normative values allowed us to directly compare performance on the 2 tests. Our goal in comparing motor performance on these 2 tasks in patients with acute stroke was to gain insight into how higher-level cognitive demands that coordinate motor execution may influence motor performance.

In the first week after stroke, we found that BBT performance for both upper extremities was significantly further from normative values than Grip Strength, suggesting that the cognitive demands inherent to the test influenced upper extremity performance. Our hypothesis was that this finding would be true mainly in the immediate poststroke period, when cognitive impairments in patients with stroke are known to be most prevalent.[7,8] Notably, although the difference in performance between the 2 tests did decrease over time, we found that BBT performance continued to be more impaired than Grip Strength at follow-up testing time points across the first 3 months after stroke. This suggests that more subtle cognitive or other nonmotor factors such as fatigue, vision, sensation, proprioception, or multisensory integration continue to influence upper extremity motor performance during the first 3 months that follow a new stroke. These results underscore the potential impact of higher-level cognitive demands on motor testing results.

We examined the effect of cognitive impairment on upper extremity motor performance. We found that patients with cognitive impairment performed worse on BBT during the first week after stroke but not at either follow-up time points or on Grip Strength at any time point. Furthermore, in the first week after stroke, we found that cognitive dysfunction explained a substantial amount (33%) of variance in BBT performance independently of lesion volume. That the effects of cognitive dysfunction were seen early after stroke but not later could be due to the fact that there was a slightly higher prevalence of cognitive dysfunction acutely or that motor performance is more susceptible to cognitive dysfunction during the acute stroke period.[25] Current findings suggest that during the first week after stroke, cognitive impairment directly and significantly affects upper extremity motor performance, but only for the task with higher cognitive demands. Post hoc analyses to investigate the effects of therapy hours on motor performance demonstrated that total therapy amount was inversely related to contralesional motor performance, likely due to the fact that patients who had more severe impairments had more therapy during the acute-subacute recovery period. Current findings are focused on motor assessment; these relationships might be important beyond the first week when the focus extends to treatment because cognitive dysfunction has been shown to affect functional gains during rehabilitation[26] and long-term functional outcomes.[10] The cognitive impairment measure used in this study was a gross cumulative measure that classified orientation, executive function, language, and inattention as disordered or not.[13] Future studies that use detailed measures of specific cognitive domains map help to further elucidate the effects of cognition on motor performance after stroke.

Differential performance on BBT vs Grip Strength and observed associations between cognitive impairment and motor performance were invariant across the more affected (contralesional) and less affected (ipsilesional) upper extremities. Deficits of the ipsilesional upper extremity have been well described after stroke and have previously been attributed to the bilaterally distributed nature of the motor system during unilateral arm movement.[27-33] The relationship between cognitive deficits and ipsilesional arm motor deficits has received limited attention.[27,34] One prior study of patients with stroke examined an average of 18 days after stroke found that dexterity was impaired in the ipsilesional upper extremity in a manner that was related to cognitive deficits and that results differed according to side of infarct.[34] In the current study, we gained further insights by directly comparing results from the contralesional and ipsilesional upper extremities and found both to be similarly affected by cognitive dysfunction. Current findings for the less affected upper extremity motor performance echo those for the more affected side: cognitive dysfunction affects motor performance, regardless of the side tested.

VLSM was used to identify brain regions in which injury was associated with a significant difference in motor performance on BBT vs on Grip Strength. We found that stroke injury to a region centered on the dAI was significantly associated with deficits in BBT performance for both contralesional and ipsilesional upper

extremities. These results are consistent with a prior study that found the cingulo-opercular network, of which the dAI is a prominent node, to be important for both motor performance and attentional control in patients with stroke.[35] Notably, while this study calculated lesion overlap with an a priori–defined cingulo-opercular network, our techniques confirmed the importance of dAI via a data-driven process. The dAI is known to be involved in cognitive control processes[36,37] and specifically in maintaining attention and goal-directed behavior throughout a task.[38-41] Connectivity studies point to robust structural and functional connections between the dAI and other cognitive control areas, specifically the anterior cingulate cortex and dorsolateral prefrontal cortex,[42,43] and more broadly to the role of dAI within cortical networks for detecting salient stimuli[44] and decision-making.[37] Studies across both speech articulation and perceptual detection have shown that as task complexity increases, reliance and demand on dAI increase.[45-47] Our findings extend these findings regarding the importance of the dAI for complex cognitive control. Notably, our data did not reveal significant clusters in other cognition-related areas such as the caudate and dorsolateral prefrontal cortex. This might reflect the specific neuroanatomic nature of BBT cognitive demands, the frequency of involvement of other structures by patients' lesions included in this study, or other factors. The current results emphasize that different neuroanatomic structures underpin tasks with different motor and cognitive demands.

There are a number of limitations to this study. A greater number of bedside tests of motor behavior with more nuanced cognitive demands would have been useful to further examine our hypotheses but were not feasible to perform in this study given the limited time available to collect additional data during the acute stroke hospitalization. Furthermore, the measure of cognitive impairment used in this study, extrapolated from the NIHSS, was coarse. However, the NIHSS was efficient and practical to administer to participants at 3 different time points after stroke, including during the first week after stroke. Future studies should use detailed and serial cognitive assessment in conjunction with motor performance testing to further parse the effects of cognition and attention on motor performance after stroke. During the study period, participants underwent standard occupational, physical, and speech therapies, which could have influenced their motor and cognitive status and thus our study findings. While we recorded the total amount of therapy received between study visits and explored this effect on motor performance, we were not able to assess the specific nature or intensity of the therapies provided. How the specific nature and frequency of therapies influence the motor outcome is an area for future study. Finally, estimating the topography of stroke injury from acute diffusion images presents clear challenges. However, our statistical mapping approaches that leverage lesion maps to reveal the neuroanatomic basis of motor performance have been validated with the approach of combining acute stroke neuroimaging with motor behavior.[48]

Our results have practical implications for upper extremity motor recovery and neurorehabilitation after stroke. While cognitive deficits have been well recognized after stroke, here we show that cognition directly affects motor performance, even when examined with relatively simple bedside tests, during recovery from stroke. For stroke recovery trials, our study points to the importance of motor outcome selection because specific motor tasks engage different neuroanatomic structures and have different degrees of motor system selectivity. Finally, our findings emphasize the integrated nature of motor and cognitive systems[49] and their recovery after stroke. Cognition should be assessed and treated in parallel with arm motor rehabilitation.[50] Understanding the effect of cognitive status on motor performance can also be used therapeutically to tailor neurorehabilitation strategies, modulating cognitive demand according to the injury features and clinical status of individual patients to maximize functional recovery after stroke.

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Disclosure

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Appendix *(continued)*

Name	Location	Contribution
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Seth P. Finklestein, MD	Massachusetts General Hospital, Boston	Drafted/revised the manuscript for content; conceptualized and designed study
Lee H. Schwamm, MD	Massachusetts General Hospital, Boston	Conceptualized and designed study; analyzed and interpreted data
Leigh R. Hochberg, MD, PhD	Massachusetts General Hospital, Boston	Drafted/revised the manuscript for content; analyzed and interpreted data
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References

1. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. Stroke 2003;34:2181–2186.
2. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56–e528.
3. Haaland KY, Mutha PK, Rinehart JK, Daniels M, Cushnyr B, Adair JC. Relationship between arm usage and instrumental activities of daily living after unilateral stroke. Arch Phys Med Rehabil 2012;93:1957–1962.
4. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009;8:1006–1018.
5. Jaillard A, Naegele B, Trabucco-Miguel S, LeBas JF, Hommel M. Hidden dysfunctioning in subacute stroke. Stroke 2009;40:2473–2479.
6. Nys GM, van Zandvoort MJ, de Kort PL, et al. The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. Neurology 2005;64:821–827.
7. Barker-Collo SL, Feigin VL, Lawes CM, Parag V, Senior H. Attention deficits after incident stroke in the acute period: frequency across types of attention and relationships to patient characteristics and functional outcomes. Top Stroke Rehabil 2010;17:463–476.
8. Barker-Collo S, Feigin V, Lawes C, Senior H, Parag V. Natural history of attention deficits and their influence on functional recovery from acute stages to 6 months after stroke. Neuroepidemiology 2010;35:255–262.
9. Heruti RJ, Lusky A, Dankner R, et al. Rehabilitation outcome of elderly patients after a first stroke: effect of cognitive status at admission on the functional outcome. Arch Phys Med Rehabil 2002;83:742–749.
10. Zietemann V, Georgakis MK, Dondaine T, et al. Early MoCA predicts long-term cognitive and functional outcome and mortality after stroke. Neurology 2018;91:e1838–e1850.
11. Raats J, Lamers I, Baert I, Willekens B, Veldkamp R, Feys P. Cognitive-motor interference in persons with multiple sclerosis during five upper limb motor tasks with different complexity. Mult Scler 2019;25:1736–1745.
12. Bruno A, Shah N, Lin C, et al. Improving modified Rankin Scale assessment with a simplified questionnaire. Stroke 2010;41:1048–1050.
13. Cumming TB, Blomstrand C, Bernhardt J, Linden T. The NIH Stroke Scale can establish cognitive function after stroke. Cerebrovasc Dis 2010;30:7–14.
14. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block test of manual dexterity. Am J Occup Ther 1985;39:386–391.
15. Massy-Westropp NM, Gill TK, Taylor AW, Bohannon RW, Hill CL. Hand grip strength: age and gender stratified normative data in a population-based study. BMC Res Notes 2011;4:127.
16. Rorden C, Bonilha L, Fridriksson J, Bender B, Karnath HO. Age-specific CT and MRI templates for spatial normalization. Neuroimage 2012;61:957–965.
17. Lin DJ, Cloutier AM, Erler KS, et al. Corticospinal tract injury estimated from acute stroke imaging predicts upper extremity motor recovery after stroke. Stroke 2019;50:3569–3577.
18. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. Nat Neurosci 2003;6:448–450.
19. Wilson SM, Henry ML, Besbris M, et al. Connected speech production in three variants of primary progressive aphasia. Brain 2010;133:2069–2088.
20. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968–980.
21. Eickhoff SB, Stephan KE, Mohlberg H, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 2005;25:1325–1335.
22. Connell LA, Tyson SF. Clinical reality of measuring upper-limb ability in neurologic conditions: a systematic review. Arch Phys Med Rehabil 2012;93:221–228.
23. Chen HM, Chen CC, Hsueh IP, Huang SL, Hsieh CL. Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. Neurorehabil Neural Repair 2009;23:435–440.
24. Cramer SC, Nelles G, Schaechter JD, Kaplan JD, Finklestein SP. Computerized measurement of motor performance after stroke. Stroke 1997;28:2162–2168.
25. Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 2003;126:2476–2496.
26. Jaywant A, Toglia J, Gunning FM, O'Dell MW. Subgroups defined by the Montreal Cognitive Assessment differ in functional gain during acute inpatient stroke rehabilitation. Arch Phys Med Rehabil 2020;101:220–226.
27. Jones RD, Donaldson IM, Parkin PJ. Impairment and recovery of ipsilateral sensory-motor function following unilateral cerebral infarction. Brain 1989;112(pt 1):113–132.
28. Bucy PC. Representation of ipsilateral-extremities in the cerebral cortex. Science 1933;78:418.
29. Mani S, Mutha PK, Przybyla A, Haaland KY, Good DC, Sainburg RL. Contralesional motor deficits after unilateral stroke reflect hemisphere-specific control mechanisms. Brain 2013;136:1288–1303.
30. Schaefer SY, Haaland KY, Sainburg RL. Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain 2007;130:2146–2158.
31. Cramer SC, Finklestein SP, Schaechter JD, Bush G, Rosen BR. Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. J Neurophysiol 1999;81:383–387.
32. Maenza C, Good DC, Winstein CJ, Wagstaff DA, Sainburg RL. Functional deficits in the less-impaired arm of stroke survivors depend on hemisphere of damage and extent of paretic arm impairment. Neurorehabil Neural Repair 2020;34:39–50.
33. Glees P, Cole J. Ipsilateral representation in the cerebral cortex; its significance in relation to motor function. Lancet 1952;1:1191–1192.
34. Sunderland A, Bowers MP, Sluman SM, Wilcock DJ, Ardron ME. Impaired dexterity of the ipsilateral hand after stroke and the relationship to cognitive deficit. Stroke 1999;30:949–955.
35. Rinne P, Hassan M, Fernandes C, et al. Motor dexterity and strength depend upon integrity of the attention-control system. Proc Natl Acad Sci USA 2018;115:e536–e545.
36. Droutman V, Bechara A, Read SJ. Roles of the different sub-regions of the insular cortex in various phases of the decision-making process. Front Behav Neurosci 2015;9:309.
37. Uddin LQ, Nomi JS, Hebert-Seropian B, Ghaziri J, Boucher O. Structure and function of the human insula. J Clin Neurophysiol 2017;34:300–306.
38. Dosenbach NU, Fair DA, Miezin FM, et al. Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci USA 2007;104:11073–11078.
39. Dosenbach NU, Visscher KM, Palmer ED, et al. A core system for the implementation of task sets. Neuron 2006;50:799–812.
40. Nelson SM, Dosenbach NU, Cohen AL, Wheeler ME, Schlaggar BL, Petersen SE. Role of the anterior insula in task-level control and focal attention. Brain Struct Funct 2010;214:669–680.
41. Eckert MA, Menon V, Walczak A, et al. At the heart of the ventral attention system: the right anterior insula. Hum Brain Mapp 2009;30:2530–2541.

42. Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb Cortex 2013;23:739–749.
43. Glasser MF, Coalson TS, Robinson EC, et al. A multi-modal parcellation of human cerebral cortex. Nature 2016;536:171–178.
44. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 2010;214:655–667.
45. Baldo JV, Wilkins DP, Ogar J, Willock S, Dronkers NF. Role of the precentral gyrus of the insula in complex articulation. Cortex 2011;47:800–807.
46. Dronkers NF. A new brain region for coordinating speech articulation. Nature 1996; 384:159–161.
47. Aben B, Buc Calderon C, Van den Bussche E, Verguts T. Cognitive effort modulates connectivity between dorsal anterior cingulate cortex and task-relevant cortical areas. J Neurosci 2020;40:3838–3848.
48. Karnath HO, Rennig J. Investigating structure and function in the healthy human brain: validity of acute versus chronic lesion-symptom mapping. Brain Struct Funct 2017;222:2059–2070.
49. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res 2008;51:S225–S239.
50. Mullick AA, Subramanian SK, Levin MF. Emerging evidence of the association between cognitive deficits and arm motor recovery after stroke: a meta-analysis. Restor Neurol Neurosci 2015;33:389–403.