

Differential Impact of Acute Lesions Versus White Matter Hyperintensities on Stroke Recovery

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Background—Understanding how the size of acute lesions and white matter hyperintensities (WMH) impact stroke recovery can improve our ability to predict outcomes and tailor treatments. The aim of this exploratory study was to investigate the role of acute lesion volume and WMH volume on longitudinal recovery of specific sensory, motor, and cognitive impairments after stroke using robotic and clinical measures.

Methods and Results—Eighty-two individuals were assessed at 1, 6, 12, and 26 weeks poststroke with robotic tasks and commonly used clinical measures. The volumes of acute lesions and WMH were measured on fluid-attenuated inversion recovery images. Linear mixed models were used to investigate the role of acute lesions and WMH on parameters derived from the robotic tasks and clinical measures. Regression analysis determined the added value of acute lesion and WMH volumes along with measures of initial performance to predict outcomes at 6 months. Acute lesion volume has widespread effects on sensory, motor, and overall functional recovery poststroke. The impact of WMH was specific to cognitive impairments. Apart from the robotic position sense task, neither lesion volume nor WMH measure had significant ability to predict outcomes at 6 months over using initial impairment as measured by robotic assessments alone.

Conclusions—While acute lesion volume and WMH may impact different impairments poststroke, their clinical utility in predicting outcomes at 6 months poststroke is limited. (*J Am Heart Assoc.* 2018;7:e009360. DOI: 10.1161/JAHA.118.009360.)

Key Words: lesion volume • rehabilitation • robotics • stroke recovery • white matter hyperintensities

Stroke is a leading cause of disability,¹ yet many factors influencing stroke recovery remain elusive. Recovery can vary greatly between individuals,² as well as within an individual across different domains, such as sensory and motor recovery.³ Predicting recovery is important to both clinicians and patients, and can assist in personalizing treatment plans and allocating resources. Commonly explored prognostic factors include age, initial severity of functional deficits, and size and location of the infarct^{4–6}; however, prognostic factors are likely specific to each domain of recovery.

Lesion volume has received significant attention as a prognostic factor following acute stroke.^{4,5,7} Reducing the size of the lesion to potentially promote better functional outcomes is the driving force behind interventions such as

intravenous tissue plasminogen activator⁸ and mechanical embolectomy.⁹ However, most studies have indicated that the correlation between infarct volume and functional outcomes are only moderate,^{7,10} if related at all.^{4,11} In addition to the size of the acute infarct, white matter hyperintensities (WMH) may also contribute to variability in stroke recovery. WMH, viewed on fluid-attenuated inversion recovery (FLAIR) images, can be used as a measure of chronic white matter damage, though the pathophysiology is unclear. While WMH are observed in normal aging,¹² they are seen in greater amounts in individuals with cognitive impairments.¹³ After stroke, WMH have been linked to neglect,¹⁴ cognitive impairment,^{15,16} and overall functional outcome.^{17–19} However, the impact of WMH on the recovery of specific sensory and motor impairments

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Portions of this work were previously presented as a poster at the Society for Neuroscience annual meeting, November 11 to 15, in Washington, DC, and as an oral presentation at the Canadian Stroke Congress, September 9 to 11, 2017, in Calgary, Alberta, Canada.

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Received May 23, 2018; accepted July 27, 2018.

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Clinical Perspective

What Is New?

- This is the first study to compare the impact of acute lesion volume to chronic white matter hyperintensities on longitudinal stroke recovery of specific sensory, motor, and cognitive impairments as measured by robotics.
- While acute lesion volume had a widespread impact on poststroke recovery, white matter hyperintensities were only found to have a specific impact on the cognitive component of sensorimotor tasks.

What Are the Clinical Implications?

- Individuals with substantial white matter hyperintensities may have poorer cognitive recovery after stroke, which can influence performance of more cognitively demanding sensorimotor tasks.
- Large differences in acute lesion or white matter hyperintensity volumes certainly influence poststroke recovery; however, they have limited clinical utility in predicting outcomes at 6 months poststroke compared with behavioral measures.

poststroke has not been previously explored. Additionally, there may be interactions between lesion volume and WMH, whereby greater amounts of WMH may exacerbate the effects of larger lesions.

A challenge in studying stroke recovery is the lack of high-resolution outcome measures. Most stroke recovery studies have used disability scales or functional measures that have poor resolution, do not discriminate between compensation and actual neurorecovery, and do not identify underlying impairments. Robotic measures offer many advantages for quantifying poststroke recovery, including accuracy, precision, and reliability. Robotic measures can also assess specific impairments that can improve our understanding of stroke recovery and lead to more targeted rehabilitation.

The objective of this study was to conduct an exploratory analysis on the effects of acute lesion volume, WMH volume, and their interaction on sensory, motor, and cognitive recovery as quantified by robotic and clinical measures. Additionally, since initial severity of deficits has previously been found to be predictive of future outcomes, we aimed to evaluate whether lesion volume and WMH volume improved our ability to predict performance at 6 months poststroke compared with initial performance alone. We hypothesized that acute lesion volume and WMH volume would impact different areas of recovery, with acute lesions impacting sensory and motor function while WMH would be associated with cognitive deficits. We also hypothesized that the presence of large amounts of WMH could increase the impact

of acute lesion volume. This study is an important step in understanding the factors influencing stroke recovery across sensory, motor, and cognitive domains, which can lead to more individualized treatment and better outcomes.

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

Participants with stroke were drawn from the larger RESTART (Rehabilitation, Stroke Deficits and Robotic Technology) Study, a prospective longitudinal study that uses clinical and robotic measures to track neurologic function poststroke. We selected participants enrolled in RESTART who had completed at least 3 of the 4 time points over the first 6 months poststroke and had a magnetic resonance imaging scan, including a FLAIR sequence. Participants were included if they had first-time unilateral clinical stroke, were between 18 and 80 years old, and could follow task instructions. Participants were excluded if they had bilateral, brainstem, or cerebellar strokes, pre-existing neurologic disease, upper extremity orthopedic conditions, or evidence of apraxia based on screening with the TULIA (Test of Upper Limb Apraxia).²⁰ Brainstem and cerebellar lesions were excluded because of challenges in accurately registering these lesions to a standard space.²¹ Bilateral, brainstem, and cerebellar lesions were also excluded because of the assessments requiring participants to have a clear “affected” and “unaffected” side in order to perform and interpret the tasks. To ensure inclusion and exclusion criteria were met, medical records were reviewed for signs of pre-existing neurologic disease, and all images were examined by neuroradiologists. A physiotherapist also assessed muscle strength and spasticity to rule out bilateral involvement or unusual presentations that could be suggestive of other neurologic diagnoses. Additionally, through doing the clinical and robotic assessments, the physiotherapist ensured that participants understood and could follow task instructions. Based on the inclusion and exclusion criteria, 86 subjects were identified. All subjects provided informed consent. This study was approved by the local ethics board, and all procedures were in accordance with institutional guidelines.

Imaging Acquisition and Analysis

Magnetic resonance imaging was acquired as part of the clinical acute stroke protocol at Foothills Hospital and included FLAIR and diffusion-weighted imaging sequences. Imaging was acquired on either a 1.5 T Siemens or 1.5 or 3T GE Medical systems scanner, with in-plane resolution at 1 mm² and slice thickness ranging from 3 to 5 mm with 0 mm interslice gap.

Acute lesions were marked with MRICron (www.nitrc.org/projects/mricron) by trained researchers (S.E.F. and J.M.K.) on each subject's FLAIR image using the diffusion-weighted imaging and apparent diffusion coefficient images to determine the location of acute damage. Only areas of acute ischemic damage indicated by diffusion-weighted imaging hyperintensities were included in the marking. Lesion markings were verified by an experienced stroke neurologist and adjusted if necessary.

WMH were marked by R.L.H. on each subject's FLAIR image using the FMRIB Software Library v5.0 (www.fmrib.ox.ac.uk/fsl) based on a previously developed approach.²² Images were skull-stripped using FMRIB Software Library's Brain Extraction Tool. Potential WMH were first identified using an individually determined intensity threshold. Areas of WMH were then grossly outlined. The final WMH map was the overlap of areas identified by the threshold and the manually defined regions, thereby removing regions falsely identified by the threshold alone. Final WMH maps also excluded any areas of acute lesions. Three subjects were excluded from this analysis because of motion artifacts interfering with delineating areas of WMH. One subject with a hemorrhagic lesion was excluded because the boundaries of the WMH could not be distinguished from the edema of the acute lesion. To verify the reliability of this approach, it was repeated in 10% of subjects and the intrarater intra-class correlation was 0.981.

All images were normalized to a FLAIR template based on 853 subjects with 2.0-mm resolution in standard Montreal Neurologic Institute space.²³ Linear and nonlinear registration was performed on individual subject's FLAIR images using FMRIB Software Library's FLIRT²⁴ and FNIRT^{25,26} tools with cost function weighting of the acute lesions to avoid distortions. The warps obtained from registering the FLAIR images to standard Montreal Neurologic Institute space were then applied to the lesion and WMH masks to transform them into standard space. The volume of the lesion and WMH masks were calculated in standard space.

Timing of Clinical and Robotic Assessments

Robotic and clinical assessments described below occurred at 4 time points: 1 week (TP1), 6 weeks (TP2), 12 weeks (TP3), and 26 weeks (TP4) poststroke. The Montreal Cognitive Assessment was only administered at TP1 because of concerns about a potential learning effect.²⁷ All subjects completed at least 3 of the 4 time points.

Robotic Assessments

At each time point, subjects underwent assessment using the KINARM exoskeleton robot (BKIN Technologies Ltd, Kingston, Ontario, Canada). Subjects were assessed on components of sensory, motor, and cognitive function using 4 standardized

tasks that have been previously described elsewhere. Visually guided reaching (VGR) assesses visuomotor abilities by having participants perform center-out reaching.²⁸ Position matching (PM) is a test of proprioception (position sense), in which the robot moves the stroke-affected arm to 1 of 9 locations, and the subject is instructed to move their other arm to the mirror-image location with vision occluded.^{29,30} Object hit (OH) is a test of bimanual sensorimotor control in which participants use virtual paddles at their fingertips to hit away balls that move toward them at increasing speed and frequency.³¹ Object hit and avoid (OHA) is similar to OH, except that subjects are instructed to only hit 2 specific shapes while 6 other shapes serve as distractors, thus requiring higher cognitive skills.³² Each task has specific parameters that performance is measured on, which are described in Table 1.

Each parameter is normalized to a z-score based on normative data that account for age effects when necessary.³³ Normative data are based on 178 subjects for VGR, 494 subjects for PM, 433 subjects for OH, and 293 subjects for OHA. Control data sets are first transformed to a normal distribution using a Box-Cox power transform.³⁴ Outliers in the control data set are identified as being outside ± 3.29 SDs (corresponds to 1 in 1000) and data are removed from the sample.³⁵ Z-scores represent the distance from the mean of control subjects in SDs (ie, z-score of 2 would indicate 2 SDs above the mean). For the stroke survivors in this article, z-scores close to zero indicate performance consistent with controls, with higher magnitudes of z-scores indicating performance further from controls. A single composite task score is also calculated for each task by calculating the root-mean-square distance of all the parameter z-scores for that task and re-normalizing compared with performance of healthy controls.^{33,35,36}

Clinical Assessments

Participants underwent clinical assessments at each time point with a trained therapist. The Chedoke-McMaster Stroke Assessment³⁷ was used to assess arm and hand motor impairment, with scores ranging from 1 (greatest impairment) to 7 (least impairment). The Thumb Localizing Test³⁸ was used to assess proprioception by having the therapist position the participant's stroke-affected upper limb and asking the participant to grasp the thumb of that limb with their other hand with their eyes closed. Performance is scored from 0 to 3, with 0 indicating the participant accurately performed the task and 3 indicating the participant is unable to locate their thumb. Visuospatial neglect was assessed with the conventional subset of the Behavioral Inattention Test.³⁹ The Behavioral Inattention Test is a pencil and paper test of visuospatial neglect and the conventional subset includes line, star, and letter cancellation, line bisection, and figure copying

Table 1. Descriptions of Each Task Parameter

Parameter		Brief Description	Sign of Z-Score Associated With Impaired Performance
Visually guided reaching (VGR)			
Posture speed	PS	Median hand speed when the hand should be at rest (postural stability)	+
Reaction time	RT	Time between destination target appearing and movement onset	+
Initial direction error	IDE	Absolute value of angular deviation between initial movement and ideal path	+
Initial distance ratio	IDR	Ratio between distance of initial movement and total movement distance	–
Speed maximum count	SMC	Total number of hand speed maxima during entire movement	+
Minimum-maximum speed difference	MMSD	Mean difference between adjacent pairs of local hand speed minima and maxima	+
Movement time	MT	Total time from movement onset to offset	+
Path length ratio	PLR	Ratio of total distance traveled by the hand and straight line distance between initial and final hand position	+
Maximum speed	MS	Maximum hand speed between movement onset and offset	–
Position matching (PM)			
Absolute error	AbsErr	Mean absolute distance error	+
Variability	Var	Mean of SD of hand position	+
Shift	Shift	Mean difference between subject's hand location and mirrored XY location of robot	+
Contraction/expansion	CE	Ratio of area formed by subject movements to area formed by robot movements. Absolute value of z-score is used, so expansion is equivalent to contraction.	+
Object hit (OH)			
Target hits	TH	Total number of balls hit	–
Median error	ME	Percentage of the way through the task when half of the errors are made	–
Hits affected/unaffected	Hits _{aff/unaff}	Number of balls hit with affected/unaffected hand.	–
Hand speed affected/unaffected	HS _{aff/unaff}	Mean hand speed across entire task by affected/unaffected hand	–
Movement area affected/unaffected	MA _{aff/unaff}	Area of space covered by each hand during the task	–
Hand bias of hits	HBH	Bias of which hand is used more often for hitting targets	–
Miss bias	MB	Bias of misses toward 1 side or the other of the work space	–
Hand transition	HT	Location where hand preference switches	–
Hand selection overlap	HSO	Effectiveness in using both hands and how often hands are overlapped	–
Hand speed bias	HSB	Bias of hand speed between 2 hands	–
Movement area bias	MAB	Bias of movement area between 2 hands	–
Object hit and avoid (OHA)			
In addition to OH parameters			
Total distractors hit	TDH	Total number of distractor objects hit	+
Distractor hits affected/unaffected	DH _{aff/unaff}	Number of distractor objects hit by affected/unaffected hand	+
Distractor proportion	DP	Number of distractor objects hit as percentage of total objects hit	+
Object processing rate	OPR	Number of objects correctly processed per second at the point in the task when 80% of the objects in the task have entered the screen.	–

A brief description of each parameter is given. The sign indicates whether positive or negative values would indicate impaired performance.

and drawing. The maximum score is 146 and scores below 130 indicate presence of visuospatial neglect. The Montreal Cognitive Assessment⁴⁰ was used to screen cognition. The

Montreal Cognitive Assessment is a screening tool for cognition and has a maximum score of 30, with scores below 25 indicating cognitive impairment. The Functional

Independence Measure (FIM) was used as a measure of functional ability.⁴¹ The FIM scores a person's ability to complete activities of daily living. Total FIM scores range from 18 (lowest) to 126 (highest) and can be broken into motor (maximum score of 91) and cognitive (maximum score of 35) subscores.

Statistical Analysis

The primary outcomes were the robotic task parameter z-scores. Linear mixed effects models were used to explore the effects of lesion volume and WMH volume on performance. Random slope and intercept models were used with fixed effects of time (in days), lesion volume (in mL), WMH volume (in mL), and the interaction of lesion volume \times WMH volume. If the interaction was insignificant, it was removed from the model. Based on visual assessment of the recovery curves, time was initially modeled as a quadratic function in the linear mixed model analysis. Likelihood ratio tests were used to compare between models with time modeled as a quadratic function to models with only a linear time term to determine which model to subsequently use. Maximum likelihood was used to estimate linear mixed effects models used with likelihood ratio tests. If the likelihood ratio test indicated no difference between the models, the simpler linear model was used; otherwise, the quadratic model was applied. The secondary clinical outcome measures, FIM and Behavioral Inattention Test scores, were also analyzed using linear mixed models as described above.

The predictive value of lesion volume and WMH volume were also explored using regression analyses. Multiple linear regression analysis was used on each of the robotic parameters to predict performance at TP4 using performance at TP1 as an explanatory variable. This analysis was repeated using lesion volume and WMH volume, as well as their interaction, as additional explanatory variables. Likelihood ratio tests and adjusted R^2 values were used to compare the 2 models to determine whether imaging results significantly improved the ability to predict performance at TP4.

Statistical analyses were done using MATLAB R2015a (Mathworks, Nantick, MA). A P -value of 0.05 was used to indicate significance. The assumptions of all models were tested and met.

Results

Subject Demographics

Subject demographics and clinical scores are shown in Table 2. In total, 82 subjects were included, with 52 having completed all 4 time points. Based on 30 subjects missing 1 time point out of a total of 328 possible data points (82 subjects across 4 time points), missing data were calculated to be 9.1%, which is in line

with other longitudinal stroke studies.⁴² Data are assumed to be missing at random. No differences were found between lesion size, WMH volume, or performance at TP1 between individuals who completed all 4 time points and those who did not.

Lesion overlap maps are shown for both acute lesions and WMH in Figure 1. Extensive variability in lesion locations can be seen for the acute lesions, while WMH followed symmetrical periventricular patterns, with more severe cases showing WMH extending further.

Robotic Performance and Recovery Patterns

Example data for each robotic task is shown in Figure 2. The recovery trajectories for the task scores (overall performance) are shown for each subject in Figure 3, color coded according to lesion or WMH volume. Significant intersubject variability can be observed. Visually, PM shows the greatest trend of larger lesions relating to higher (more impaired) task scores; however, there are many exceptions to this. No other easily visible trends of acute lesion or WMH size impacting performance are present. The results of the linear mixed model analyses are shown in Figure 4 and reported for each task below.

Visually Guided Reaching

There was a significant lesion volume \times WMH volume interaction for min-max speed difference (95% confidence interval [CI], 0.0001, 0.002) and maximum speed (CI, 0.0003, 0.002). Lesion volume was a significant main effect only for reaction time (CI, 0.002, 0.020). The impact of lesion volume on reaction time was given by a β value of 0.011, meaning an increase in 1 mL of lesion volume corresponded to an increase in z-score of 0.011. Applying this to our sample, the difference between a 10th percentile (1.3 mL) and 90th percentile (98.4 mL) lesion would correspond to a z-score change of 1.05, or ≈ 86 ms. WMH volume was not a significant main effect for any parameter.

Position Matching

There was a significant lesion volume \times WMH volume interaction for overall task score (CI, 0.0003, 0.0018), absolute error (CI, 4.34×10^{-5} , 0.0014), and contraction/expansion ratio (CI, 0.0001, 0.0012), indicating that greater amounts of WMH exacerbated the negative effects of lesion volume on performance. There was a significant effect of lesion volume for task score (CI, 0.001, 0.018), absolute error (CI, 0.002, 0.018), variability (CI, 0.010, 0.026), and shift (CI, 0.013, 0.027) indicating that increased lesion volume was associated with poorer performance. To place these findings into context, for variability, the difference between lesion volume in the 10th to 90th percentile of our sample would correspond to a change in z-score of 1.738, or ≈ 3.4 cm of variability. Outside

Table 2. Demographic Data and Clinical Score by Time Point

Age (y)	60.6±13.1			
Sex	59M, 23F			
Affected arm	43R, 39L			
Ischemic/hemorrhagic	78 ischemic, 4 hemorrhagic			
Symptom onset to imaging	3.2±5.8 d (median 1 d)			
Lesion volume, mL	27.6±38.4			
WMH volume, mL	11.1±11.9			
Vascular territory	2 ACA, 54 MCA, 19 PCA, 4 ACA+MCA, 2 MCA+PCA, 1 ACA+MCA+PCA			
	TP1	TP2	TP3	TP4
Clinical scores				
N	82	74	74	69
Days since stroke	9.3±6.7	47.1±7.1	90.8±12.6	191.7±17.8
CMSA-arm [1,2,3,4,5,6,7]	[8,1,10,6,18,13,26]	[1,5,3,6,3,15,41]	[3,2,4,2,6,14,43]	[1,0,4,4,1,11,48]
CMSA-hand [1,2,3,4,5,6,7]	[10,0,7,6,23,17,19]	[3,3,2,5,15,15,31]	[3,2,3,1,7,23,35]	[0,2,3,2,9,12,41]
TLT [0,1,2,3]	[40,25,11,5]*	[56,12,2,4]	[53,16,4,1]	[55,9,5,0]
BIT	133.4±18.4	140.1±8.4	141.6±4.9	142.4±4.9
MoCA	23.7±5.2	NT	NT	NT
FIM-total	99.9±24.2	116.0±13.8	119.5±11.6	122.4±7.7
FIM-motor	70.5±20.5	84.6±10.4	86.9±8.9	88.8±5.4
FIM-cognitive	29.4±6.1	31.5±5.0	32.7±3.9	33.5±3.1
Robotic task scores				
VGR	3.98±2.46	2.47±2.18	2.14±1.94	1.74±1.69
PM	2.44±1.68	1.83±1.38	1.57±1.25	1.36±1.23
OH	4.27±2.95	3.14±2.88	2.84±2.57	2.06±2.21
OHA	3.29±1.85	2.34±1.84	1.96±1.54	1.49±1.30

Values are reported as mean±SD. ACA indicates anterior cerebral artery; BIT, Behavioral Inattention Test; CMSA, Chedoke-McMaster Stroke Assessment; FIM, Functional Independence Measure; MCA, middle cerebral artery; MoCA, Montreal Cognitive Assessment; NT, not tested; OH, object hit; OHA, object hit and avoid; PCA, posterior cerebral artery; PM, position matching; TLT, Thumb Localizing Test; TP, time point; VGR, visually guided reaching.

*One subject was not tested.

of interactions with lesion volume, WMH volume demonstrated no significant effect on any parameters of PM.

Object Hit

A significant lesion volume×WMH volume interaction was found only for hand transition (CI, 0.0002, 0.0026). Parameters indicative of overall performance (task score, total hits, and median error) all demonstrated a negative effect of lesion volume on performance (task score: CI, 0.018, 0.044; total hits: CI, −0.020, −0.008; median error: CI, −0.022, −0.010). When examining parameters representative of the affected arm, lesion volume was a factor for the number of hits (CI, −0.032, −0.015) and hand speed (CI, −0.039, −0.008), however, not for movement area. To illustrate the impact of lesion volume on hits with the affected arm, we found a change in lesion volume from the 10th to 90th percentile would correspond to a change

of z-score of −2.268, or ≈28 fewer hits. For the unaffected arm, lesion volume is also a factor for number of hits (CI, −0.016, −0.002), hand speed (CI, −0.021, −0.003), and movement area (CI, −0.026, −0.003). The effect of lesion volume is at least twice as large for the affected side compared with the unaffected side for number of hits and hand speed, as shown in Figure 4. Analysis of the measures of bilateral performance and symmetry indicated that lesion volume was a factor for hand bias of hits (CI, −0.048, −0.020) and miss bias (CI, −0.013, −0.002) but not for hand transition (apart from interaction), hand selection overlap, or movement area bias. WMH volume was not a significant factor for any parameter in OH.

Object Hit and Avoid

The lesion volume×WMH interaction was not significant for any OHA parameter. As with OH, the parameters of overall

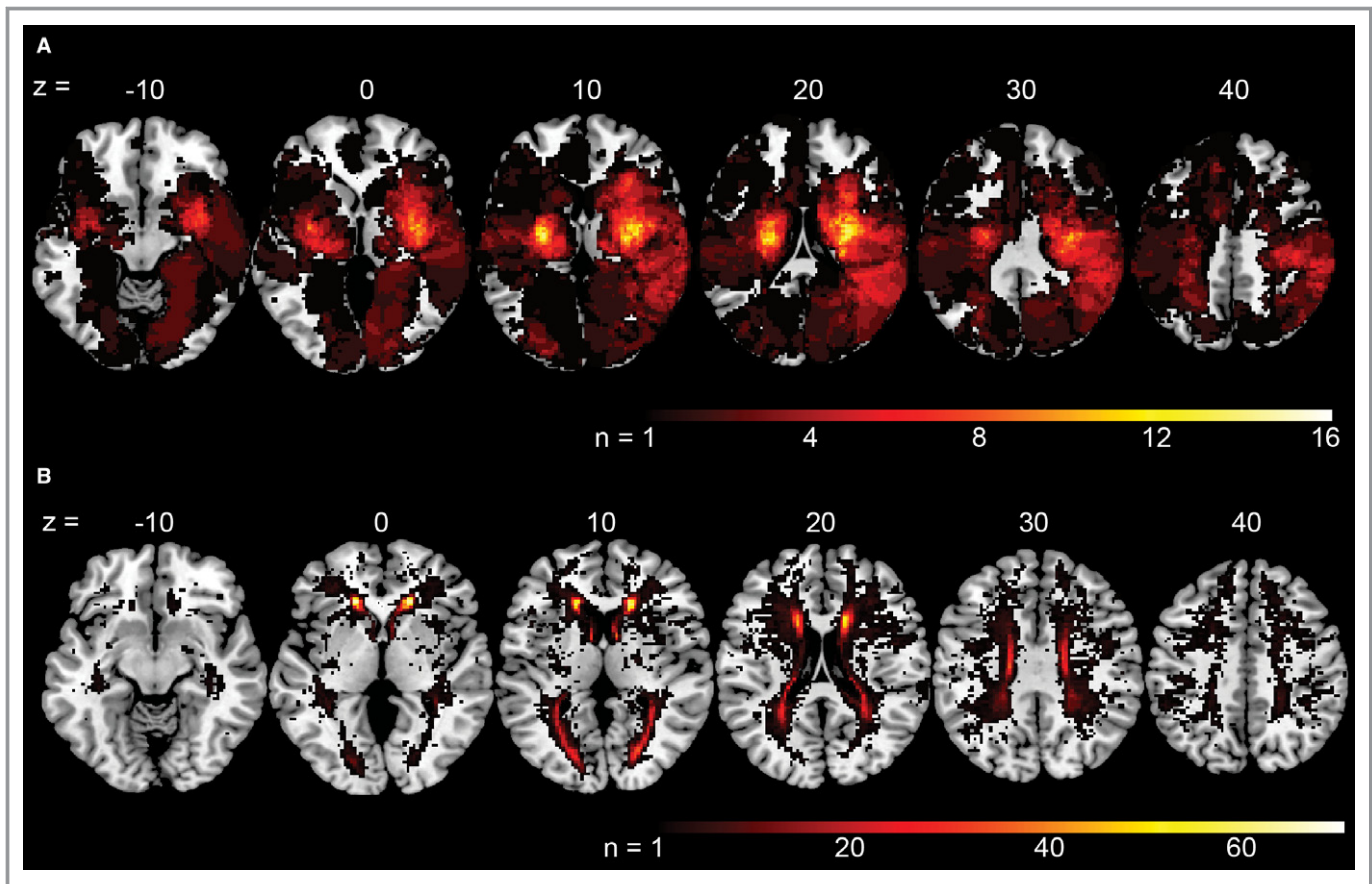


Figure 1. Lesion overlap maps. A, Acute lesions and (B) white matter hyperintensity regions. The number of subjects with lesions in each location is indicated by the color scale.

performance (task score, total hits, and median error) all showed negative effects of lesion volume (task score: CI, 0.006, 0.023; total hits: CI, -0.022 , -0.010 ; median error: CI, -0.0156 , -0.0070). Parameters representing motor performance of the affected hand showed an effect of lesion volume for hits affected (CI, -0.028 , -0.009) and hand speed affected (CI, -0.026 , -0.002), but not for movement area affected. For parameters relating to the unaffected hand, the same pattern was seen, with an effect of lesion volume found for hits unaffected (CI, -0.02 , -0.007) and hand speed unaffected (CI, -0.018 , -0.001), but not movement area. For the bilateral metrics, miss bias (CI, -0.011 , -0.001) and hand bias of hits (CI, -0.027 , -0.001) had an effect of lesion volume, while hand speed bias, hand transition, and hand selection overlap did not. For parameters with greater cognitive demands (distractors hit by either hand and total distractors hit, distractor proportion, object processing rate), lesion volume was only a factor for distractor proportion (CI, 0.005, 0.017) and object processing rate (CI, -0.015 , -0.005).

WMH showed a significant effect on median error (CI, -0.046 , -0.005), with greater WMH volumes linked to more errors earlier in the task. WMH had no significant effect on parameters representing performance of either the affected

or unaffected hand, or bilateral metrics. WMH was a factor for all parameters with greater cognitive demands (total distractors hit: CI, 0.020, 0.067; distractors hit affected: CI, 0.010, 0.047; distractors hit unaffected: CI, 0.021, 0.083; distractor proportion: CI, 0.028, 0.083; object processing rate: CI, -0.062 , -0.015), with the effect from WMH being greater than that of lesion volume for this subset of parameters. To contextualize these findings, a change in WMH volume from the 10th percentile (2.7 mL) to 90th percentile (25.4 mL) would correspond to a change in z-score of 0.984, or ≈ 19 distractors.

Clinical Scores

Clinical scores for each time point are shown in Table 2. The results of the linear mixed models for clinical scores are shown in Table 3. The significant lesion volume \times WMH volume interaction for FIM total, FIM cognitive, and Behavioral Inattention Test indicate that higher amounts of WMH increase the negative impact of lesion volume on performance. Additionally, lesion volume had a negative impact on FIM motor and FIM cognitive subscales, while WMH only impacted FIM cognitive.

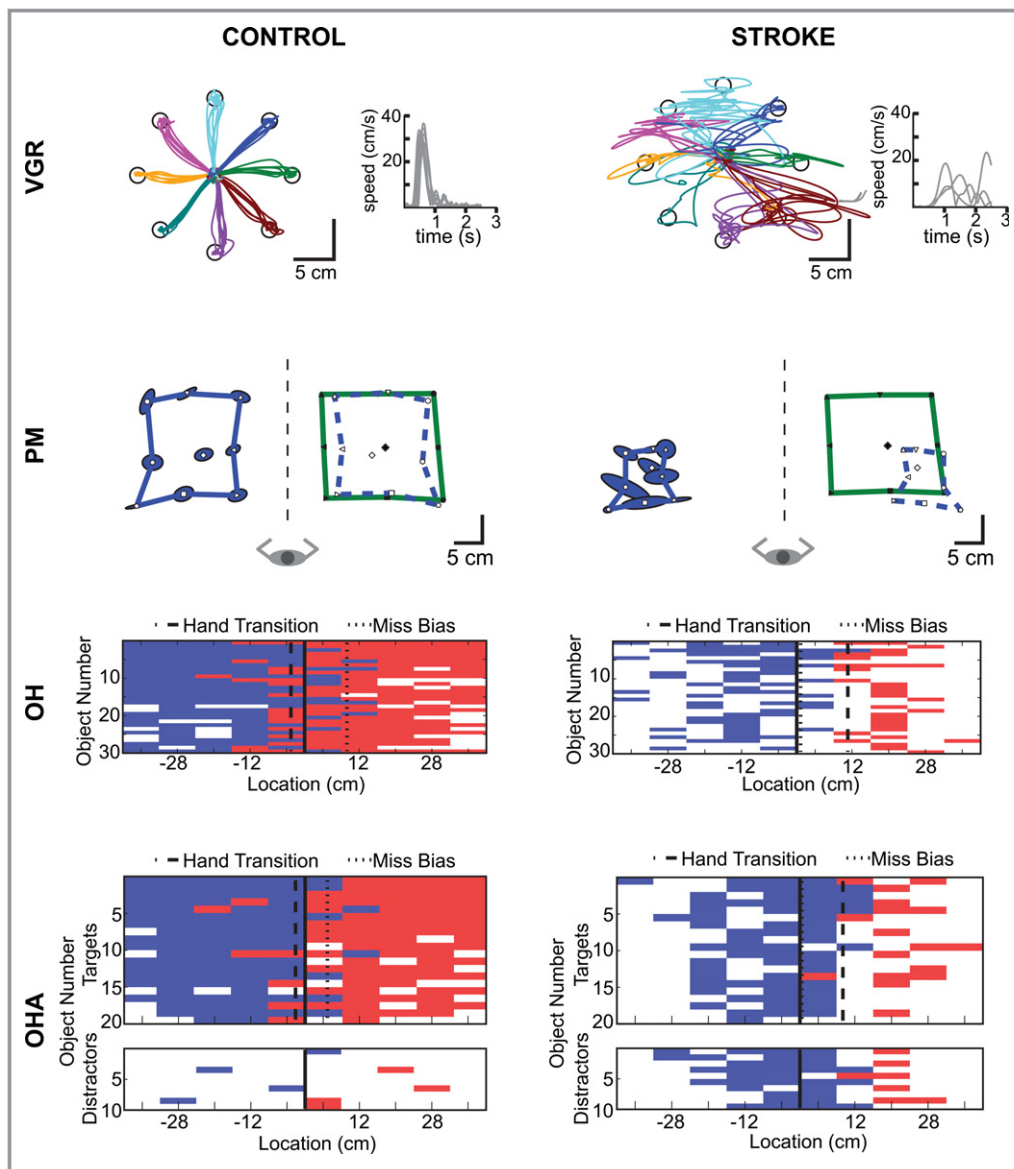


Figure 2. Example data. Each task is shown for a control and a stroke subject (right side affected). Visually guided reaching (VGR): Hand paths are depicted from the center target to each peripheral target. Speed profiles are also shown for 1 example target. Position matching (PM): The robot moved the right hand to 1 of 9 targets (outer 8 targets connected by the green lines) and the subject mirror matched with the left hand. The locations the subject matched are shown with blue ellipses and the outer 8 are connected with blue lines. Dashed blue lines reflect the outside matched target locations. Object hit (OH) and object hit and avoid (OHA): Figures indicate spatial pattern of hits. X-axis denotes the bin location from which objects fall. Y-axis indicates the cumulative number of objects from each bin, with objects falling faster over time. Boxes are colored if a hit occurred (red for right hand and blue for left hand) at that location and time.

Predictive Value of Lesion Volume and WMH Volume

Table 4 displays the adjusted R^2 values for regressions predicting TP4 using TP1 only versus TP1 with lesion volume, WMH volume, and the interaction of lesion volume \times WMH volume as additional explanatory variables for each parameter. For VGR, the addition of the imaging results did not explain additional variance in performance at TP4. For PM,

likelihood ratio tests found differences between the models with and without imaging results for task score ($P < 0.0001$), absolute error ($P = 0.004$), variability ($P < 0.0001$), and contraction/expansion ratio ($P < 0.0001$). For OH, differences between models were only found for hand bias of hits ($P = 0.019$). For OHA, imaging results significantly improved the model for task score ($P = 0.046$), median error ($P = 0.004$), and movement area bias ($P = 0.002$). For some parameters, adjusted R^2 values decreased because of increasing the

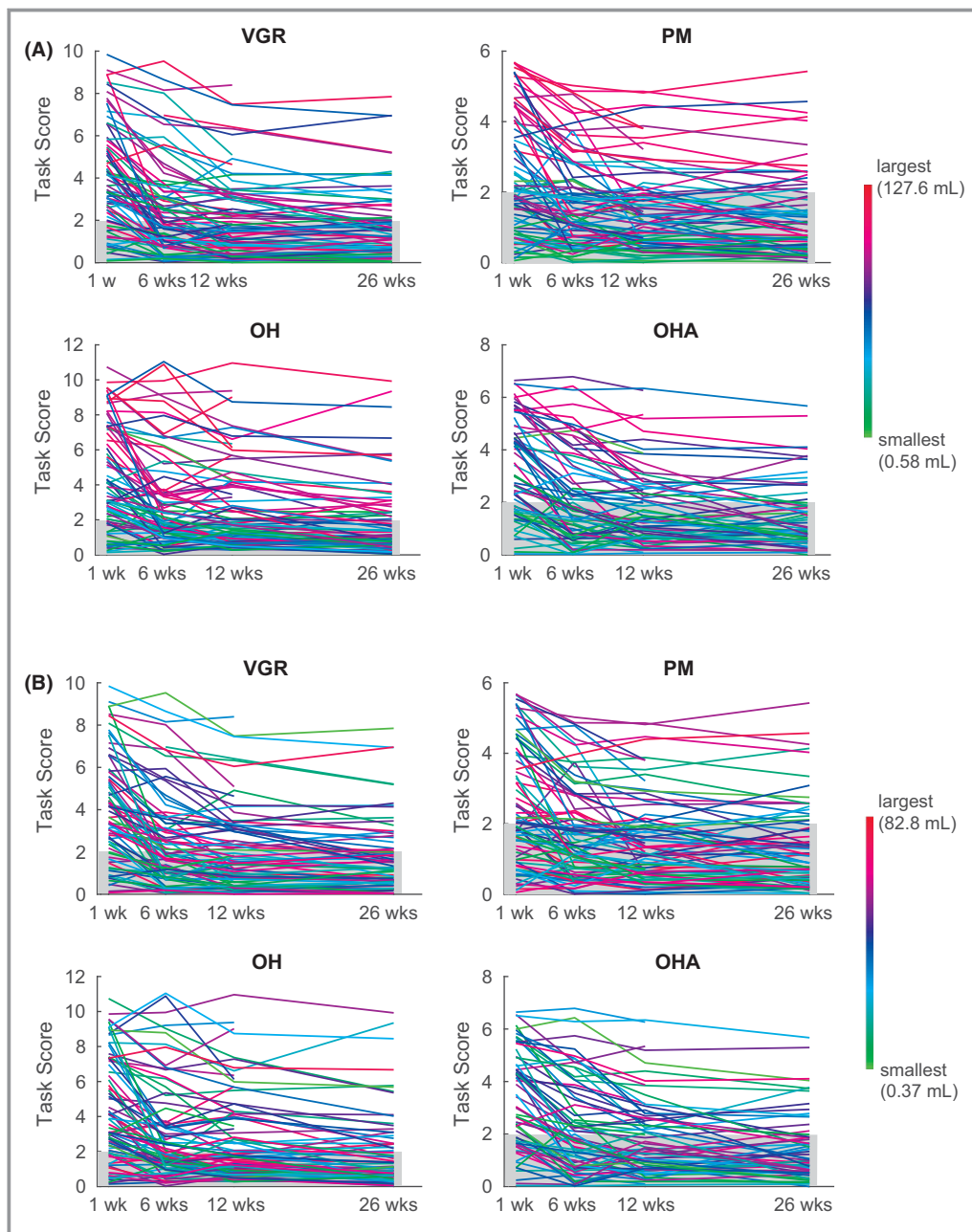


Figure 3. Recovery trajectories. Each subject's overall performance (task scores) is shown, with the color of the line indicating the rank of the lesion (A) or WMH (B) size from smallest to largest. The gray boxes indicate the normative range. OH indicates object hit; OHA, object hit and avoid; PM, position matching; VGR, visually guided reaching; WMH, white matter hyperintensity.

number of variables without improving the amount of variance explained.

Discussion

The main finding of this study was that acute lesion volume and WMH volume influence different domains of recovery poststroke. Independently, acute lesion volume has a widespread impact on sensory and motor impairments poststroke,

as well as overall function, while the impact of WMH volume was limited to cognitive deficits. A small proportion of parameters also had significant acute lesion volume and WMH volume interactions, where it can be observed that greater amounts of WMH increased the effect of the acute lesion volume. While lesion volume and WMH volume were found to negatively impact longitudinal recovery, in general they did not offer any benefit in predicting outcomes at 6 months poststroke over using initial performance alone, suggesting

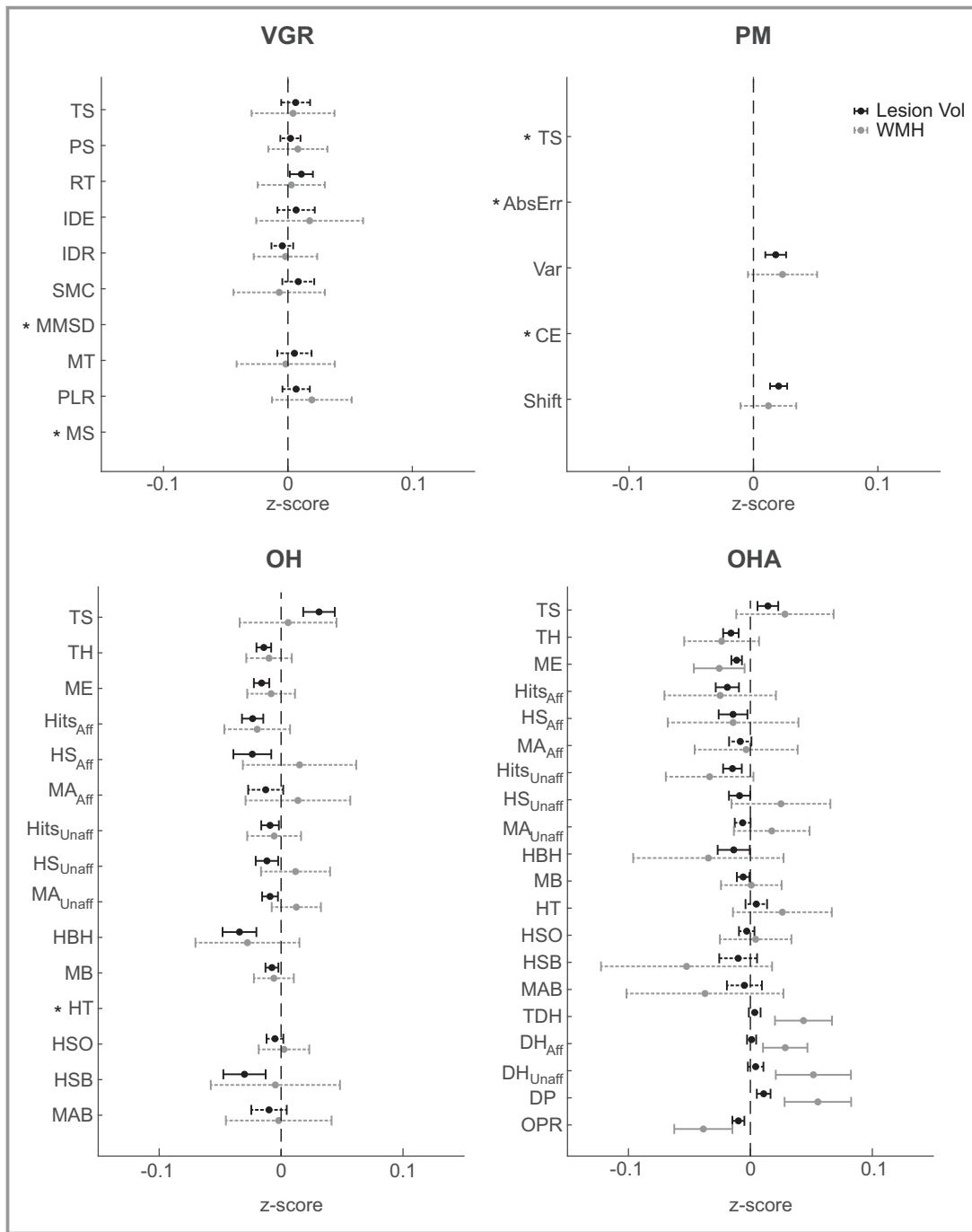


Figure 4. Coefficient estimates and 95% confidence intervals for robotic assessments. Confidence intervals are shown for lesion volume (black) and WMH volume (gray) for each parameter where there were no interactions, and are depicted as solid lines if the effect is significant and dashed lines if it is not significant. The asterisk indicates that a significant interaction was found between lesion volume and WMH, and therefore the main effects are not shown. The coefficient estimates can be interpreted as the change in z-score across all time points for a 1-mL increase in lesion volume or WMH volume, holding all other factors constant. AbsErr indicates absolute error; CE, contraction/expansion; DH_{aff/unaff}, distractor hits affected/unaffected; DP, distractor proportion; HBH, hand bias of hits; Hits_{aff/unaff}, hits affected/unaffected; HS_{aff/unaff}, hand speed affected/unaffected; HSB, hand speed bias; HSO, hand selection overlap; HT, hand transition; IDE, initial direction error; IDR, initial distance ratio; MA_{aff/unaff}, movement area affected/unaffected; MAB, movement area bias; MB, miss bias; ME, median error; MMSD, minimum-maximum speed difference; MS, maximum speed; MT, movement time; OH, object hit; OHA, object hit and avoid; OPR, object processing rate; PLR, path length ratio; PM, position matching; PS, posture speed; RT, reaction time; SMC, speed maximum count; TDH, total distractor hits; TH, target hits; TS, task score; Var, variability; VGR, visually guided reaching; WMH, white matter hyperintensity.

Table 3. Coefficient Estimates and 95% CI of Clinical Assessments

	Estimate	CI	P Value
FIM total			
Lesion volume	−0.033	[−0.106, 0.040]	0.371
WMH	−0.072	[−0.248, 0.102]	0.413
Lesion volume×WMH	−0.008	[−0.016, −0.001]	0.047
FIM motor			
Lesion vol	−0.046	[−0.090, −0.002]	0.040
WMH	−0.056	[−0.191, 0.078]	0.412
Lesion volume×WMH
FIM cognitive			
Lesion volume	−0.029	[−0.053, −0.004]	0.021
WMH	−0.060	[−0.118, −0.002]	0.043
Lesion volume×WMH	−0.003	[−0.005, −0.001]	0.040
BIT			
Lesion volume	−0.012	[−0.060, 0.036]	0.624
WMH	−0.003	[−0.119, 0.113]	0.963
Lesion volume×WMH	−0.008	[−0.013, −0.003]	0.003

The coefficient estimates can be interpreted as the change in clinical score across all time points for a 1-mL increase in lesion volume or WMH volume, holding all other factors constant. BIT indicates Behavioral Inattention Test; CI, confidence interval; FIM, Functional Independence Measure; WMH, white matter hyperintensity.

that their prognostic value is minimal. The notable exception to this is performance on the PM task. This task requires transferring sensory information from the tested arm across the brain to execute a motor movement with the other arm, and was found to be more impacted by imaging findings.

Our use of robotic measures may have allowed us to detect the influence of lesion volume, which may be somewhat underappreciated with clinical measures. Clinically meaningful effects of lesion volume were found across certain aspects of all robotic tasks. However, as shown in the results, it takes large differences in lesion volumes to appreciate a clinically meaningful impact. This may be one reason lesion volume has limited prognostic ability. Additionally, for a small number of parameters, the interaction of lesion volume and WMH volume was significant, whereas lesion volume alone was not. This indicates that for some parameters, including total FIM score, the combination of high amounts of WMH along with large lesion volumes can cause greater detriments than large lesion volume alone.

A key finding of our study was that WMH specifically affected cognitive aspects of recovery, and to a greater extent than lesion volume. Previous studies have linked increased WMH with cognitive deficits, both in older adults with mild cognitive impairment,⁴³ and in individuals poststroke.^{15,16} What differentiates this study from previous work is that

rather than quantifying cognition based on cognitive testing, we examined cognition within a complex sensorimotor task. The use of distractors on the OHA task, where WMH was found to play a significant role, increases cognitive load as greater attention is required to differentiate between targets and distractors.³² This task requires inhibiting motor actions to avoid distractors, an important cognitive aspect of voluntary motor behavior.⁴⁴ Our findings were further supported by WMH contributing to performance on the cognitive subscale of the FIM, showing that the impact extends into functional measures.

The primary limitation of this study was that our analysis did not account for lesion location. While lesion volume may be a therapeutic target in treatments of tissue plasminogen activator and mechanical embolectomy, lesion location can impact what deficits are seen and modulate the impact of lesion size.⁴⁵ The importance of lesion location versus lesion size may vary with task, with simpler motor tasks such as VGR having a heavier reliance on lesion location, whereas tasks involving more diffuse brain networks, including PM, OH, and OHA, potentially being more impacted by lesion volume. However, because of the complex networks in the brain as well as difficulty in measuring isolated impairments, correlating lesion location with specific deficits remains a challenge. Future analysis using machine learning algorithms may offer improved insight into links between behavior and lesion locations. Additionally, because of our image analysis procedures and robotic assessments used, our results can only be generalized to individuals with unilateral lesions not involving the cerebellum or brainstem. To fully characterize how lesions and WMH impact stroke recovery, future analysis should consider bilateral, brainstem, and cerebellar lesions.

Our study may underestimate the contribution of WMH on recovery. Diffusion tensor imaging has previously detected diffusivity changes in normal-appearing white matter in addition to visibly hyperintense regions.⁴⁶ Furthermore, WMH may be present in the control sample used to establish the normative values for the robotic tasks, and we do not know whether the WMH may have led to deficits in our participants before their stroke. A criticism of our work is that changes in performance over time could reflect either “true” recovery, a learning effect, or a combination of both. In a large cohort of healthy young adults using the same robotic tasks as in the present study, learning effects were only observed in 3 parameters of the OH task (total hits, hits with the dominant hand, and median error).⁴⁷ Thus, we expect that the impact of any learning effects in the present study were likely minimal. Individuals with significant cognitive deficits who were unable to follow 3-step commands were excluded from this study; therefore, we were unable to assess the role of lesion volume and WMH on more severe cognitive deficits.

Table 4. Comparison of R^2 Values Between Prognostic Models

Parameter	R^2 : TP1	R^2 : TP1+Imaging	Parameter	R^2 : TP1	R^2 : TP1+Imaging
VGR			PM		
TS	0.494	0.472	TS*	0.450*	0.557*
PS	0.241	0.260	AbsErr*	0.257*	0.355*
RT	0.405	0.409	Var*	0.297*	0.503*
IDE	0.541	0.524	CE*	0.481*	0.596*
IDR	0.462	0.474	Shift	0.034	0.068
SMC	0.400	0.376	OHA		
MMSD	0.106	0.107	TS*	0.308*	0.362*
MT	0.431	0.429	TH	0.399	0.426
PLR	0.395	0.375	ME*	0.240*	0.359*
MS	0.221	0.244	Hits _{Aff}	0.389	0.396
OH			HS _{Aff}	0.401	0.387
TS	0.435	0.464	MA _{Aff}	0.283	0.284
TH	0.484	0.474	Hits _{Unaff}	0.484	0.500
ME	0.342	0.315	HS _{Unaff}	0.429	0.436
Hits _{Aff}	0.422	0.432	MA _{Unaff}	0.334	0.328
HS _{Aff}	0.430	0.438	HBH	0.421	0.422
MA _{Aff}	0.388	0.401	MB	0.132	0.123
Hits _{Unaff}	0.355	0.339	HT	0.210	0.185
HS _{Unaff}	0.340	0.336	HSO	0.114	0.103
MA _{Unaff}	0.287	0.280	HSB	0.399	0.428
HBH*	0.048*	0.136*	MAB*	0.317*	0.435*
MB	0.061	0.027	TDH	0.311	0.327
HT	0.188	0.168	DH _{Aff}	0.135	0.139
HSO	0.151	0.122	DH _{Unaff}	0.254	0.275
HSB	0.267	0.279	DP	0.393	0.418
MAB	0.361	0.348	OPR	0.285	0.307

" R^2 : TP1" refers to the R^2 value of using only performance at time point 1 (TP1) to predict performance at TP4. " R^2 : TP1+Imaging" refers to the adjusted R^2 value when also using lesion volume, WMH volume, and the lesion volume \times WMH volume interaction to predict performance at TP4. AbsErr indicates absolute error; CE, contraction/expansion; DH_{aff/unaff}, distractor hits affected/unaffected; DP, distractor proportion; HBH, hand bias of hits; Hits_{aff/unaff}, hits affected/unaffected; HS_{aff/unaff}, hand speed affected/unaffected; HSB, hand speed bias; HSO, hand selection overlap; HT, hand transition; IDE, initial direction error; IDR, initial distance ratio; MA_{aff/unaff}, movement area affected/unaffected; MAB, movement area bias; MB, miss bias; ME, median error; MMSD, minimum-maximum speed difference; MS, maximum speed; MT, movement time; OH, object hit; OHA, object hit and avoid; OPR, object processing rate; PLR, path length ratio; PM, position matching; PS, posture speed; RT, reaction time; SMC, speed maximum count; TDH, total distractor hits; TH, target hits; TS, task score; Var, variability; VGR, visually guided reaching; WMH, white matter hyperintensity.

*Significant results of likelihood ratio tests comparing the 2 models.

Longitudinal studies present significant challenges in terms of maintaining participants for follow-up assessments. Our missing data of 9.1% are in line with previous large prospective cohort studies and randomized clinical trials in stroke recovery; however, we acknowledge that our missing data do present a limitation in fully characterizing individual's recovery over 6 months poststroke. Lastly, we conducted exploratory analyses on the data, given the novel robotic techniques that we used. Necessarily this involved examining a large number of parameters, which can increase the risk of a

Type I error. Future studies may choose to focus on certain parameters to decrease this risk.

In conclusion, this study utilized robotic assessments of sensory, motor, and cognitive function as well as commonly used clinical scales to explore the role of lesion volume and WMH on recovery poststroke. We found that acute lesions and WMH impact different aspects of recovery, with WMH being specific to cognitive performance. Though large differences in lesion and WMH volumes could contribute to clinically meaningful differences in performance, the effects of

either lesion type were generally insignificant when it comes to predicting long-term outcomes. While these findings further our knowledge on factors contributing to specific domains of stroke recovery, further work is needed to improve our ability to predict stroke recovery.

Acknowledgments

We acknowledge Janice Yajure and Mark Piitz for assistance in data collection.

Sources of Funding

This work was funded by a Canadian Institutes of Health Research operating grant (MOP 106662) and a Heart and Stroke Foundation of Canada Grant-in-Aid. Hawe was supported by a University of Calgary Eyes High Postdoctoral Fellowship. Kenzie and Findlater were supported by Alberta Innovates Health Solutions.

Disclosures

Dr Scott is the cofounder and Chief Scientific Officer of BKIN Technologies, manufacturer of the KINARM robot. The remaining authors have no disclosures to report.

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