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TRIAL-BY-TRIAL VARIATION IN UPPER EXTREMITY MOVEMENT SMOOTHNESS AFTER ACUTE STROKE RELATES TO CLINICAL ASSESSMENTS AND CORTICOSPINAL TRACT INJURY

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Abstract

Background. Variability in movement is critical for performance under dynamic conditions. Stroke causes focal injury to the motor system, disrupts voluntary motor control, and leads to less smooth and more variable upper extremity movements. Few studies have characterized trialby-trial

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variation in upper extremity movement smoothness and its clinical and neuroanatomic correlates in the first week post-stroke.

Objective. To evaluate trial-by-trial variation in upper extremity movement smoothness during planar reaching and relate it to clinical outcomes and neuroanatomical injury after acute stroke.

Methods. Twenty-two patients (4.4 ± 1.7 days poststroke) and twenty-two able-bodied adults completed a planar center-out reaching task. Smoothness was quantified with spectral arc length (SPARC). Median and interquartile range (IQR, quantification of trial-by-trial variation) of SPARC values were assessed. Patients completed a clinical assessment battery acutely and at 90 days post-stroke. MRI-derived stroke lesions were analyzed to estimate basal ganglia, motor cortex, and corticospinal tract injury. Intraclass correlation, Spearman's correlation, and multivariate regression evaluated trial-by-trial variation and its relation to clinical assessments, outcomes, and neuroanatomical injury.

Results. Post-stroke reaching was less smooth and more variable (larger IQR) compared to able-bodied adults. Variability in post-stroke smoothness was primarily driven by within-subject, trial-by-trial variation. More variable smoothness, even after controlling for median smoothness, related to worse clinical assessment performance and 90-day outcomes. More variable smoothness related to greater corticospinal tract injury (ρ=0.537, p=0.011), but not to basal ganglia or motor cortex injury.

Conclusion. Trial-by-trial variation of movement is valuable for understanding sensorimotor control post-stroke and has implications for targeted neurorehabilitation.

Keywords

stroke; kinematics; reaching; variability; upper limb; motor control

Introduction

The pioneering neurophysiologist Nikolai Bernstein introduced the concept of "repetition without repetition" in motor control to mean that no movement is performed the exact same way twice[1]. On the one hand, variability in movement can be viewed as the output of an inherently noisy nervous system, where noise infuses uncertainty into the brain's process of transmitting signals to generate movement[2-4]. With this perspective, a long-held theory is that goal-directed movements can be optimized by reducing noise and minimizing variability[5-7]. Variability has also been appreciated as critical to ensuring that movements can be performed under different and dynamically changing task constraints and environmental conditions[8]. Indeed, variability can be beneficial in many ways— it is a core feature of how the motor system explores and acquires new skills[9-11]. Numerous methods have been developed to quantify variability in movement trajectories represented as time series[12] and across trials of movement[8,13-15].

Neural activity in different brain areas and pathways has been shown to be a source of the observed variability in motor output. In premotor and primary motor (M1) cortices, differences in preparatory neural firing predict observed trial-by-trial variation in reaching movements[16]. Neural activity in basal ganglia structures are critical for

generating and regulating motor system variability[17-19], particularly for modulating the relationship between variability and feedback[20-22]. Furthermore, changes in excitability of the corticospinal tract, the predominant descending motor pathway for transmitting brain signals to the spinal cord for precise, voluntary, dexterous upper extremity movements[23], are related to trial-by-trial variation during reach-to-grasp tasks[24,25]. Taken together, neurophysiology in different cortical (premotor-M1) and subcortical (basal ganglia and corticospinal tracts) structures all likely have a role in the observed movement variability of the able-bodied motor system.

In the case of focal neural injury to the motor system due to stroke, upper extremity movements have been observed to be more variable[26,27]. With rehabilitation after stroke, movement variability decreases[28]. These observations imply that movement variability after stroke is directly associated with the neuroanatomic injury and its resulting neurophysiologic effects. However, variability in upper extremity movements after stroke, particularly during the first few days post-stroke (i.e., acute stroke), has been underexplored. Insights regarding variability in movement in acute stroke would most purely reflect the behavioral effect of brain lesions: in this time window, patients have not typically developed significant spasticity[29], compensatory strategies[30,31], or biomechanical complications (such as soft tissue/muscular contractures and shoulder impingement[32]), which limit movement and impact kinematic measurements in chronic stroke[33,34]. Furthermore, stroke lesions commonly impact the motor cortex, basal ganglia, and corticospinal tract[35-37], but systematically quantifying the impact of lesions on these areas in relation to movement variability has not been performed. Assessing upper extremity movement variability during acute stroke and relating movement variability to patterns of stroke-induced neuroanatomical injury could provide important insights into the role of variability in motor control and its disruption when the motor system is injured. These insights could inform neurorehabilitation.

Given the relative lack of upper extremity kinematic studies in acute stroke[38], the aims of this study were thus to (1) evaluate upper extremity movement variability in the more-affected (contralesional) and less-affected (ipsilesional) upper extremity of individuals after acute stroke, and (2) ask whether upper extremity movement variability relates to clinical assessments, 90-day outcomes, and patterns of neuroanatomical injury after stroke. To achieve these aims, we assessed 22 patients within the first eight days after acute stroke with a two-dimensional, planar center-out reaching task on an end-effector robot. We focused on movement smoothness to quantify the spatial and temporal discontinuities in movement trajectories, and its trial-by-trial variation; smoothness is a well-accepted measure of overall upper extremity movement quality in both able-bodied[39-41] and post-stroke[42-45] individuals. Our specific hypotheses were that stroke movements would be less smooth and more variable than able-bodied movements, and that greater variability in smoothness would relate to more impaired clinical assessments and 90-day outcomes after stroke and greater direct injury to motor system structures.

Methods

Study Participants

Patients were recruited from an ongoing, single-center, longitudinal cohort study of upper extremity motor recovery after stroke, the Stroke Motor reHabilitation and Recovery sTudy (SMaHRT https://clinicaltrials.gov/show/NCT03485040)[36,37]. Eligible patients from the Massachusetts General Hospital's inpatient stroke service were recruited to the study if they: (1) were between 18 and 90 years old, (2) had unilateral upper extremity weakness after ischemic stroke as defined by the National Institutes of Health Stroke Scale (NIHSS) Q5A or Q5B score ≥ 1, (3) were without significant impairments in consciousness (NIHSS score on Q1a and Q1b ≥ 1, and Q1c = 0), and (4) could follow simple commands in English. Participants were excluded if they had prior history of developmental, neurologic, or major psychiatric disorder resulting in functional disability, or prior history of visual or auditory disorders limiting ability to participate in testing. The robot used in this study's kinematic assessment is located in the therapy gym of the Massachusetts General Hospital Neurology Service. The assessment required the availability of clinical staff to ensure the safety of the patients. To complete the assessment using the robot, patients were transferred from their hospital room by trained research staff to the therapy gym. Between October 2018 and April 2023, 110 individuals with acute stroke were enrolled in the parent study and consented to participate in the kinematic assessment component. Ultimately, 31 patients completed the kinematic assessment (27 were too ill to participate, 23 were unable to proceed due to the unavailability of clinical staff to assist, and 29 were discharged from the acute hospital before assessments could be conducted).

Data from 22 able-bodied control subjects (mean age = 51.0 years), who completed the same upper extremity kinematic assessment as the acute stroke group, were included as the reference population for analyses. Eligible control participants between the age of 18 and 89 years of age with the ability to follow simple commands in English and without (1) developmental, neurologic, or major psychiatric disorders resulting in functional disability, (2) upper extremity sensory or motor impairment, and (3) visual or auditory disorders limiting their ability to participate in testing procedures were recruited to participate from the Providence VA Medical Center.

All participants in the studies provided written informed consent. These studies were approved by the Mass General Brigham and Providence VAHCS Institutional Review Board.

Clinical Measures

Upper Extremity Fugl-Meyer Assessment (FMA-UE) was used to assess overall upper extremity motor impairment and synergistic movement patterns[46-48]. The Box and Blocks (BBT) and 9-Hole Peg (9HP) tests were used to assess upper extremity fine motor coordination. To be comparable with FMA-UE and BBT in which larger scores indicate better performance, 9HP scores were negated. These three assessments were collected for all patients at the acute time point and for 13 of the patients at the 90-day time point. The modified Rankin Scale (mRS) is an ordinal measure, scored through patient interviews, which is used to assess global disability. This scale was collected for 18 of the patients at the

90-day time point. All assessors were formally trained and were recertified annually in all assessments.

Kinematic Task

Upper extremity planar reaching was measured using the InMotion2 ARM Interactive Therapy System (Figure 1A). This end-effector robot provides gravity compensation and facilitates a high intensity of movement repetitions[49-51]. Participants' trunks were secured via a harness to prevent trunk compensation and forearms were secured in the manipulandum allowing movement in the horizontal plane of the table. Participants were seated at a distance that allowed them to comfortably reach all targets while keeping their trunk secured. The table and manipulandum height were adjusted to ensure that the participant's shoulder was not elevated. If participants could not maintain an active grasp on the manipulandum joystick, their hand was secured via straps. The monitor in front of the participants displayed the task and their hand position as represented by a circular cursor.

Participants were instructed to make 80 movements between eight circular targets with 1 cm radii, arrayed radially at 14 cm and a central start position. They were instructed to make smooth, controlled, straight movements toward the intended target with a controlled stop in the center of each target. Trials alternated in cuing the participant to move to one of the peripheral targets, presented in a clockwise order, and then from that peripheral target back to the center target. Once the target appeared, the participant had 10 seconds to complete the movement. No additional feedback of movement parameters was provided during the task. Acute stroke patients were tested on both upper extremities and able-bodied participants were tested on their dominant upper extremity. All participants completed the assessment without any actuated assistance from the robot.

Kinematic Analysis

Preprocessing: Upper extremity position data was analyzed using MATLAB (Mathworks, USA). Position time-series were rotated so the direction of movement was always along the x-axis, low-pass filtered (8 Hz 8th-order Butterworth) and differentiated to yield velocity and acceleration. The peak speed of each trial was defined as the first zero-crossing of acceleration above a threshold of 10 cm/s. If a trial did not have a peak speed as defined by these parameters, the maximum velocity value of that trial was chosen as the peak speed. The movement start was when, prior to the peak speed, the speed exceeded 2 cm/s. The movement end was when, after the peak speed, the speed was less than 2 cm/s for at least 25 ms[52]. Trials were rejected if they were non-goal directed, ended at less than 33% of the target distance, or did not have a movement-end. Trials were defined as successful or unsuccessful depending on whether the movement ended inside or outside the intended target, respectively (Figure 1B). Smoothness analyses were conducted on both successful and unsuccessful, non-rejected trials.

Movement Smoothness

We quantified movement smoothness in the frequency domain using spectral arc length (SPARC). SPARC calculates the arc length of the Fourier magnitude spectrum of a given velocity profile and is independent of temporal movement scaling[39,45]. Less smooth

movements have more complex and higher frequency components[39,53]. The SPARC value of every non-rejected trial for all participants was computed (Figure 1C). The trial distributions of SPARC values per subject as well as per group were not normal, thus we computed the median and interquartile range (IQR) of each participant's trials. Additionally, the able-bodied smoothness range (ASR), the SPARC value range in which the majority of able-bodied trials fell in, was computed by the following formula:

$$\mathrm{ASR} = \mathrm{MM}_{\text{able-bodied}} \pm 1.48 * \mathrm{MI}_{\text{able-bodied}}$$

where $\mathrm{MM}_{\text{able-bodied}}$ is the median of the median values of all included trials for each able-bodied participant and $\mathrm{MI}_{\text{able-bodied}}$ is the median of the IQR values of all included trials for each able-bodied participant. The value 1.48 was used as the non-parametric analog to 2 standard deviations in normal distributions[54].

Magnetic Resonance Image Processing and Analysis

Stroke topography was determined with magnetic resonance diffusion-weighted images obtained as part of the standard-of-care acute stroke inpatient workup. Lesion delineation, spatial normalization, and registration were performed using well-established methods (see Methods in Supplementary Material)[46,55-57]. Participants had unilateral lesions, except 2 individuals who had punctate injury in the other hemisphere. This was not regarded as exclusionary and thus not further considered in subsequent analyses (see Methods in Supplementary Materials). Right-sided stroke lesions were flipped onto the left hemisphere to allow for group comparisons.

To examine the patterns of neuroanatomical injury related to upper limb movement variability, we calculated overall lesion volume, lesion overlap with premotor-M1 and the basal ganglia, and corticospinal tract (CST) injury (quantified via both normalized maximum lesion overlap and weighted lesion load)[36,58]. The premotor and M1, basal ganglia, and CST templates were obtained from the Julich Histological atlas[59], the automated anatomical atlas[60], and the Johns Hopkins University white matter tractography atlas[36], respectively (Figure 3B).

Statistical Analysis

The average and variability in movement smoothness for each participant's included trials were quantified as the median and IQR, respectively. We performed pairwise comparisons among groups (stroke more-affected upper extremity, stroke less-affected upper extremity, and able-bodied dominant upper extremity) of the medians and IQRs using the Wilcoxon Rank Sum and Signed Rank Tests. To assess whether there were any learning effects on smoothness across consecutive trials, Spearman's correlation was used to assess whether there was a significant relationship between smoothness values and time.

Intraclass correlations (ICC), a ratio of between-participant variance (σ_P^2) to total variance ($\sigma_P^2 + \sigma_T^2$), were computed to investigate the sources of observed movement variability in each of the three groups. A small ICC (close to 0) indicates that most of the observed variability is due to trial-by-trial differences within participants, suggesting that participants

exhibit variability across their trials but perform similarly overall to other participants. A high ICC (close to 1), in contrast, suggests that the observed variability predominantly arises from differences across participants, with each participant performing relatively consistently across their own trials.

$$\mathrm{ICC} = \frac{\sigma_P^2}{\sigma_P^2 + \sigma_T^2}$$

To evaluate how smoothness differed based on motor impairment severity, participants were divided into mild and moderate-to-severe impairment groups based on their FMA-UE scores[48]. A Wilcoxon Rank Sum test was used to compare differences in smoothness median and IQR between these two groups. To assess the relationship between movement smoothness (median and IQR) and clinical outcome measures (FMA-UE, 9HP, BBT), Spearman's correlations were first obtained. To account for the relationships between smoothness median and IQR, and vice versa, the analyses were repeated with semi-partial Spearman's correlation. Finally, we computed four separate linear regression models, each using acute smoothness median and IQR as independent variables. In each model, one of the four 90-day clinical outcome scores—FMA-UE, 9HP, BBT or mRS—was used as the dependent variable. This approach allowed us to assess whether smoothness variability was a predictor of 90-day clinical outcomes scores. To ask whether smoothness measures predicted 90-day outcomes beyond initial upper extremity impairment level, we repeated the regressions with baseline Fugl-Meyer included as an independent variable (see Methods in Supplementary Materials). Independent variables were tested for collinearity using a Belsley collinearity test.

To assess the impact of neuroanatomical injury on smoothness, Spearman's correlation was used to examine whether (1) overall stroke lesion volume, (2) basal ganglia-lesion overlap, (3) premotor-M1-lesion overlap, (4) weighted-CST lesion load, or (5) normalized maximum CST area overlap related to movement smoothness median or IQR.

All imaging and statistical analyses were conducted using MATLAB (2019b and 2023a) and R Statistical Software (v4.3.1).

Data Availability

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

Results

A total of 31 patients with unilateral upper extremity weakness after acute ischemic stroke consented to participate in this study and completed robotic and standardized clinical outcome assessments within the first 8 days after stroke. Data from 9 patients were excluded for one of the following reasons: did not complete all trials of the reaching assessment due to fatigue (n=5), did not complete all standardized outcome assessments (n=1), less than 50% of their trials passed pre-processing (n=3). Included in the final analysis were 22

stroke patients (age = 66.3 ± 12.6, mean ± SD; female participants = 41%). Participants were assessed within 4.4 ± 1.7 days post-stroke. Demographic and clinical characteristics are summarized in Table 1. Able-bodied adults completed the same planar reaching task on an identical robot system (n = 22, age: 51.0 ± 15.7; female participants = 45.5%).

For stroke patients, as expected, the more-affected upper extremity reaching trials were less smooth when compared to the less-affected upper extremity reaching trials (Wilcoxon Signed Rank Test, W=−3.49, p<0.001). The more-affected and less-affected upper extremities of stroke patients were also both less smooth when compared to able-bodied reaching (Wilcoxon Rank Sum Test, W=−4.21, p<0.001 and W=−2.55, p=0.011, respectively) (Figure 2A)[61]. Correlations between trial smoothness and time revealed no significant learning effects in any of the groups (ρ=0.07, p=0.505 stroke more-affected upper extremity, ρ=0.13, p=0.354 stroke less-affected upper extremity, and ρ=0.05, p=0.481 able-bodied groups) (Figure S1). There were also no learning effects when examining successful trials only (i.e., trials in which the target was achieved) (see Results in Supplementary Materials).

The more-affected upper extremity reaching trials demonstrated greater IQR (i.e., trial-by-trial variation) compared to the less-affected upper extremity reaching trials (W=3.91, p<0.001). The more-affected and less-affected upper extremities of stroke patients both showed greater IQRs when compared to able-bodied reaching (W=4.73, p<0.001 and W=2.15, p=0.032, respectively). The majority of smoothness variation in all three of these groups was explained by within-participant, trial-by-trial differences as opposed to between-participant differences (intraclass correlation analyses, ICC = 0.34, 0.16, and 0.33 for stroke more-affected, stroke less-affected, and able-bodied groups) (Figure 2B).

For the more-affected upper extremity of stroke patients, there was overall no effect of reaching direction on smoothness, either median or IQR (see Results in Supplementary Materials). The group of patients with moderate-severe motor impairment (FMA-UE < 44, n=7) after stroke had both reduced median smoothness (W=−2.33, p=0.020) and greater trial-by-trial variation (i.e., larger IQR, W=2.82, p=0.005) compared to those with mild motor impairment (FMA-UE ≥ 44, n=15)[47,48]. Notably, even for patients with moderate-to-severe impairment, there was a substantial number of more-affected upper extremity trials that fell within the able-bodied smoothness range (33%). Figure S2 highlights movement trials that fell within and outside the able-bodied smoothness range for one participant with FMA-UE score of 19.

Using Spearman's rho correlations, we found statistically significant associations between smoothness median and IQR with each of the clinical assessments collected acutely, FMA-UE, 9HP, and BBT (Table 2A). In semi-partial correlation analysis, after controlling for the relationships with median smoothness, we found that performance on 9HP and BBT remained significantly associated with smoothness IQR (9HP, ρ = −0.63, p = 0.002; BBT, ρ = −0.55, p = 0.009; Table 2A) and the relationship between FMA-UE and smoothness variability trended toward significance (ρ = −0.41 p = 0.068). In contrast, median smoothness was not significantly associated with any of the clinical assessments after accounting for the relationships with smoothness IQR. We related smoothness after

acute stroke to 90-day clinical outcomes using four separate multivariate linear regressions with 9HP, BBT, FMA-UE or mRS as the dependent variable, and acute smoothness median and IQR (variability) as independent variables. These models explained between 36-62% of variance in 90-day outcomes. Smoothness IQR independently explained variance observed in 90-day 9HP, FMA-UE and mRS scores (Table 2B). Smoothness median was not independently significant in any of these models. When baseline FMA-UE was included as a covariate, the additional variance explained in 90-day outcomes by smoothness median and IQR increased by up to 60% (Table S2). Taken together, these analyses show that acute smoothness is a valuable feature for predicting motor function after stroke; specifically, variability in smoothness is related to clinical assessments, both acutely and with respect to long-term outcomes, beyond what is captured by the median.

Finally, we examined neuroanatomical factors that influenced variability in upper extremity movement smoothness. Stroke lesion-overlap of all participants in this study is shown in Figure 3A. There was no correlation between stroke volume, basal ganglia injury or premotor-M1 injury and movement smoothness median or IQR (Table 3). We found significant associations between the degree of CST injury, as measured by both weighted CST lesion load and normalized maximum CST area overlap, and both smoothness median and variability (Table 3). Specifically, as injury to the CST increased, movements were less smooth, and there was more trial-by-trial variation (Figure 3C).

Discussion

In this study, we evaluated upper extremity movement variability after acute stroke and investigated how this variability contributes to our understanding of post-stroke motor control. We used a planar center-out reaching task on an end-effector robot to assess the more-affected and less-affected upper extremity smoothness of 22 patients after acute stroke compared to able-bodied adults. Our main findings were that (1) smoothness in patients with stroke was more variable than able-bodied movements, for both upper extremities (ipsilesional and contralesional), (2) smoothness variability related to clinical assessments and outcomes, even after controlling for median smoothness, and (3) greater smoothness variability related to a higher degree of injury to the corticospinal tract. Together, these findings emphasize that trial-by-trial variation in movement smoothness of planar reaching contributes valuable information toward understanding motor control after stroke.

Prior work has shown that movement variability is a fundamental aspect of motor control, particularly as related to learning new motor tasks and exploring new motor strategies[8-10,62]. There has been limited prior research on upper extremity movement variability in the context of stroke. The few studies done thus far show that movements are more variable after stroke and that this variability tends to decrease with recovery and rehabilitative training[26,28,63,64]. Here we show that in the case of acute focal injury to the nervous system, more-affected upper extremity (contralesional) reaching movements are not only more impaired overall, but they are substantially more variable. Furthermore, we found that individuals with more severe motor impairment, as measured by the FMA-UE, exhibited greater trial-by-trial variation of smoothness. These findings could indicate that smoothness variability may reflect initial sensorimotor adaptation to stroke-induced motor deficits.

Future studies exploring the relationships between variability and severity of motor deficits in different phases after stroke could help further clarify this hypothesis. Our findings extend prior work that highlights increased variability in post-stroke kinematics[26,28,43,64] by specifically identifying smoothness variability as a potential measure of upper extremity motor impairment post-stroke.

The current standard of care for assessing post-stroke motor ability is to use standardized clinical outcome measures, which are performed by a trained rehabilitation clinician. Earlier studies have demonstrated that kinematic metrics (including smoothness) correlate with clinical assessments[43,49,65-67]. Here we show that both the median and IQR of smoothness relate to clinical measures, providing evidence for smoothness variability's concurrent validity as an objective measure of post-stroke motor ability. Notably, there was a significant relationship between clinical assessments and trial-by-trial variation (IQR), even after controlling for the association with the median smoothness value. The opposite was not true: after controlling for trial-by-trial variation, the association between median and clinical assessments was no longer significant. Thus, the relationship between the clinical measures and smoothness is primarily driven by trial-by-trial variation, further highlighting the value of high-resolution kinematic measures in the assessment of post-stroke movement. Furthermore, we found that smoothness variability measured in the acute phase after stroke significantly explained variance in 90-day outcomes (9HP, FMA-UE and mRS), even when accounting for baseline motor impairment (Table S2). Taken together, this underscores smoothness variability's potential predictive validity for motor recovery.

Patterns of relationships between kinematic and clinical assessments can provide further insights into post-stroke motor control. The center-out reaching task used to capture smoothness variability was performed on the InMotion2 system which requires shoulder and elbow coordination. The Box and Blocks and 9-Hole Peg tests require fine manipulation of blocks and pegs, respectively. The Fugl-Meyer Assessment[47] is primarily an assessment of movements in and out of synergy[68]. We found strong and significant relationships between fine, dexterous object manipulation (BBT and 9HP) and planar movement smoothness (two-dimensional shoulder–elbow coordination) after stroke. The relationship between synergies (FMA-UE) and planar shoulder-elbow coordination was less robust. Our findings thus suggest that the ability to coordinate joint movements, both with the shoulder and elbow during gross reaching movements and fingers during fine object manipulation, are possibly under the same neural control[69]. Further examination of the relationships between specific post-stroke motor behaviors, measured via high-resolution kinematics, and central nervous system injury is an area of future interest to better understand neural control of movement.

We investigated neuroanatomical patterns that could impact variability of upper extremity movement smoothness and found that smoothness variability was related to CST injury. In able-bodied individuals, changes in CST excitability are related to trial-by-trial variation during reach-to-grasp tasks[24,25]. Here, greater stroke-induced injury to the CST led to both more impaired upper extremity movement overall (median smoothness was reduced) as well as to more variable upper extremity movements (smoothness IQR increased). CST injury after stroke thus not only leads to weaker transmission of signals from motor cortical regions to spinal cord, manifesting as greater static impairment, but also to noisier

transmission of those weaker signals, manifesting as greater variability in coordinated multi-joint movements[36,37]. The lack of relationship between smoothness variability and lesion overlap with the basal ganglia or premotor-M1 regions may reflect the nature of the task in this study. Our task required repeated execution of goal-directed reaching rather than motor learning (indeed there was minimal learning observed over trials)[16,20-22]. The lack of relationship with total stroke lesion volume highlights that motor impairments after stroke are more dependent on location rather than total injury[36,70-72]. Future work should explore topography of the CST as related to trial-by-trial variation, as well as other neuroanatomic correlates of variability in upper extremity movement.

We examined whether reaching direction influenced variability in smoothness. On both a group- and individual-level, there were minimal effects of reaching direction on patterns of variability in smoothness of the more-affected upper extremity. Previous studies have found post-stroke direction-dependent differences in smoothness and additional kinematic metrics (e.g., movement time, path length and shoulder-elbow inter-joint coordination) during reaching tasks[44,73]. However, those studies focused on the average values of these metrics (rather than trial-by-trial variation) and participants in the sub-acute[73] and chronic[44] stages of recovery. Thus, the direction-dependent differences may be related to peripheral biomechanical properties of post-stroke upper extremity motor impairment such as spasticity or contractures, which are more prominent later after stroke. Future work should explore trial-by-trial variation in smoothness longitudinally to ascertain if direction-based variability changes with time post-stroke.

The significant variability we observed in upper extremity reaching movements has implications for stroke neurorehabilitation. Brain and spinal cord stimulation have emerged as promising strategies for enhancing motor control and recovery after stroke[74-77]. With each of these central nervous system stimulation strategies, pulses are delivered at high resolution time scales (i.e. on a trial-by-trial basis of movement)[35]. Our observed substantial variability in upper extremity movement after stroke that relates to clinical assessments and neuroanatomical substrates opens the possibility to optimizing stimulation protocols based on trial-by-trial variation[35]. Given that patients with severe stroke motor dysfunction have movements that range from very abnormal to near-normal (at least as quantified by smoothness in this project), adaptive brain stimulation protocols could be tailored to reinforce movement patterns[78,79] during trials that more closely resemble those of able-bodied individuals (e.g., apply brain stimulation during trials that are more “normal” appearing). An alternative strategy could be to apply negatively reinforcing stimulation during trials that are further from normal. Understanding patterns of neural activity (via neuroimaging) associated with kinematic variability is an important next step toward optimizing brain stimulation parameters. Together, our findings of substantial trial-by-trial variability in post-stroke upper extremity movement opens the door to applying real-time kinematic assessment to guide neurotechnological approaches to restoring limb function.

Limitations

There are several limitations to this study. While it served as an important initial investigation, our study had a relatively small sample size. Longitudinal and larger (or

multi-site) studies with harmonized protocols would be especially valuable to (1) understand how variability changes over time as well as for predicting the effect of variability on clinical outcomes, and (2) mitigate data skew (i.e., heteroscedasticity) as seen in smaller datasets. Furthermore, participants only performed the task once thus precluding an analysis of test-retest reliability of smoothness. Future studies should investigate inter-day reliability of movement smoothness. The able-bodied participants used as a control group in this study were younger than the stroke patient population. Future work should collect age-matched control data. Target distances in the center-out task were not adjusted for individual anthropomorphic measures (e.g., arm length); future protocols should standardize distances relative to each subject's proportions. Our study utilized one end-effector robot, the InMotion2. To ensure the generalizability of our results, further sessions could be run with the same protocol using different planar robots (i.e., Kinarm robotic exoskeleton, BKIN Technologies). Ultimately, the clinical utility of kinematic measures for assessment of post-stroke movement will need to account for the cost, time and training associated with these robotic devices. Variability analyses are influenced by the choice of task and kinematic metrics, which can limit the generalizability of these findings. Further work should examine variability in other spatial and temporal kinematic metrics and approaches (e.g., speed, path deviation, average squared Mahalanobis distance) in addition to smoothness to provide additional insights into post-stroke movement dynamics[52]. Furthermore, while 2D kinematics can provide a standardized measure of movement quality post-stroke, planar reaching paradigms are by definition limited (e.g., don't allow for assessment of naturalistic movement or movement during functional tasks)[64,65]. 3D kinematic data captured via motion capture technology (i.e., optical systems or inertial measure units) or higher degree of freedom robots would allow for measurement of more dynamic and functional movements[38,80]. Finally, this study leveraged acute stroke structural imaging. The use of functional and diffusion tensor MRI as well as repeated structural imaging at later time points post-stroke paired with kinematic assessment would be valuable for probing circuits related to movement variability.

Conclusion

Here we showed that trial-by-trial variation in upper extremity movement smoothness in the first week after stroke is related to clinical assessments, recovery at 90 days, and damage to the CST. These results support that high-resolution kinematics provide robust and individualized insights into motor control and outcomes after stroke. Trial-by-trial variation of movement after acute stroke could guide early, personalized, and targeted neurorehabilitation, potentially by optimizing treatment protocols based on observed variability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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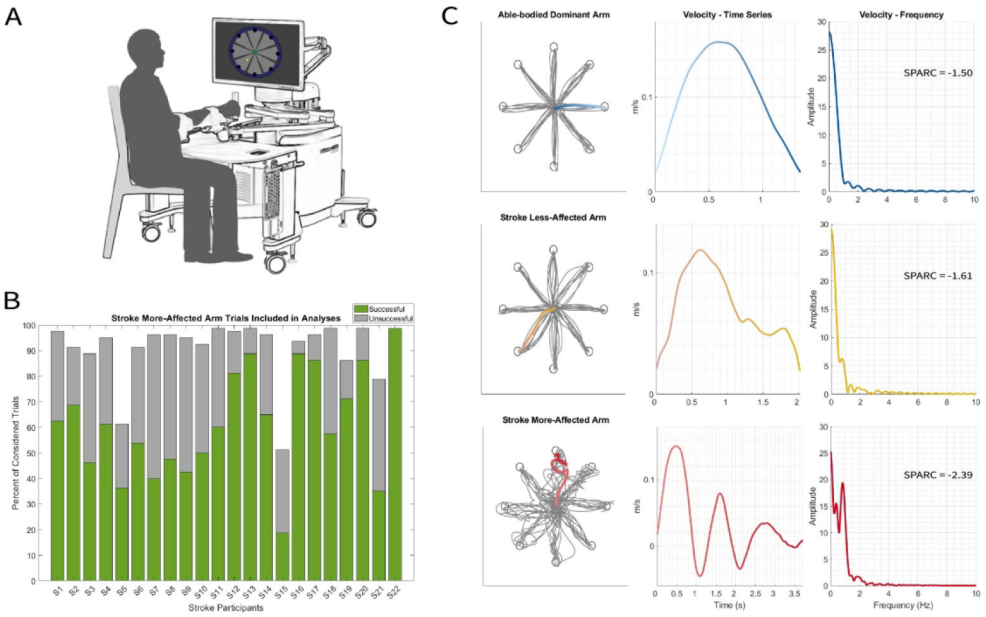

Figure 1.

(A) Schematic of center-out task on the InMotion2 Robotic System. (B) Percent of stroke participants' more-affected upper extremity trials included in analyses. Trials were rejected if they were non-goal directed, ended less than 33% of the target distance, or did not have a movement-end. Trials were defined as successful or unsuccessful depending on whether the movement ended inside or outside the intended target, respectively. Analyses were conducted on both successful and unsuccessful, non-rejected trials. (C) Sample center-out trajectories with accompanying velocity and frequency profiles for an able-bodied adult dominant upper extremity, acute stroke more-affected upper extremity (contralesional), and acute stroke less-affected upper extremity (ipsilesional) trial.

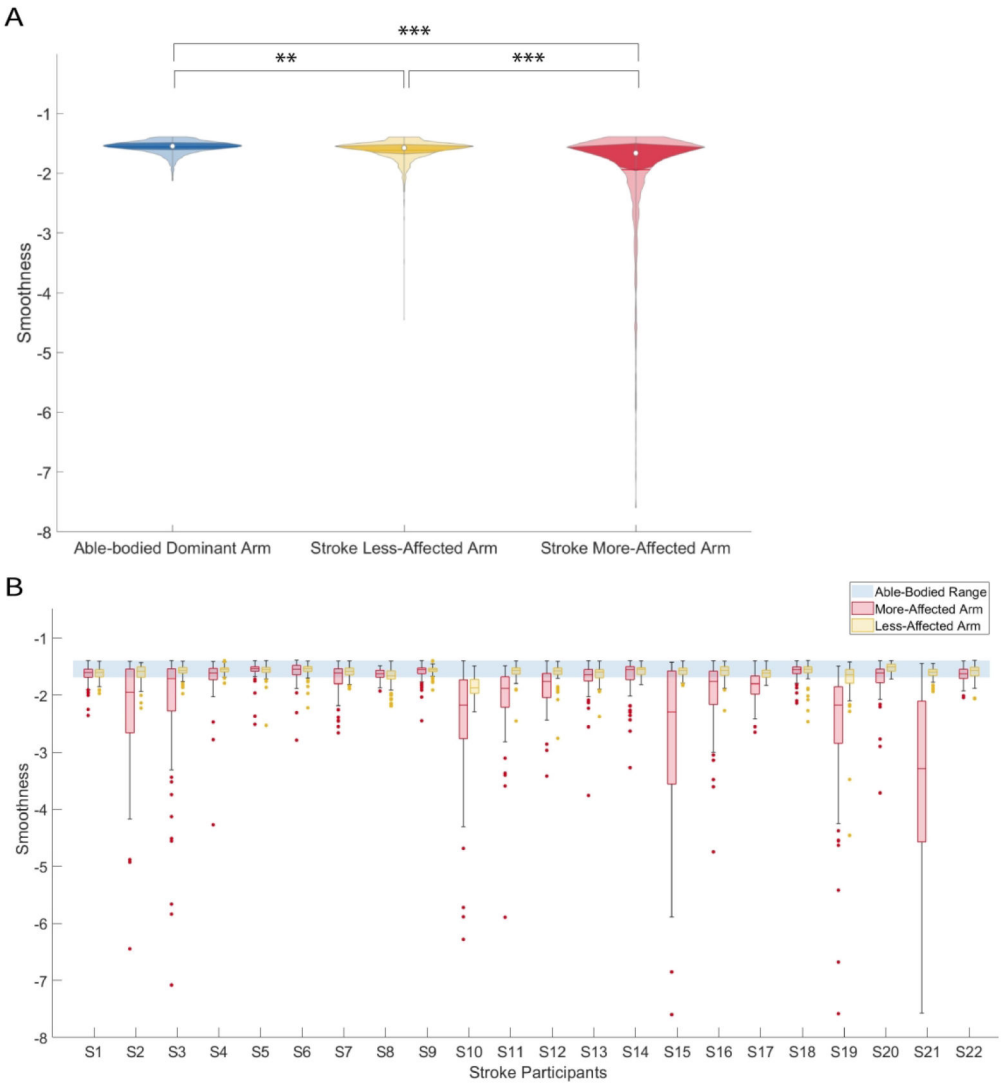

Figure 2.

(A) Violin plots of movement smoothness, as measured by spectral arc length, for able-bodied dominant upper extremity (n=22), acute stroke more-affected upper extremity and less-affected upper extremity (n=22) planar reaching trials. **p=0.01, ***p<0.001. Wider portions of the violin plots indicate a higher percentage of observations. (B) These box plots show the distribution of smoothness values of the more-affected and less-affected upper extremity for each of the 22 stroke patients. The light blue bar represents the able-bodied range of smoothness values.

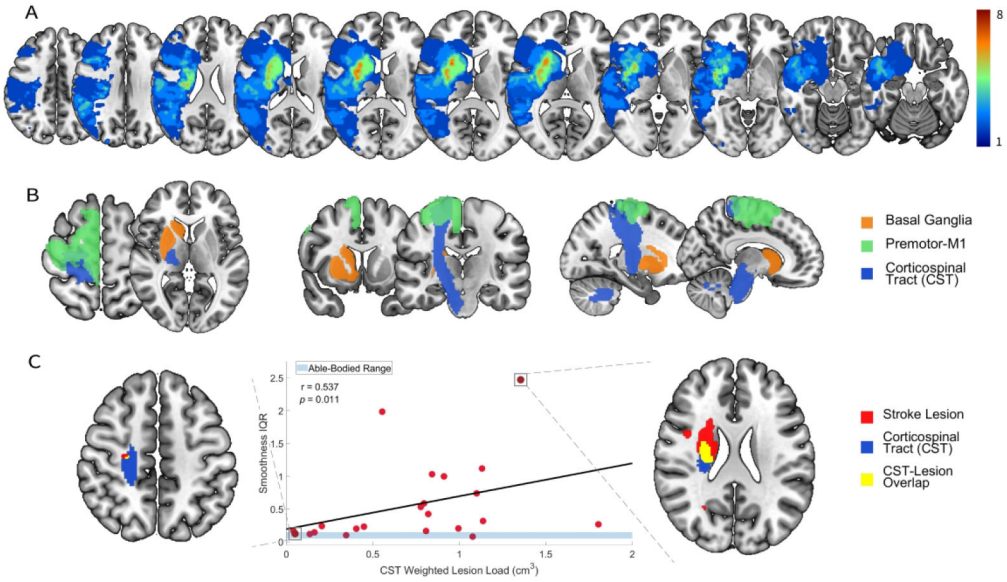

Figure 3.

(A) Total number of lesions included: n = 22. Color bar (right) shows the number of lesions overlapped with dark blue to red showing increasing overlap. (B) Templates of the basal ganglia (orange), premotor-primary motor (M1) cortices (green), and corticospinal tract (blue) used in analyses. (C) Scatter plot of smoothness variability (interquartile range, IQR) vs. corticospinal tract weighted lesion load. The light blue bar represents the able-bodied range of smoothness variability. Two example participants' scores and lesions are highlighted to illustrate the correlation between weighted lesion load and smoothness variability.

Table 1.

Demographics

			Stroke	Able-bodied
No.			22	22
Age, mean ± SD, y			66.3 ± 12.6	51.0 ± 15.7
Days poststroke, mean ± SD, d			4.4 ± 1.7	
Female, n (%)			9 (41)	10 (45.5)
Right-hand dominant, n (%)			19 (86)	21 (95.5)
Affected upper extremity, n (%)				
	Right		10 (45.5)	
	Left		12 (54.5)	
Infarct hemisphere, n (%)				
	Right		10 (45.5)	
	Left		10 (45.5)	
	Bilateral		2 (9)	
Infarct territory, n (%)				
	Middle Cerebral Artery		18 (82)	
		Cortical	6	
		Subcortical	7	
		Mixed	5	
	Posterior Cerebral Artery		1 (4.5)	
	Brainstem		1 (4.5)	
	Multi-territory		2 (9)	

Table 2.

Relationships between Smoothness Metrics and Clinical Scores

A. Spearman Correlations				
		Acute Clinical Outcome Scores		
		FMA-UE	**BBT**	**9HP**
Naïve Correlation	*Smoothness Median*	0.52 (0.012) [a]	0.63 (0.002) [a]	0.59 (0.004) [a]
	Smoothness IQR	−0.66 (0.001) [a]	−0.82 (<0.001) [a]	−0.82 (<0.001) [a]
Semi-partial Correlation	*Smoothness Median*	−0.10 (0.678)	−0.17 (0.458)	−0.26 (0.251)
	Smoothness IQR	−0.41 (0.068)	−0.55 (0.009) [a]	−0.63 (0.002) [a]
Cell values are presented as [Spearman's ρ value (*p*-value)]				
B. Multivariate Linear Regression				
	90-day Clinical Outcome Scores			
	mRS	**FMA-UE**	**BBT**	**9HP**
Intercept	4.20 ± 2.02 (0.055)	28.90 ± 19.29 (0.165)	32.71 ± 38.34 (0.413)	292.08 ± 131.53 (0.051)
Smoothness IQR	1.99 ± 0.85 (0.034) [a]	−14.32 ± 6.02 (0.039) [a]	−24.92 ± 11.97 (0.064)	126.22 ± 41.08 (0.012) [a]
Smoothness Median	2.12 ± 1.35 (0.136)	−20.26 ± 12.49 (0.136)	−12.64 ± 24.83 (0.622)	174.66 ± 85.19 (0.067)
R^2 Value	0.359	0.428	0.617	0.564
p Value	0.036	0.061	0.008[b]	0.016
Cells values are presented as [β (estimated coefficient) ± SE (standard error) (*p*-value)]				

A. Separate naïve and semi-partial Spearman's Correlations were computed between each movement smoothness measure (median or IQR) and each acute clinical assessment. ρ was considered significant if [a]$p < 0.05$. B. Four multivariate linear regression models were computed, each including smoothness median and IQR as independent variables, and one of the four 90-day clinical outcomes as the dependent variable. β was considered significant if [a]$p < 0.05$. Overall regression models were considered significant only if [b]$p < 0.013$ to correct for multiple comparisons.

Table 3.

Neuroanatomical Features: Cohort Range and Spearman's Correlations with Smoothness Metrics

	Range	Spearman's Correlation	
		Smoothness Median	Smoothness IQR
Total Lesion Volume	0.70 – 142.49 cm^3	−0.05 (0.836)	0.25 (0.265)
Basal Ganglia Injury	0 – 15.89 cm^3	0.18 (0.415)	−0.06 (0.785)
Premotor-M1 Injury	0 – 6.02 cm^3	0.17 (0.457)	−0.13 (0.566)
Weighted Corticospinal Tract Lesion Load	0.04 – 1.80 cm^3	−0.49 (0.023) [a]	0.54 (0.011) [a]
Normalized Maximum CST Area Overlap	0.04 – 0.72	−0.43 (0.044) [a]	0.50 (0.017) [a]

Cell values for range are presented as [minimum - maximum values] of the cohort. Cell values for the Spearman's correlation are presented as [Spearman's ρ value (*p*-value)]. ρ values were considered significant if [a] $p < 0.05$.

Stroke Participants

Subject ID	Age	Gender	Days Post Stroke	Stroke Location	More-Affected Side (UE)	More-Affected Arm Smoothness Median	More-Affected Arm Smoothness IQR	Less-Affected Arm Smoothness Median	Less-Affected Arm Smoothness IQR	UE Fugl-Meyer Assessment (Acute)	9-Hole Peg Test (Acute)	Box and Blocks Test (Acute)	Modified Rankin Score (90-day)	UE Fugl-Meyer Assessment (90-day)	9-Hole Peg Test (90-day)	Box and Blocks Test (90-day)
S1	63	M	3	Bilateral multiterritory	L	−1.60	0.14	−1.61	0.13	63	58.03	41	1	64	42.56	52
S2	63	M	8	R MCA mixed	L	−1.95	1.12	−1.58	0.18	42	180	0	2	52	180	16
S3	83	F	3	R MCA subcortical	L	−1.71	0.74	−1.56	0.10	53	180	10	3	55	60.37	30
S4	77	F	5	R MCA mixed	L	−1.62	0.20	−1.55	0.07	64	67.44	20	N/A	N/A	N/A	N/A
S5	38	M	4	L MCA subcortical	R	−1.53	0.08	−1.56	0.09	58	46.98	40	1	65	25.16	54
S6	68	M	8	R MCA cortical	L	−1.54	0.17	−1.54	0.09	55	39.71	32	N/A	N/A	N/A	N/A
S7	58	F	5	Bilateral multiterritory	L	−1.61	0.27	−1.58	0.12	54	68.92	27	0	61	26.49	42
S8	78	M	2	L MCA subcortical	R	−1.62	0.12	−1.66	0.14	60	32.29	44	0	N/A	N/A	N/A
S9	85	F	6	R MCA mixed	L	−1.55	0.10	−1.55	0.06	52	54.52	24	1	N/A	N/A	N/A
S10	67	M	4	R MCA cortical	L	−2.17	1.03	−1.87	0.24	28	180	0	1	65	35.63	36
S11	76	F	2	R MCA subcortical	L	−1.88	0.53	−1.56	0.11	19	180	0	1	54	34.59	44
S12	56	M	4	L MCA cortical	R	−1.76	0.42	−1.57	0.12	42	95.33	15	1	55	31.75	44
S13	78	F	3	L MCA cortical	R	−1.64	0.20	−1.60	0.15	61	36.03	33	N/A	N/A	N/A	N/A
S14	60	M	4	R MCA mixed	L	−1.55	0.23	−1.55	0.12	23	180	0	1	52	62.69	47
S15	79	M	4	Brainstem	L	−2.29	1.98	−1.56	0.11	7	180	0	3	46	108.19	24
S16	77	M	4	L PCA mixed	R	−1.76	0.59	−1.56	0.15	45	180	8	N/A	N/A	N/A	N/A

Subject ID	Age	Gender	Days Post Stroke	Stroke Location	More-Affected Side (UE)	More-Affected Arm Smoothness Median	More-Affected Arm Smoothness IQR	Less-Affected Arm Smoothness Median	Less-Affected Arm Smoothness IQR	UE Fugl-Meyer Assessment (Acute)	9-Hole Peg Test (Acute)	Box and Blocks Test (Acute)	Modified Rankin Score (90-day)	UE Fugl-Meyer Assessment (90-day)	9-Hole Peg Test (90-day)	Box and Blocks Test (90-day)
S17	57	F	2	R MCA subcortical	L	−1.80	0.32	−1.62	0.13	53	54	21	1	N/A	N/A	N/A
S18	41	F	5	L MCA subcortical	R	−1.55	0.12	−1.54	0.11	65	23.39	58	1	58	29.76	41
S19	71	M	8	L MCA subcortical	R	−2.18	1.00	−1.65	0.24	57	124.15	14	3	57	36.84	28
S20	71	F	5	L MCA cortical	R	−1.61	0.24	−1.51	0.12	51	65.47	24	3	N/A	N/A	N/A
S21	64	M	4	L MCA mixed	R	−3.29	2.47	−1.59	0.11	34	180	1	2	N/A	N/A	N/A
S22	49	M	4	L MCA cortical	R	−1.62	0.17	−1.56	0.15	51	28.3	49	2	54	21.6	68
											Units = seconds	Units = # of blocks			Units = seconds	Units = # of blocks

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Able-bodied Participants

Subject ID	Age	Gender	Dominant Arm	Dominant Arm Smoothness Median	Dominant Arm Smoothness IQR
A1	67	M	R	−1.55	0.13
A2	27	M	R	−1.58	0.10
A3	27	M	R	−1.52	0.07
A4	61	M	R	−1.58	0.14
A5	71	M	R	−1.56	0.12
A6	53	F	R	−1.54	0.09
A7	56	M	R	−1.53	0.07
A8	38	M	R	−1.53	0.07
A9	32	M	R	−1.56	0.11
A10	70	M	R	−1.54	0.13
A11	28	F	R	−1.59	0.09
A12	54	M	L	−1.53	0.09
A13	63	F	R	−1.48	0.11
A14	38	F	R	−1.56	0.13
A15	58	F	R	−1.79	0.15
A16	62	M	R	−1.54	0.07
A17	46	F	R	−1.59	0.13
A18	31	F	R	−1.50	0.08
A19	75	F	R	−1.50	0.08
A20	56	M	R	−1.54	0.08
A21	70	F	R	−1.55	0.11
A22	38	F	R	−1.52	0.08