Association Between Gait Asymmetry and Brain Lesion Location in Stroke Patients

Lisa D. Alexander, MPT; Sandra E. Black, MD; Kara K. Patterson, BScPT, MSc; Fuqiang Gao, MD; Cynthia J. Danells, BScPT, MSc; William E. McIlroy, PhD

Background and Purpose—Associations between the site of brain injury and poststroke gait impairment are poorly understood. Temporal gait asymmetry after stroke is a salient index of gait dysfunction that has important functional implications. The current study investigated whether subtraction lesion analysis could distinguish brain regions associated with persisting temporal gait asymmetry in chronic stroke patients.

Methods—Analysis was conducted on 37 chronic ambulatory stroke patients (17 symmetrical gait, 20 asymmetrical gait). Spatiotemporal gait parameters were recorded using an instrumented walking surface. Lesions were traced from 3D T1-MRI, and region of interest images were generated. The lesion overlay of patients with symmetrical gait was subtracted from patients with asymmetrical gait to highlight voxels more frequently lesioned in asymmetrical patients and relatively spared in symmetrical patients.

Results—Demographic data were comparable between the 2 groups. Asymmetrical patients exhibited significantly higher National Institute of Health Stroke Scale neglect scores and more severe motor impairment. Gait asymmetry was significantly correlated to Chedoke-McMaster Stroke Scale leg \((r = -0.767, P<0.001)\) and foot \((r = -0.759, P<0.001)\) scores, whereas gait speed correlated less strongly. After subtraction analysis, injury to the posterolateral putamen was evident 60% to 80% more frequently in the asymmetrical group compared to the symmetrical group.

Conclusions—In this sample of ambulatory chronic stroke patients, damage to the posterolateral putamen was associated with temporal gait asymmetry. Further advances in our understanding of the neural correlates of gait asymmetry may provide prognostic markers for future persistent gait dysfunction and lead to early targeted rehabilitation when key regions are damaged. (Stroke. 2009;40:000-000.)

Key Words: stroke ■ gait ■ MRI ■ rehabilitation ■ putamen

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measures of gait impairment such as speed and energy expenditure in stroke patients. The FIM does not provide any specific information about the “quality” or competency of walking and has a significant ceiling effect for independent ambulators. Achieving independent walking or relatively higher walking speeds does not suggest that walking is “recovered” or “normal.” In fact, persisting challenges in motor control as evidenced by gait asymmetry are very common among stroke patients who are considered independent community ambulators.

As such, an essential element of the present investigation was, as suggested by previous authors, using a primary index of walking competency that reflects an important domain of gait impairment. As an index of impairment, a temporally asymmetrical gait pattern after stroke is associated with minimizing paretic limb single-support time to return to the more stable double-support phases. Measures of temporal symmetry reflect this contribution of each lower limb to walking by accounting for the ratios of paretic and nonparetic limb swing and stance time. Also, well-controlled walking encompasses 4 main elements: (1) adequate progression (velocity), (2) stability control to minimize fall risk, (3) energy efficiency (metabolic cost/endurance), and (4) musculoskeletal injury minimization (shock absorption). There is a clear association between gait asymmetry and the ability to control walking speed. Also, an asymmetrical gait pattern has been shown to have a higher metabolic cost and to increase the risks of articular joint degeneration in the nonparetic lower limb and of bone density loss in the paretic limb. Accordingly, we characterized gait using temporal symmetry measures in the current investigation, as we feel that measures of symmetry better reflect the 4 components of gait control.

Thus, the aim of this investigation was to determine the association between lesion location and gait asymmetry using subtraction lesion analysis, as no previous work provides insight into this specific association. We also examined the relationships between gait speed, symmetry, and motor impairment to further verify the utility of temporal symmetry for quantifying poststroke gait dysfunction.

Methods

Study Participants

A cross-sectional sample of all participants with chronic supratentorial unilateral stroke (≥3 months postictus) and with MRI and gait data available (collected ≥3 months postictus) in a research database of community-dwelling chronic stroke patients was analyzed for this study. Patients were selected solely on the basis of the presence of the abovementioned criteria, without knowledge of their clinical characteristics. Participants provided written informed consent to participate in research studies which were approved by the Research Ethics Board at Sunnybrook Health Sciences Centre. Persons included in the current study walked without human assistance or gait aids, could follow verbal instructions, and reported no premorbid gait impairments.

Impairment Measurements

The foot and leg dimensions of the Chedoke-McMaster Stroke Assessment (CMSA), which is a reliable and valid measure, were used to assess lower extremity impairment. Larger CMSA scores indicate less severe motor impairment and better selective motor control, with 7 indicating no impairment. The National Institutes of Health Stroke Scale (NIHSS), which is also reliable and valid, was used to assess participants’ stroke-related neurological deficits. In the current study, the CMSA was administered by a physiotherapist and the NIHSS was assessed by a physiotherapist, research assistant, stroke nurse, or a stroke neurologist, all of whom were NIHSS-certified.

Spatiotemporal Gait Measures

Spatiotemporal gait parameters were measured using an instrumented walking surface (GaitRite, CIR Systems). The GaitRite mat is 366 cm by 81 cm and contains a grid of sensors that record footfalls. Gait measurements were averaged over 3 trials performed at participants’ preferred walking speed. Based on the previous work of Patterson et al, a temporal symmetry ratio (TSR) for gait was calculated using the following equation:

\[
TSR = \frac{\text{paretic swing time/stance time}}{\text{nonparetic swing time/stance time}}
\]

The occurrence of temporal asymmetry among participants was determined using a 95% confidence interval created around the mean symmetry values for 24 healthy adults (young controls: mean age 32.87±6.36; older controls: mean age 59.22±3.99). There were no age-related differences in symmetry, and so the data for the healthy controls were pooled. A normal TSR range was determined to be 0.9 to 1.1, and asymmetry was defined as a ratio outside of this interval. A TSR greater than 1.1 reflects reduced paretic limb stance time and increased weight-bearing time on the nonparetic limb during ambulation.

Image Acquisition

Anatomic imaging was performed at least 3 months postictus on a dedicated research MRI scanner (1.5 T, GE Medical Systems, software version LX 8.2.5, NV/i hardware platform). High-resolution T1-weighted images were obtained using a standard 3-dimensional fast spoiled gradient-echo anatomic imaging sequence (Repetition time=12.4 ms; Echo time=5.4 ms; Flip Angle, \(\theta = 35^\circ\); Acquisition Matrix=256×192; Slices=124; Slice Thickness=1.4 mm; Field of View=22×16 cm).

Lesion Tracing

Manual image alignment, lesion tracing, and lesion volume calculations were completed using ANALYZE 6.0 software (Biomedical Imaging Resource, Mayo Foundation). Tracing was performed with knowledge of patients’ side of hemiparesis but blind to all other clinical data. Lesions were visually identified as having altered signal intensity in relation to equivalent contralateral tissue. Lesions were traced from digital T1 images by a trained image analyst and confirmed by an experienced research neuroradiologist. Both the dark core and altered perifarct regions were included in the tracing. Lacunes were differentiated from Virchow-Robin vascular spaces in accordance with recommended criteria.

Lesion Analysis

The tracings were coregistered to the Montreal Neurological Institute brain template using 16 nonlinear transformations and cost function masking and region of interest (ROI) images were generated using MRicrho software (www.mricro.com). The proportion of right and left hemisphere lesions was not significantly different between or within groups, so ROI images were transformed to the right hemisphere and overlapped for each group to indicate the frequency of injury for each voxel. This procedure of transferring ROIs to the right hemisphere was performed because the relatively small number of patients in subgroups created for a lateralized evaluation may have reduced the power of lesion overlays. We felt confident that this procedure would not adversely affect our results, given that previous investigations have suggested that lesion laterality has no significant influence on locomotor function or recovery. The Talairach coordinates acquired in MRicrho were used to identify relevant...
Whitney Stroke Assessment. stroke; Location of Lesion.

mensions of the NIHSS, were examined for correlation with gait coefficients. All clinical measures, including each of the 11 subdi-
determined using Pearson correlation or Spearman rank correlation

A total of 37 patients (17 symmetrical gait, 20 asymmetrical
groups were evaluated with independent samples

Statistical Analysis

All statistical analyses were performed using SPSS version 15.0
LEAD Technologies Inc). Each variable was tested for normality
using the Shapiro-Wilks test. Chi-square analysis was used to
compare variable frequencies between groups. Differences between
groups were evaluated with independent samples t tests, or Mann–
Whitney U tests for nonparametric data, and correlations were
determined using Pearson correlation or Spearman rank correlation
coefficients. All clinical measures, including each of the 11 subdi-
ensions of the NIHSS, were examined for correlation with gait
speed and temporal symmetry.

Results

Patient Demographic and Clinical Characteristics

A total of 37 patients (17 symmetrical gait, 20 asymmetrical
gait) were identified for analysis (Table 1). All patients
experienced ischemic stroke, with one case of hemorrhagic
conversion. One patient in the symmetrical group had a
lacunar stroke. Mean age, time of MRI poststroke, and time
of gait assessment were comparable between groups. There
was an equal frequency of right and left hemisphere lesions
between the 2 groups ($\chi^2=0.027$, df=1, $P=0.869$) and within
the symmetrical ($\chi^2=0.059$, df=1, $P=0.808$) and asymmetrical
($\chi^2=0.200$, df=1, $P=0.655$) groups. There was also no
significant difference in the frequency of lesion location
cortical, subcortical, mixed) between the 2 groups

Table 1. Comparison of Demographic and Clinical Features of Patients With Stroke

<table>
<thead>
<tr>
<th></th>
<th>Symmetric</th>
<th>Asymmetric</th>
<th>$P$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>17</td>
<td>20</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.5 (14.4)</td>
<td>50.6 (15.4)</td>
<td>0.052‡</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>11/6</td>
<td>13/7</td>
<td>0.630†</td>
</tr>
<tr>
<td>Side of brain lesion, L/R</td>
<td>9/8</td>
<td>9/11</td>
<td>0.869†</td>
</tr>
<tr>
<td>Location of lesion, C/S/M</td>
<td>2/8/7</td>
<td>1/8/11</td>
<td>0.611†</td>
</tr>
<tr>
<td>MRI time poststroke, mo</td>
<td>19.4 (22.5)</td>
<td>42.0 (40.9)</td>
<td>0.087‡</td>
</tr>
<tr>
<td>Gait assessment time poststroke, mo</td>
<td>38.3 (32.4)</td>
<td>57.7 (53.2)</td>
<td>0.297‡</td>
</tr>
<tr>
<td>NIHSS</td>
<td>1.5 (0–5)*</td>
<td>3 (0–10)*</td>
<td>0.019‡</td>
</tr>
<tr>
<td>NIHSS neglect</td>
<td>0 (0)*</td>
<td>0 (0–2)*</td>
<td>0.012‡</td>
</tr>
<tr>
<td>NIHSS motor leg</td>
<td>0 (0)*</td>
<td>0 (0–1)*</td>
<td>0.125</td>
</tr>
<tr>
<td>CMSA leg</td>
<td>6 (5–7)*</td>
<td>5 (3–7)*</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>CMSA foot</td>
<td>7 (3–7)*</td>
<td>3 (2–6)*</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Lesion volume, cm³</td>
<td>35 (48)</td>
<td>171 (251)</td>
<td>0.141‡</td>
</tr>
<tr>
<td>Speed, cm/s</td>
<td>89.8 (29.8)</td>
<td>58.4 (30.3)</td>
<td>0.003§</td>
</tr>
<tr>
<td>Temporal gait symmetry ratio</td>
<td>1.0 (0.06)</td>
<td>1.89 (0.8)</td>
<td>&lt;0.001‡</td>
</tr>
</tbody>
</table>

Values are mean (SD), except * indicates median (range); Age at time of stroke; Location of Lesion. C/S/M indicates cortical, subcortical, and mixed cortical & subcortical; NIHSS, National Institutes of Health Stroke Scale; CMSA, Chedoke-McMaster Stroke Assessment.

Table 2. Correlations Between Clinical Measures

<table>
<thead>
<tr>
<th></th>
<th>Speed</th>
<th>Temporal Gait Symmetry Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.032 (0.851)*</td>
<td>−0.231 (0.170)</td>
</tr>
<tr>
<td>Side of brain lesion</td>
<td>−0.079 (0.644)</td>
<td>0.114 (0.502)</td>
</tr>
<tr>
<td>NIHSS total</td>
<td>−0.546 (0.001)†</td>
<td>0.477 (0.004)†</td>
</tr>
<tr>
<td>NIHSS neglect</td>
<td>−0.200 (0.264)</td>
<td>0.333 (0.059)</td>
</tr>
<tr>
<td>NIHSS motor leg</td>
<td>−0.399 (0.022)†</td>
<td>0.321 (0.068)</td>
</tr>
<tr>
<td>CMSA leg</td>
<td>0.534 (0.001)†</td>
<td>−0.767 (&lt;0.001)†</td>
</tr>
<tr>
<td>CMSA foot</td>
<td>0.548 (0.001)†</td>
<td>−0.759 (&lt;0.001)†</td>
</tr>
<tr>
<td>Lesion volume, cm³</td>
<td>−0.166 (0.325)</td>
<td>0.180 (0.285)</td>
</tr>
<tr>
<td>Speed</td>
<td>−0.587 (&lt;0.001)</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are Spearman R ($P$ value), except * indicates Pearson R; Age at time of stroke; NIHSS, National Institutes of Health Stroke Scale; CMSA, Chedoke-McMaster Stroke Assessment. †Significant correlation ($P \leq 0.05$).

(χ²=0.985, df=2, $P=0.611$). Mean lesion volumes were larger in the asymmetrical group, and although these differences did not reach statistical significance ($P=0.141$), this relatively low probability value may indicate a trend toward observing significantly larger lesion volumes in asymmetrical patients. The median NIHSS total score for symmetrical patients was significantly lower than the asymmetrical group ($P=0.019$), indicating that on average patients with gait asymmetry were moderately more neurologically impaired; however, neither group would be considered severely neurologically impaired. Among the 11 NIHSS subdimensions between groups, only the neglect score showed a significant difference between groups ($P=0.012$). Median CMSA leg and foot scores were significantly lower in the asymmetrical group ($P<0.001$), indicating that lower extremity selective motor deficits were more severe among asymmetrical patients.

Associations Between Clinical Variables

As shown in Table 2, lesion volume was not significantly associated with speed, symmetry, or CMSA foot ($r=−0.074$, $P=0.682$) or leg ($r=−0.085$, $P=0.639$) scores. The total NIHSS scores were significantly correlated to both speed ($r=−0.546$, $P=0.001$) and gait symmetry ($r=0.477$, $P=0.004$) measures. NIHSS neglect scores also showed a trend toward significant association with gait asymmetry ($r=0.333$, $P=0.059$). Of the 7 patients who exhibited neglect, all belonged to the asymmetrical group. There was also a strong correlation between gait asymmetry and CMSA leg ($r=−0.767$, $P<0.001$) and foot ($r=−0.759$, $P<0.001$) scores, while gait speed correlated less strongly.

Lesion Analysis

The lesion overlay of symmetrical patients revealed an area of overlap in the midcorona radiata (Figure 1a), whereas the overlay of asymmetrical patients showed areas of overlap in the putamen and midcorona radiata (Figure 1b). When the overlay of symmetrical patients was subtracted from asymmetrical patients, an area of peak involvement was identified in the posterolateral putamen (region surrounding Talairach x, y, z = −30, −11, −2; Figure 2a). Lesions involving this
region of the putamen were observed 60% to 80% more frequently in asymmetrical patients than symmetrical patients. Because of the strong correlation observed between temporal symmetry and lower extremity motor impairment, post hoc subtraction analysis was conducted to determine whether these metrics were redundant (providing similar information.) For this additional subtraction analysis (Figure 2b), patients were dichotomized based on leg impairment, specifically those with synergistic movements (CMSA leg ≤5; n=15) and those capable of coordinated and more rapid movements (CMSA leg >5; n=18: missing CMSA values for 4 patients). Lesions involving the external capsule (−31, 7, −7), posterior putamen (−30, −9, −3), and midcorona radiata (−27, −9, 23) were observed 60% to 80% more frequently in patients with more severe leg motor deficits. These differences between subtraction analyses, along with the modest degree of dissociation indicated by the correlation between asymmetry and CMSA leg scores ($r=-0.767$, $P<0.001$), suggest that temporal asymmetry is not solely a product of lesions that impact on lower limb impairment, and that walking competency cannot simply be inferred from limb impairment measures.

Discussion
Advancing our understanding of the neural circuitry involved in human locomotion is of considerable scientific importance, as this may facilitate a melding of clinical and neuroradiological data into targeted rehabilitation programs. Unlike previous studies on the relationship between lesion location and walking function, we used a bottom-up approach where patients were grouped according to behavior (symmetrical versus asymmetrical gait) rather than lesion location. This approach reduced the possibility of overlooking structures outside predetermined regions of interest that could be involved in the control of gait. Our analysis suggests that damage to the inferior portion of the posterolateral putamen is associated with asymmetrical ambulation in the chronic stage of stroke recovery. Based on the findings of Rorden and
Figure 2. a. Subtraction analysis where overlay of symmetrical patients was subtracted from overlay of asymmetrical patients. The colors indicated in the key denote frequencies, where voxels that were more often damaged in asymmetrical patients and spared in symmetrical patients appear toward the yellow end of the spectrum. Voxels that were more frequently damaged in symmetrical patients appear on the blue end of the spectrum. In the enlarged image, the putamen and globus pallidum are outlined in yellow. Lesions involving the posterior putamen were observed 60% to 80% more frequently in asymmetrical than symmetrical patients. b. Overlay of patients with mild leg motor impairment (CMSA leg ≥5) subtracted from patients with more severe impairment (CMSA leg ≤5). Voxels that were more frequently damaged in more severely impaired patients appear on the yellow end of the spectrum. Lesions involving the external capsule, posterior putamen, and midcorona radiata were observed 60% to 80% more frequently in patients with more severe leg motor deficits.
Karnath in which subtraction analysis of a cerebral function with well-known localization (primary visual field defects, VFD) showed that lesions of the optic radiation and primary visual cortex were apparent 60% to 80% more frequently in patients with VFD than those without VFD.29 we suggest that our finding that putaminal lesions were present 60% to 80% more frequently in asymmetrical than symmetrical patients is a clinically relevant result.

Evidence from previous lesion studies lends support to our findings. For example, Chen and colleagues14 found that putaminal lesions greater than 22 cm³ were associated with lower locomotor FIM scores at 6 months poststroke. Similarly, Miyai found that injury to the putamen was associated with poor functional outcome in chronic stroke patients.15 The putamen has long been thought to play a central role in motor control through basal ganglia-thalamocortical circuits.31 The putamen receives projections from the primary motor cortex, premotor areas, supplementary motor area, and primary somatosensory cortex, and projects to the globus pallidus and thalamus.31 Thus, injury to the putamen could disrupt multiple avenues of communication between cortical and subcortical motor areas. Indirect support for the role of the putamen in motor control and ambulation can be gleaned from functional neuroimaging studies. Functional MRI (fMRI) studies have reported putamen activation during active ankle dorsi-flexion in healthy subjects.32 Ankle dorsi-flexion is thought to have reasonable face validity as an activation paradigm for walking, as this movement is a critical component of the healthy gait cycle.32

Although both cortical and subcortical structures are thought to contribute to the control of bipedal walking,32–34 the current analysis identified an association between a focal subcortical structure and gait asymmetry. While this region may play a central role in locomotor movements, it is also possible that the putamen emerged in this analysis because of a difference in potential for recovery after stroke relative to other regions thought to be involved in the control of gait. Functional reorganization after stroke is a commonly-hypothesized phenomenon. It is thought to play an essential role in the functional recovery that occurs during the first 3 to 6 months after stroke through the recruitment of alternative neural pathways.35 Although the recruitment of cortical contralesional sensorimotor areas has been documented after subcortical stroke,35 it is not clear whether subcortical reorganization also occurs after subcortical stroke. In an fMRI study where Luft and colleagues compared brain activation during active knee movements between patients stratified by chronic cortical or subcortical stroke, contralesional activation of the putamen was observed during movement for patients with cortical stroke but not for patients with subcortical stroke.36 This relationship was also demonstrated in a similar fMRI study involving upper extremity movements.37 These authors concluded that brain activation during movement differs between patients with cortical and subcortical stroke, reflecting a relationship between neural network reorganization and lesion location. Perhaps subcortical contralesional structures do not exhibit the same potential for reorganization as cortical areas, which may thereby dampen neuroplastic adaptation and lead to persistent locomotor dyscontrol.

An important aspect of the present study was the use of a specific index of gait control and quality. Our results showed a stronger relationship between temporal gait asymmetry and motor impairment (CMSA) than between gait speed and motor impairment. This finding may be attributable to the paretic lower limb extension and flexion synergies exhibited by some stroke patients during the stance and swing phases of gait respectively. These synergies can provide a relatively stable limb for support and propulsion,9 and may allow a stroke patient with more pronounced selective movement deficits to walk at a similar speed as a patient with fewer deficits. However, movement synergies have a deleterious effect on gait symmetry: patients tend to take relatively small steps with the paretic limb to minimize paretic single-support time and return to the more stable double-support phase, thereby leading to asymmetry.9 Consequently, although gait speed is undoubtedly a relevant functional variable,36 we support the assertion that symmetry may better characterize hemiparetic gait than measures of speed.10,19 Symmetry appears to be more indicative of movement quality10 and has been more closely linked with motor impairment (selective movement deficits).10,19

Another notable finding in the current investigation was the trend toward significant association between temporal gait asymmetry and neglect. This finding is similar to that of Kollen et al.39 who found that visuospatial inattention was negatively correlated with gait recovery in the first year after stroke. Patients with neglect often demonstrate small limits of standing postural stability (impaired weight-shifting) and a static weight-bearing asymmetry where more weight is shifted toward the nonparetic leg.40 During a dynamic activity such as ambulation, this “favoring” of the nonparetic leg could manifest as temporal gait asymmetry.

Given that neuroimaging data are beginning to have more influence on rehabilitation practices,41 our results may have considerable clinical implications. For instance, during the early stages after stroke when the most recovery may be possible,3,11 patients with putaminal lesions, and perhaps those with neglect, may particularly benefit from gait retraining, as these patients may be the most at risk for developing persisting gait asymmetry. Chronic gait asymmetry poses a risk to patients because the increased weight bearing and propulsional demands placed on the nonparetic lower limb may increase the potential for developing musculoskeletal injury and articular joint degeneration.10 Although there is debate regarding which treatment strategies may improve symmetry, several treadmill training techniques have reported improvements in symmetry for persons with stroke.42–44 Along with improving symmetry, gait training techniques with an aerobic component offer additional benefits such as increasing ambulatory endurance,45 which has been shown to be significantly reduced in persons with stroke.4
the subcortical structure implicated in our analysis is relatively symmetrical in size and location within both hemispheres. Another possible limitation was that transforming lesions to the right hemisphere may have obfuscated the relationship between neglect and asymmetry. However, given that there was an equal number of right and left hemispheric lesions in the asymmetrical group and that lesions involving the putamen were found to be up to 80% more frequent in asymmetrical patients, it can be deduced that lesions involving the putamen (and not simply regions associated with neglect) contributed to asymmetry in patients with right hemispheric lesions.

The relationship between lesion location and poststroke gait impairment requires further study. Future investigations with a larger sample size could allow for the analysis of lesions using voxel-based lesion-symptom mapping. Also, future studies could include measures such as proprioception, vestibular dysfunction, spasticity, clonus, and visuospatial perception to help determine further clinical correlates of gait asymmetry in stroke patients using multivariate analysis.

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Disclosures

None.

References


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