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Brain mapping for long-term recovery of gait after supratentorial stroke

A retrospective cross-sectional study

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Abstract

The recovery of independent gait after stroke is a main goal of patients and understanding the relationship between brain lesions and the recovery of gait can help physicians set viable rehabilitation plans. Our study investigated the association between variables of gait parameters and brain lesions.

Fifty poststroke patients with a mean age of 67.5 ± 1.3 years and an average duration after onset of 62.2 ± 7.9 months were included. Three-dimensional gait analysis and magnetic resonance imaging were conducted for all patients. Twelve quantified gait parameters of temporal-spatial, kinematic, and kinetic data were used. To correlate gait parameters with specific brain lesions, we used a voxel-based lesion symptom mapping analysis. Statistical significance was set to an uncorrected P value $<.005$ and cluster size >10 voxels.

Based on the location of a brain lesion, the following results were obtained: The posterior limb of the internal capsule was significantly associated with gait speed and increased knee extension in the stance phase. The hippocampus and frontal lobe were significantly associated with cadence. The proximal corona radiata was significantly associated with stride length and affected the hip maximal extension angle in the stance phase. The paracentral lobule was significantly associated with the affected knee maximal flexion angle in the swing phase and with the affected ankle maximal dorsiflexion angle in the stance phase. The frontal lobe, thalamus, and the lentiform nucleus were associated with kinetic gait parameters.

Cortical, proximal white matter, and learning-related and motor-related areas are mainly associated with one's walking ability after stroke.

Abbreviations: 3DMA = three-dimensional motion analysis, MRI = magnetic resonance imaging, ROI = region of interest, VLSM = voxel-based lesion symptom mapping.

Keywords: brain mapping, gait, rehabilitation, stroke rehabilitation, stroke

1. Introduction

Approximately one-third of stroke survivors are unable to walk 6 months after stroke.[1] The degree of walking deficit following stroke can vary widely because human walking is a complex task that is controlled by numerous different muscles, as well as the skeletal and nervous system.[2,3] The ability to walk is an important part of returning to one's home and community after stroke.[4] Therefore, a better understanding of the relationship between walking outcome and stroke lesions would help physicians to develop the most effective therapeutic program after stroke.

The relationship between stroke lesion and walking outcome remains unclear. Previous studies reported the relationship between corticospinal tract damage and leg weakness,[5,6] functional ambulation category[7] or walking speed.[6,8] Other studies showed that damage to the putamen, insula, and external capsule were related to gait asymmetry,[9] and that damage to the putamen was related to walking speed.[1] However, these studies were limited to a clinical category or gait parameter. Because gait is a complex process, a single parameter is not enough to evaluate the relationship between the brain lesion and walking function, and therefore, various quantitative parameters must be taken into consideration.

Three-dimensional (3D) motion analysis (3DMA) is an accurate system for quantitatively measuring the spatiotemporal,

Editor: Peipeng Liang.

This study was supported by a VHS Medical Center Research Grant, Republic of Korea (VHSMC 17017). This study was supported by grants from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (HWK: 2016 R1A2B4015878).

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:16(e0453)

Received: 18 December 2017 / Received in final form: 7 March 2018 / Accepted: 22 March 2018

http://dx.doi.org/10.1097/MD.0000000000010453

kinematic, and kinetic gait parameters. Prior studies have shown the classification of poststroke gait patterns and treatment effects for gait function using 3DMA.[9,10] However, there is no report on the association between the stroke lesion location and gait parameters measured by 3DMA. Therefore, the purpose of this study was to determine whether any measures of spatiotemporal, kinematic, and kinetic gait parameters were related to patients' brain lesion.

2. Methods

2.1. Subjects

This study retrospectively reviewed the medical records of patients with stroke who were admitted to our hospital between January 2014 and December 2016. Among 124 potential subjects, 50 poststroke patients who met the following inclusion and exclusion criteria were enrolled. Inclusion criteria were as follows: patients with first-ever unilateral stroke confirmed by computed tomography or magnetic resonance imaging (MRI), those with supratentorial stroke, patients aged at least 18 years old, those who could perform independent gait for at least 10 m for 3DMA, patients who underwent MRI and 3DMA within a 2-week interval, at least 6 months after the onset of stroke, and those with stroke onset at least 6 months prior to study enrollment. Exclusion criteria were as follows: patients with infratentorial stroke and those with coexisting neurological and/or orthopedic disease that could influence gait function. Age-matched healthy control subjects without neurological or musculoskeletal disorders were enrolled for the comparison of 3DMA data.

The institutional review board at our hospital approved the procedures and protocols of this study (approval no. 2016-09-004). The institutional review board committee waived the requirement for informed consent given the retrospective nature of the study.

2.2. MRI acquisition

All images were acquired using a 3-Tesla clinical whole-body magnetic resonance scanner (Siemens, Erlangen, Germany) using a 20-channel head coil. A high-resolution three-dimensional T1-weighted image was obtained in all patients. The 3D T1-weighted image parameters were as follows: repetition time/echo time = 1900/2.57 ms, matrix = 256×256, field of view = 230×230 mm^2, flip angle = 9, and slice thickness = 1 mm.

2.3. 3DMA

Gait analysis was conducted using an 8 infrared, 60-Hz camera motion analysis system (Motion Analysis Corp, Santa Rosa, CA) and 3 force plates (sampling rate 1200 Hz; Kistler Corp, Amherst, NY). Reflective markers were placed on predefined anatomical landmarks of the pelvis, thigh, knee, shank, and foot.[11] Simultaneous recordings of the spatiotemporal and lower extremity kinematics, and kinetics (foot-floor contact patterns) were obtained as patients walked 6 m barefoot at their self-selected walking speed. Joint kinematics and external moments were calculated by the Cortex program (Motion Analysis Corp). Ground reaction forces were normalized to body weight while joint moments were reported as Nm/kg. This study used the following 12 specific variables: spatiotemporal domain-walking speed (cm/s), stride length (cm), and cadence (steps/min); kinematic domain-affected hip maximal extension angle in stance phase, affected knee maximal extension angle in stance phase, affected ankle maximal dorsiflexion angle in stance phase, affected hip maximal flexion angle in swing phase, affected knee maximal flexion angle in swing phase, and affected ankle maximal dorsiflexion angle in swing phase; and kinetic domain-affected hip maximal extensor moment, affected knee maximal extensor moment, and affected ankle maximal plantar flexor moment.

2.4. Voxel-based lesion symptom mapping and statistical analyses

For the voxel-based lesion symptom mapping (VLSM) analysis, we performed the following procedures. First, the lesion of each patient was drawn on the high-resolution T1-weighted image in the native space using MRIcro software (http://www.mricro.com). Second, images of 22 patients with lesions in the right hemisphere were flipped to locate the lesion area of all patients within the left hemisphere to create a lesion-overlapping map and conduct statistical comparisons. Third, each individual's T1-weighted image and native-space lesion image were nonlinearly transformed to the standardized Montreal Neurological Institute space using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Lastly, VLSM uses the lesion status at each voxel as a grouping variable, and then it compares the lesioned and nonlesioned groups for all dependent variables using a custom MATLAB script. At each voxel, we performed an independent sample *t*-test to identify differences in gait parameters between the lesion and nonlesion regions. Significant brain regions were determined at a threshold of cluster-level corrected $P < .05$, which corresponded to a voxel-level threshold $P < .005$ and cluster size $k > 21$ voxels. The cluster size was determined through a Monte Carlo simulation using AFNI's 3dClustSim program (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) with 10,000 iterations.[12] Analysis between patients' and normal control group was performed using an independent *t*-test. Significance level was $P < .05$.

2.5. Post-hoc analysis for the lesion associated with walking speed

Post-hoc analysis was performed for the contradicted results to evaluate the association between stroke lesion and walking speed. All patients were divided into the lesioned or the nonlesioned group according to whether their lesion occupying more than 1 voxel overlapped with the walking speed-related brain regions. We compared our 12 specific variables between lesioned and nonlesioned groups using an independent *t*-test. The level of significance was set to a P value $<.05$.

2.6. Reliability study

To test reliability of the drawn lesion regions of interest (ROIs), an expert physician with experience in assessing brain MRIs depicted the ROIs for lesions twice for each individual using the T1-weighted images. Subsequently, we computed the volume and the center of mass coordinates and performed intraclass correlation analysis using these measures.

3. Results

3.1. Sample characteristics

Patients' mean (± standard error) age was 67.5 ± 1.3 years and the average duration after stroke onset to study enrollment was 62.2 ± 7.9 months. The mean lesion volume was $31.9 \pm 6.7\,cm^3$

Table 1

General characteristics and gait analysis variables of the included patients.

	Patients	Control	*P* value
Age, y	67.5±1.3	64.8±1.5	.197
Sex (male: female)	50: 0	50: 0	
Height, cm	165.3±0.9	166.4±1.1	.294
Weight, kg	67.1±1.3	66.5±1.2	.187
Affected hemisphere (Rt: Lt)	22: 28		
Ischemia: haemorrhage	46: 4		
ACA/MCA/PCA/Lacunar infarction	5/32/6/3		
BG/thalamic hemorrhage	2/2		
Disease duration, mo	62.2±7.9		
Spatiotemporal parameters			
Speed, cm/s	48.9±3.1*	93.2±2.7	<.001
Stride length, cm	64.3±3.0*	107.8±2.4	<.001
Cadence, steps/min	92.4±4.6*	103.4±1.5	<.001
Kinematics			
Maximal hip Ex in ST, degree	14.7±1.4*	-15.9±1.2	<.001
Maximal knee Ex in ST, degree	18.0±1.7*	2.1±1.0	<.001
Maximal ankle DF in ST, degree	11.8±0.8*	17.3±0.8	<.001
Maximal hip Fl in SW, degree	39.6±1.2*	25.2±1.4	<.001
Maximal knee Fl in SW, degree	53.2±1.8	50.8±1.3	.284
Maximal ankle DF in SW, degree	7.7±1.2*	4.4±0.6	.013
Kinetics			
Maximal hip Ex moment, Nm/kg	0.5±0.1*	0.7±0.4	.003
Maximal knee Ex moment, Nm/kg	0.9±0.1*	0.4±0.2	<.001
Maximal ankle PF moment, Nm/kg	0.7±0.1*	0.1±0.1	<.001

Values are presented mean±SE.
ACA=anterior cerebral artery, BG=basal ganglia, MCA=middle cerebral artery, PCA=posterior cerebral artery.
* $P < .05$ versus control group.

(range 2.2–222.9 cm^3). Twenty-two strokes occurred in the right hemisphere, and 28 occurred in the left hemisphere. Five of 46 ischemic stroke patients were administered tissue plasminogen activators. Forty-seven of 50 patients were placed under inpatient rehabilitation programs during the subacute phase for 3 months, and 21 patients resumed outpatient rehabilitation programs at least twice a week after inpatient rehabilitation. The mean gait velocity was 48.9±3.1 cm/s. All variables of 3DMA except maximal knee flexion angle in swing phase were significantly worse than normal control group. Detailed data of patients and control participants are summarized in Table 1. Figure 1 summarizes the lesion data.

3.2. Associations between the lesion location and temporal-spatial gait parameters

Lesions in corona radiata and posterior limb of the internal capsule were significantly associated with an increased walking speed (corrected $P < .05$; Table 2, Fig. 2A). A lesion in the hippocampus was significantly associated with a decreased cadence but a lesion in the frontal lobe was significantly associated with an increased cadence (corrected $P < .05$; Table 2, Fig. 2B). Lesions in the proximal corona radiata were significantly associated with an increased stride length (corrected $P < .05$; Table 2, Fig. 2C).

3.3. Associations between the lesion location and kinematic gait parameters

A lesion in the proximal corona radiata was significantly associated with increased hip extension in the stance phase (corrected $P < .05$; Table 2, Fig. 2D). A lesion in the posterior limb of the internal capsule was significantly associated with increased knee extension in the stance phase (corrected $P < .05$; Table 2, Fig. 2E). A lesion in the paracentral lobule, including the cortical area, was significantly associated with decreased ankle dorsiflexion in the stance phase and knee flexion in the swing phase (corrected $P < .05$; Table 2, Fig. 2F, G). No lesion was significantly associated with the affected hip maximal flexion angle in the swing phase or affected ankle maximal dorsiflexion angle in the swing phase (corrected $P < .05$).

3.4. Associations between the lesion location and kinetic gait parameters

A lesion in the frontal lobe was associated with increased hip and ankle moment (corrected $P < .05$; Table 2, Fig. 2H, J). Lesions in

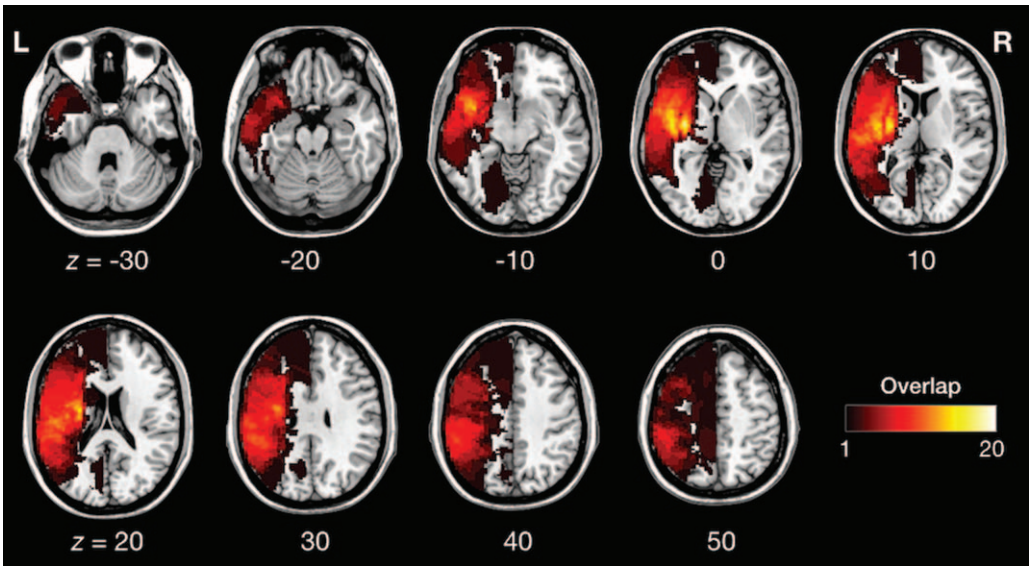

Figure 1. Overlap map showing the lesion location in the 50 patients with stroke. A T1-weighted template is used to demarcate the lesions of each patient. Warmer colors indicate greater lesion overlap. z, Montreal Neurological Institute z coordinates (units: number of patients with a lesion in this region).

Table 2

Results of the voxel-based lesion symptom mapping analysis correlating with gait analysis variables.

	Cluster size	Px	Py	Pz	Max T	Location
Temporo-spatial parameters						
Speed	49	−22	−26	12	7.37	Corona radiata, posterior
Cadence	78	−24	−16	4	3.86	Hippocampus
	37	−18	24	22	2.57	Frontal lobe
Stride length	43	−64	−50	20	3.56	Parietal lobe
	25	−46	−40	46	2.89	Inferior parietal lobule
	56	−18	−26	34	3.03	Corona radiata
	22	−26	−28	12	2.92	Corona radiata, posterior
Kinematic parameters						
Hip Ex in ST	56	−18	−26	34	2.78	Corona radiata, posterior
Knee Ex in ST	39	−26	−16	18	3.43	Internal capsure, posterior limb
Ankle DF in ST	275	−36	20	36	3.02	Frontal lobe
	64	−14	−4	48	3.31	Frontal lobe
	32	−20	−50	58	3.31	Parietal lobe
	122	−52	−50	16	2.85	Superior temporal gyrus
Knee Fl in SW	391	−26	−2	46	3.42	Frontal lobe
	62	−18	−40	52	3.20	Parietal lobe
Kinetic parameters						
Hip moment	527	−20	36	12	5.37	Frontal lobe
	34	−44	−68	26	3.89	Angular gyrus
	37	−28	−14	28	3.74	Corona radiata
Knee moment	27	−14	−20	0	4.47	Thalamus
	68	−14	0	−8	2.86	Lentiform nucleus
	439	−20	36	12	4.05	Frontal lobe
Ankle moment	38	−40	26	42	4.05	Frontal lobe
	47	−20	10	30	4.05	Corona radiata

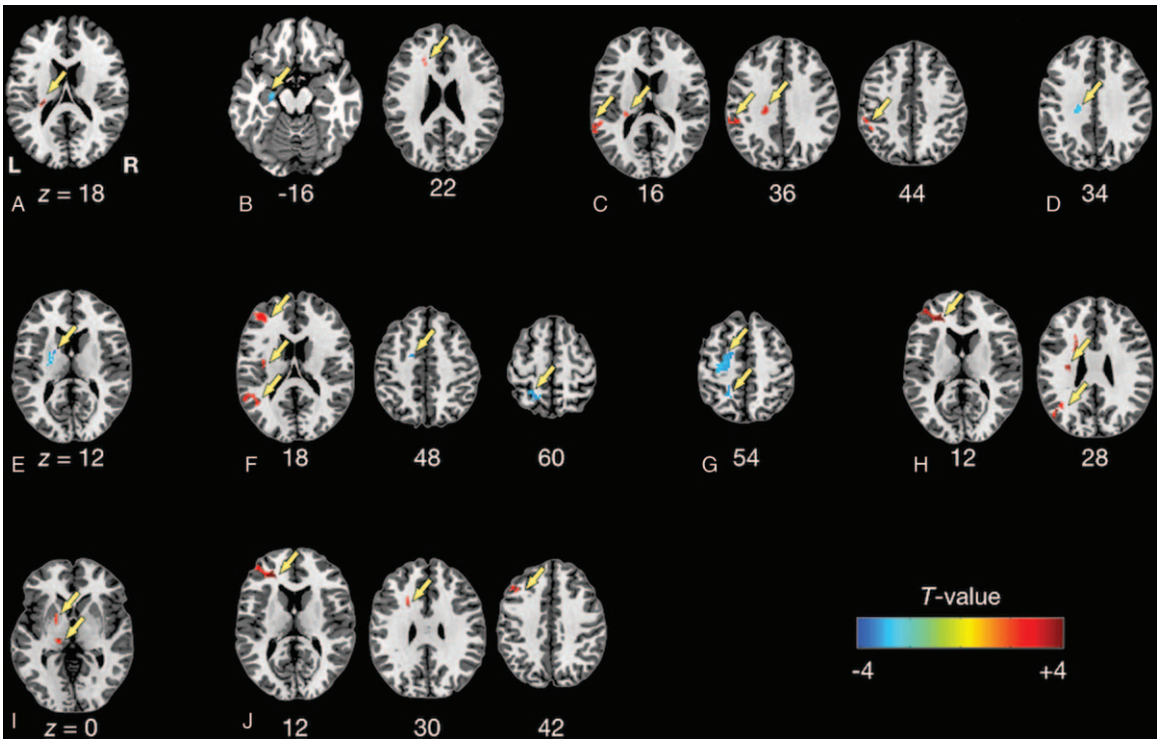

Figure 2. Voxel-based lesion symptom mapping associated with spatiotemporal, kinematic, and kinetic gait parameters. A, velocity; B, cadence; C, stride length; D, affected hip maximal extension angle in stance phase; E, affected knee maximal extension angle in stance phase; F, affected ankle maximal dorsiflexion angle in stance phase; G, affected knee maximal flexion angle in swing phase; H, affected hip maximal extensor moment; I, affected knee maximal extensor moment; J, affected ankle maximal plantarflexor moment. z, Montreal Neurological Institute z coordinates. Statistical threshold: corrected $P < .05$. Arrows colored in yellow indicate the brain regions showing significant differences in gait variables between lesion and nonlesion groups.

Table 3

Post-hoc analysis of speed-related brain region.

	Lesioned	Nonlesioned
Spatiotemporal parameters		
Speed, cm/s	54.2±6.0	47.1±3.6
Stride length, cm	70.9±5.9	63.0±3.4
Cadence, steps/min	101.6±13.7	89.4±3.9
Kinematics		
Maximal hip Ex in ST, degree	11.0±3.2	15.9±1.6
Maximal knee Ex in ST, degree	16.3±2.7	18.6±2.2
Maximal ankle DF in ST, degree	10.9±1.3	12.1±1.0
Maximal hip Fl in SW, degree	38.5±2.9	40.0±1.3
Maximal knee Fl in SW, degree	54.4±3.3	52.8±2.2
Maximal ankle DF in SW, degree	6.9±2.2	8.0±1.4
Kinetics		
Maximal hip Ex moment, Nm/kg	0.4±0.1	0.5±0.1
Maximal knee Ex moment, Nm/kg	1.1±0.2	0.9±0.1
Maximal ankle PF moment, Nm/kg	0.7±0.1	0.8±0.1

Lesioned, patients lesioned in speed-related brain region; nonlesioned, patients without lesioned in speed-related brain region.

the thalamus and lentiform nucleus were associated with increased knee moment (corrected $P < .05$; Table 2, Fig. 2I).

3.5. Results of post-hoc analysis between the lesioned and nonlesioned groups in walking speed-related brain regions

Results of post-hoc analysis did not reveal any significance between lesioned and nonlesioned groups in walking speed-related brain regions ($P > .05$). The stride length and step length tended to be longer in the lesioned group than the nonlesioned group. Most of the kinematic and gait parameters tended to be worse in the lesioned group than in the nonlesioned group, except affected knee maximal flexion in the swing phase and affected knee maximal knee extensor moment (Table 3).

3.6. Reliability results for region of interest

According to the intraclass correlation analysis, the lesion ROIs that were used for group-level inference were highly reliable (ICC>0.95, $P < .001$).

4. Discussion

Knowledge of the association between stroke lesion and walking outcome is important to target rehabilitation goals after stroke.[13] Unlike previous studies using the clinical categorization of gait with the clinical evaluation of lower extremity function,[1,9,14] we used 3DMA to assess walking characteristics in detail. The corona radiata was a common region for spatiotemporal and kinematic parameters. Furthermore, brain regions of motor regulation were associated with kinetic parameters.

Most functional recovery occurs within 6 months poststroke onset and the gait pattern after stroke changes completely during recovery.[10,15] The average period after onset in our patients was 62.2 months (Table 1), so their functional recovery and adaptive processes reached a plateau at the point of inclusion in this study. The results of this study should be carefully interpreted because we analyzed the association between the injured brain lesion for chronic stroke and final walking characteristics. Furthermore, all patients could walk at least 10 m independently; therefore, the results do not refer to the ability to walk alone, but rather take into consideration the compensatory walking pattern after stroke. The lesion associated with worse gait parameters was regarded as a critical area in which other intact brain regions could not compensate for the functional loss. Furthermore, we also analyzed the lesions associated with increased walking speed to identify the gait patterns able to compensate for the patients' disability.

The interesting finding of this study is the association between increased walking speed and the lesions in the corona radiata and posterior limb of the internal capsule through which pass the lower leg fibers.[16,17] The post-hoc analyses demonstrated that the lesioned group had better cadence, stride length, and maximal knee flexion in the swing phase even if most of the kinetic parameters were worse than in the nonlesioned group (Table 3). The possible explanation for this may be that the recovery process of lower leg fibers archived their self-selected walking speed fast. The recovery mechanisms following corticospinal tract injury are still unclear but thought to involve subcortical reorganization. Although the subcortical lesion areas have less recovery potential than cortical lesion areas, subcortical lesions may occur after stroke.[9,18] The bilateral hemispheric connection in the lower legs may also influence the recovery mechanisms. Most previous studies have reported that corticospinal pathway injury correlates with poorer upper extremity motor function in post-stroke patients,[7,19] but not with gait function.[6,8,14] The bilateral connection in the lower legs may reinnervate in 2 ways, either by connecting with ipsilesional fibers or by connecting with contralesional fibers, and this process may result in compensatory gait pattern after injury of the corona radiata and posterior limb of the internal capsule. The better knee flexion in the swing phase was one of the compensatory motions in the lesioned group, which connects with longer stride length and increased cadence (Table 3). The flexion angle in the affected side is mainly influenced by muscle weakness with extension synergies after stroke.[9,20] The lesioned group may compensate the injury of lower leg fibers with various recovery processes and less extension synergy linked with better walking speed. However, these contradictory results could not be fully explained by the results of this study, and therefore additional studies specifically addressing this point are warranted.

The lesion in the hippocampus was associated with decreased cadence. Our results are consistent with those of previous studies showing that the hippocampus is a key human brain region involved in memorization and locomotion.[21,22] Functional MRI studies have implicated the hippocampus in walking,[23,24] and the hippocampus is known to store the motor patterns that are recalled during walking.[22] One study demonstrated that the value of cadence was maintained during aging even if the other gait parameters had a decreasing trend.[25] This phenomenon could be explained by the fact that the cadence is affected by the individuals' experience and learning. The hippocampus is involved in learning and may have crucial roles in terms of cadence that could not be replaced by any other intact brain regions. However, a lesion of the frontal lobe was associated with increased cadence. The frontal lobe plays important roles in the execution of gait initiation and motor programs of voluntary movements.[26,27] The main regions reported supplementary motor area and premotor area in frontal lobe,[3,27] but the exact role of a specific small lesion in frontal lobe to gait recovery is still unknown. Further study is needed for the interpretation with our results.

Stride length and hip extension were mainly associated with the proximal corona radiata, which passes lower leg fibers.[16,17] Our

results are in line with those of previous studies reporting a positive correlation between maximal hip extension and stride length.[20,28] Stride length, especially, depends on muscle strength and the weight-supporting capacity of the affected limb. Since the single support time of the affected side is significantly shorter than the unaffected side after stroke, a shorter single support time reduces the maximal hip extension in the stance phase. Furthermore, reduction of the maximum hip extension in the stance phase decreases the stride length.[9,20] Numerous complex structures, including the corticospinal tract, may be involved in asymmetric walking after stroke. Alexander et al[9] reported that damage to the external capsule, putamen, and insula was related to gait asymmetry, whereas lesions in the corona radiata and basal ganglia were also demonstrated to be associated with lower extremity motor impairments.[14] Our results indicated that the increase of maximum hip extension with stride length consistently correlated with the proximal corona radiata. As we previously discussed, with increased walking speed, the proximal corona radiata may have similar recovery mechanisms, and this area may have residual potential for recovery probably because it is near the cortex.[18]

The paracentral lobule, including the cortical area, was mainly associated with decreased ankle dorsiflexion in the stance phase and reduced knee flexion in the swing phase. The 2 main factors affecting gait performance are diminished muscle strength and abnormal muscle tone.[20] Decreased knee flexion in the swing phase and decreased ankle dorsiflexion in the stance phase are typical subtypes of poststroke gait patterns.[20,29] These phenomena are usually caused by increased muscle tone, especially of the ankle plantarflexor muscle in the stance phase and knee extensor muscle in the swing phase. The onset of spasticity after stroke is highly variable, but tends to occur shortly after or approximately 1 year after stroke.[30] The mechanism of spasticity is still unclear, but elimination of the inhibitory signal of upper motor neurons causes over-activation of spinal motor neurons in the chronic stage of upper motor lesions.[31] The result of this study is consistent with that of past studies reporting that an association of spasticity with the gray matter includes the corticospinal tract pathway.[32]

Moments of the hip, knee, and ankle joints were associated with multiple brain areas. Interestingly, certain areas are consistently related to motor regulation, and these include the frontal lobe and basal ganglia. Hip and ankle moments were significantly related to the frontal area, whereas knee moment was associated with the thalamus and lentiform nucleus. The slow walking speed group of poststroke patients had increased extensor moment,[20] thus the deficit of motor planning and regulation may have affected gait velocity in our results. As kinetic variables are the cause of the kinematic and temporal-spatial parameters of gait, further studies are needed to confirm these results.

There were limitations of this study that should be considered when interpreting the results. First, our study had a relatively small sample size, with heterogeneity in initial stroke severity, onset duration, intensity of rehabilitation training, and etiology. We also flipped all images to visualize the lesion within left hemisphere; thus, the contribution of laterality to gait function is still unclear. Future studies are required to investigate these aspects. Second, our study included only male patients because of our institutional characteristics. Because the gait characteristics between men and women are different in many clinical study populations, the generalizability of our results to all populations remains uncertain. Third, we used the MNI template for the process of VLSM analysis, but it was developed based on subjects in Western countries. Because of the morphological difference between east Asian and western populations,[33,34] future study will be needed to use Asian specific brain template. Fourth, our study had a retrospective cross-sectional design. To understand the role of rehabilitation training on the prognosis of locomotion in further detail, a prospective, longitudinal study is required. However, this is the first study on brain mapping of walking function using the quantitative parameters of 3DMA.

5. Conclusion

Mainly the cortical and corticospinal tract lesions for lower extremities are associated with spatiotemporal and kinematic variables of gait after stroke. The roles of these areas for gait could be replaced after recovery; however, the hippocampus may not be replaced by any other recovery mechanisms. Furthermore, motor regulation-related areas may affect joint moments during gait after stroke.

Author contributions

Data curation: Dae Hyun Kim, Suk Jung.
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Visualization: Dae Hyun Kim.
Writing – original draft: Dae Hyun Kim.
Writing – review & editing: Hyong Keun Cho, Hye Won Kim.

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