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Neuronal injury in the motor cortex after chronic stroke and lower limb motor impairment: a voxel-based lesion symptom mapping study

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Abstract

Many studies have examined motor impairments using voxel-based lesion symptom mapping, but few are reported regarding the corresponding relationship between cerebral cortex injury and lower limb motor impairment analyzed using this technique. This study correlated neuronal injury in the cerebral cortex of 16 patients with chronic stroke based on a voxel-based lesion symptom mapping analysis. Neuronal injury in the corona radiata, caudate nucleus and putamen of patients with chronic stroke could predict walking speed. The behavioral measure scores were consistent with motor deficits expected after damage to the cortical motor system due to stroke. These findings suggest that voxel-based lesion symptom mapping may provide a more accurate prognosis of motor recovery from chronic stroke according to neuronal injury in cerebral motor cortex.

Key Words: *nerve regeneration; magnetic resonance imaging; stroke; cerebral cortex; motor cortex; voxel-based lesion symptom mapping; motor function; prognosis; neural regeneration*

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Introduction

Stroke is the leading cause of adult disability in the United States (Roger et al., 2012). Stroke often impairs motor function impacting the activities of daily living and quality of life (Zhu et al., 2010). Understanding the relationship of injury to the brain and resulting deficits in motor function can lead to a better prognosis of recovery. Voxel-based lesion symptom mapping (VLSM) is an analysis that provides information on the relationship between spatial locations in the brain and behavioral data, and is used in the area of language and speech deficits (*i.e.*, aphasia and apraxia). Few studies have examined lower limb motor deficits as a result of neural injury from stroke. The aim of the present study was to examine the relationship between neuronal injury after chronic stroke and lower limb motor impairment through the use of VLSM.

Numerous methods can be used to infer the brain regions involved with motor control. For example, techniques such as functional MRI (fMRI), event related potentials, and single cell recording in animal studies can reveal regions that are activated during a task. One limitation with these activation measures is that they cannot discriminate with regions that are merely involved with a task from those that are required to successfully perform the task. In contrast, VLSM correlates impairments in neurological patients with the location of brain injury in an attempt to identify the brain areas required for good performance.

Several studies examined motor impairments using VLSM. However, these have not specifically looked at lower body impairment. For example, Zhu et al. (2010) and Lo et al. (2010) used MRI and VLSM to gain a better understanding of the prognosis of upper motor function recovery in people with chronic stroke. Lo et al. (2010) found correlations between damage at the junction of the corona radiata and corticospinal tract and decreased motor performance, as well as limited recovery potential in individuals with chronic stroke. VLSM analysis conducted on individuals with chronic stroke revealed increased corticospinal atrophy was associated with internal capsule lesions and lesions overlapping the pyramidal tract (Globas et al., 2011). Furthermore, Zhu et al. (2010)

discovered that lesions that overlapped the corticospinal tract, instead of lesion size, predicted motor impairment. Likewise, Rorden et al. (2009) examined acute motor impairments and stroke location, but their analysis did not discriminate from lower or upper body impairments.

VLSM is a useful technique for comparing behavioral data to localized lesions, such as lesions located in the cerebellum (Timmann et al., 2008, 2009). Schoch et al. (2006) examined upper and lower limb impairment in individuals with cerebellar lesions. However, their participants included individuals with acute and chronic stroke, as well as individuals with tumors in the cerebellum. VLSM was used to compare regions of interest of cerebellar injury and behavioral scores of ataxia (based on the International Cerebellar Ataxia Rating Scale, or ICARS). Lower limb ataxia was correlated with lesions of vermal and paravermal lobules III–IV, whereas upper limb ataxia was correlated with lesions of the vermal, paravermal, and hemispheral lobules IV–VI (Schoch et al., 2006).

Shelton and Reding (2001) used a region of interest method (rather than voxelwise analyses) and found that the closer the lesion progressed from cortex to corona radiata to internal capsule, the greater the deficits in upper motor function. Lo et al. (2010) found lesion overlap in the supplemental motor area (SMA) and primary sensory cortex (S1), noting that the SMA and S1 are important in the sensory and motor integration of complex motor feedback and performance. Shelton and Reding (2001) suggest that poor motor recovery results from the interruption of thalamacortical somatosensory afferents traveling through the posterior limb of the internal capsule.

Individuals who have experienced stroke in the middle cerebral artery (MCA) often present with contralateral hemiplegia with pre-central gyrus damage. Premotor injury could lead to contralesional weakness and motor apraxia (Augustine, 2008). Loubinoux et al. (2007) studied finger-tapping during fMRI to measure motor recovery after stroke and concluded that subsequent preserved tissue in the M1, S1, and insula may lead to better prognosis in motor recovery. However, Fregni and Pascual-Leone (2006) suggest that plasticity during recovery may account for why some individuals recover given damage to the same regions after stroke, and Shelton and Reding (2001) argue that sensory feedback may be a critical impetus for cortical reorganization. While these studies have provided valuable insight, a combination of techniques, such as fMRI and VLSM, may provide more thorough answers on the degree of tissue damage, motor deficit, and prognosis after stroke.

VLSM analyses determine if behavioral symptoms can be predicted by the spatial location of the brain lesion (Rorden et al., 2007). VLSM tests each voxel to statistically determine whether individuals with lesions to that location are more likely to experience deficits than those without injury in this location. The approach is useful for drawing conclusions on anatomical structure damage and motor performance found in stroke (Lo et al., 2010). A conventional VLSM analysis computes a *t*-test at each voxel to identify regions that are consistently injured in people with a deficit yet spared for individuals who are unimpaired. Here we use a more non-parametric rank order test (Rorden et al., 2007) that is more appropriate when the assumptions of the *t*-test are violated (Brunner and Munzel, 2000). The test is considered normal in conditions where there are at least 10 observations per group (Schoch et al., 2006; Neubert and Brunner, 2007). Modern versions of NPM precisely calculate the statistical probability for small samples using permutation allowing this test to be applied to small sample sizes (Medina et al., 2010).

The aim of the present study was to compare the relationship between lesion location and lower motor impairment in individuals with chronic stroke (time from stroke was at least 6 months). As noted, numerous studies have examined upper motor impairment, but to the best of our knowledge, no VLSM study of cortical regions has specifically examined lower motor deficits. We were particularly concerned with lower limb motor control and balance as this significantly impacts disability needs and self-reliance. It was hypothesized that the behavioral motor scores would indicate impairment, the VLSM analysis would result in lesion locations that are associated with motor deficits as indicated by poorer performance on measures of physical function. Demonstrating a cohort of individuals in the chronic phase of stroke, with damage in regions of the corticospinal tract associated with lower limb deficits, is the first step in therapeutically targeting specific systems.

Subjects and Methods

Participants

Imaging and motor assessments were collected between July 2009 and March 2012. Behavioral assessments and structural imaging data were collected on separate study days. Motor assessments were collected by certified physical therapists at the Physical Therapy Rehabilitation Lab at the University of South Carolina (USC) during a session that was approximately 2 hours long. A 3-Tesla Siemens Magnetic Resonance Imaging (MRI) Scanner (Siemens, Co., Munich, Germany; McCausland Center for Brain Imaging at Palmetto Richland Memorial Hospital, Columbia, SC, USA) was used for the anatomical measurements. Structural Magnetic Resonance Imaging (sMRI) scans were collected at the McCausland Center for Brain Imaging (Columbia, SC, USA) sessions lasting approximately 1 hour. Both sessions included consent and debriefing.

Twenty individuals (14 males, 6 females) with a clinical presentation of unilateral hemiplegia after chronic stroke (time after stroke > 6 months) were recruited from motor rehabilitation studies at the institution. We chose patients with chronic strokes in order to examine damage that was still present after the acute phase of the stroke. We wanted to focus on portions of the cortex that had not healed during primary recovery, as the majority of recovery occurs during the acute phase.

In order to meet the minimum criteria for the behavioral assessments, participants were required to be able to walk 20 feet with occasional moderate assistance and to stand with the support of a cane or walker for 5 minutes with minimal assistance. Participants were required to understand and

Table 1 Descriptive statistics and deficit values for behavioral motor data

	Mean	SD	Range	Deficit
TUG (second)	21.08	12.12	9.26–47.81	≥ 14 (Shumway-Cook et al., 2000)
BBS (score)	47.75	5.76	35.00–56.00	≤ 45 (Blum and Korner-Bitensky, 2008)
LEFM (score)	23.47	4.97	16.00–31.00	≤ 28 (Yates et al., 2002)
Gait speed (m/s)	0.47	0.21	0.10–0.83	< 0.50 (Brincks and Nielsen, 2012) .

SD: Standard deviation; TUG: Timed Up and Go; BBS: Berg Balance Scale; LEFM: Lower-Extremity Fugl-Meyer.

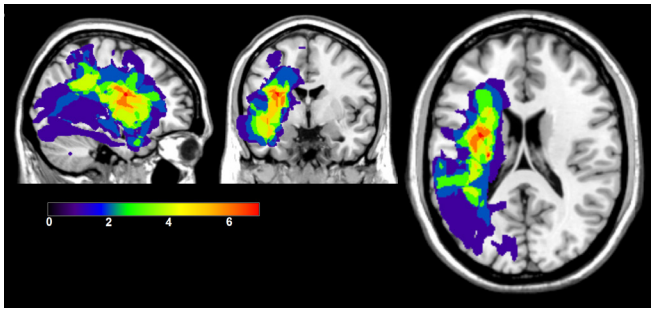

Figure 1 Lesion overlap map showing the frequency of injury across brain locations, regardless of motor impairment, in individuals with chronic stroke.
Left, middle, and right images reflect the same location in 3 dimensions (sagittal, coronal, and axial views, respectively). Maximal overlap (red); the Talairach coordinations for the maximal overlap's center of mass were $X = -29$ mm, $Y = -4$ mm, $Z = 18$ mm, with this location injured in 7 of the 16 individuals we examined.

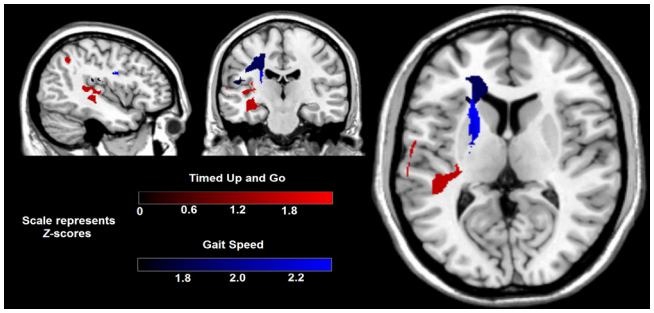

Figure 2 Timed Up and Go and gait speed lesion symptom mapping results of individuals with chronic stroke.
Left, middle, and right images reflect the same location in 3 dimensions (sagittal, coronal, and axial views, respectively). Timed Up and Go scores associated with damage in left postcentral gyrus, superior temporal pole, and inferior parietal lobule (in red; *Z*-score = 1.74 for false-discovery rate = 0.05); gait speed associated with corona radiata, caudate nucleus, middle frontal gyrus, and insula damage (in blue; *Z*-score = 2.36 for false-discovery rate = 0.01). Scales refer to the *Z*-scores generated from the Brunner-Munzel test for motor measures (Timed Up and Go *Z*-score range: –1.903 to 2.366; gait speed *Z*-score range: –2.820 to 3.320).

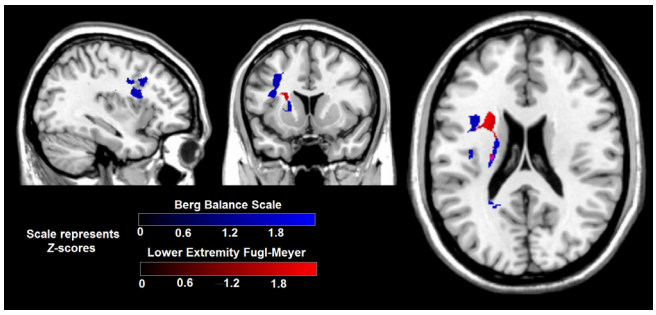

Figure 3 Berg Balance Scale and lower extremity Fugl-Meyer lesion symptom mapping results of individuals with chronic stroke.
Left, middle, and right images reflect the same location in 3 dimensions (sagittal, coronal, and axial views, respectively). Berg Balance Scale scores and lesion location (in blue) associated with damage in the caudate nucleus, precentral gyrus, and putamen (in blue; *Z*-score = 1.91 for false-discovery rate = 0.05); Lower Extremity Fugl-Meyer scores were associated with damage to the corona radiata and left putamen (in red; *Z*-score = 1.73 for false-discovery rate = 0.05). Scales refer to the *Z*-scores generated from the Brunner-Munzel test for motor measures (Berg Balance Scale *Z*-score range: –2.737 to 2.118; Fugl-Meyer *Z*-score range: –1.903 to 2.366).

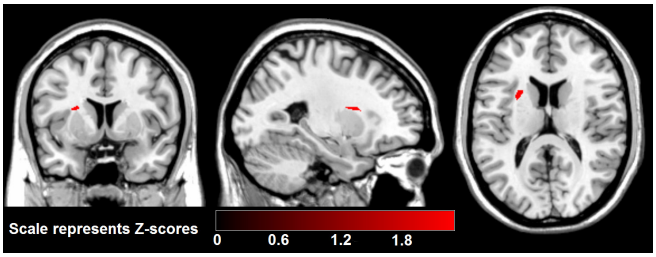

Figure 4 *Post hoc* gait speed lesion symptom mapping results of individuals with chronic stroke.
Left, middle, and right images reflect the same location in 3 dimensions (coronal, sagittal, and axial views, respectively). Participants with gait speed deficits demonstrated damage to descending motor tract in the corona radiata, extending from the putamen to the caudate nucleus (in red; *Z*-score = 2.64 for false-discovery rate = 0.01). Scales refer to the *Z*-scores generated from the Brunner-Munzel test for the gait speed measures (*Z*-score range: 0.000 to 2.644).

follow two simple motor commands in sequence (otherwise indicating speech comprehension deficits). In addition, individuals needed to have the capability to sit independently without support for 5 minutes (otherwise suggesting damage that extended into the extrapyramidal motor pathways lying outside the corticospinal tract). Extrapyramidal pathways control posture and muscle tone and include regulatory functions outside of voluntary control (Albanese, 1990).

Three participants were excluded: contraindication for MRI ($n = 2$, *i.e.*, stent, lens implant); extensive brain damage in both right and left hemispheres ($n = 1$). One participant's data were lost due to computer malfunction. The remaining 16 participants (12 males; age 57.1±15.2 years) suffered primarily left hemisphere damage, except for two participants who showed sole right hemisphere damage. All participants read and signed an informed consent form approved by the local institution's Institutional Review Board (IRB). All the procedures were in accordance with the ethical standards

of the responsible committee on human experimentation of the local institution and with the *Helsinki Declaration* of 1975, as revised in 2000 (WMA, 2013).

Behavioral Measures - Motor

Four measures assessing physical function were used in the analyses: Fugl-Meyer (Lower Extremity) Motor Assessment (LEFM), Timed Up and Go (TUG), Berg Balance Scale (BBS), and Gait Speed (3 Meter Walk). The LEFM is a valid and reliable stroke-specific test that assesses general motor function, joint and sensation function, and balance (Duncan et al., 1983; Wood-Dauphinee et al., 1990; Sanford et al., 1993; Sullivan et al., 2011; Hiengkaew et al., 2012). The maximum score for lower extremity motor performance is 34; lower scores signify increased motor impairment (Fugl-Meyer et al., 1975; Gladstone et al., 2002). Researchers use a lower extremity score cut-off of ≤ 28 points as an indicator of motor impairment (Patel et al., 2000; Yates et al., 2002) as well as a higher risk of falls (Yates et al., 2002).

The TUG is a test of functional mobility, which measures, in seconds, the time it takes for a participant to get up from a sitting position in a chair, walk 3 m, turn around, walk back, and return to a sitting position (Shumway-Cook et al., 2000; Faria et al., 2012; Hiengkaew et al., 2012). A score of ≥ 14 seconds demonstrates a higher risk of falling (Shumway-Cook et al., 2000; Andersson et al., 2006). Scores of 30 seconds or greater demonstrate more dependence in daily living transfer tasks (Shumway-Cook et al., 2000).

The BBS is a valid and reliable measure of functional balance used by physical therapists in the stroke population (Berg et al., 1992; Liston and Brouwer, 1996; Mao et al., 2002; Flansbjer et al., 2012; Hiengkaew et al., 2012; La Porta et al., 2012). It measures static and dynamic balance and has a maximum global score of 56 (Berg et al., 1992). Berg Balance scores are also predictive of falls. Balance impairment is affiliated with score ranges from 0 to 20, with scores of 21 to 40 representing acceptable balance, and good balance with a score of 41 and higher (Blum et al., 2008). A score of ≤ 45 on the BBS is associated with a high risk of falls; each one point reduction in score ranging from 54–36 is associated with a 6–8% increase in falls (Blum et al., 2008; Muir et al., 2008).

Gait velocity is a validated test of walking speed (Green et al., 2002; Flansbjer et al., 2005; Hiengkaew et al., 2012; Peters et al., 2012; Van Bloemendaal et al., 2012) that is correlated with balance confidence and functional ability. It serves as a potential predictor of mortality and functional decline, as well as future health status (Fritz and Lusardi, 2009). Gait speed in the present study was measured using the 3 Meter Walk test. A tape measure was used to mark off 7 m, with 2 m on each end serving as acceleration and deceleration distances; the middle 3 m served as the recorded or timed zone. The participant was asked to "walk at a comfortable pace" for three trials. The time for each trial was recorded in seconds and the gait speed was computed by calculating distance/time. Walking speeds of less than 0.50 m/s are considered less mobile (Brincks and Nielsen, 2012).

MRI Acquisition

A 3-Tesla Siemens Magnetic Resonance Imaging (MRI) Scanner (Siemens Co., Munich, Germany; McCausland Center for Brain Imaging at Palmetto Richland Memorial Hospital, Columbia, SC, USA) was used for anatomical measurements. Localizers were obtained for alignment, followed by 3D T1 and T2-weighted scans. The original Digital Imaging and Communications in Medicine (DICOM) files were converted to the NIfTI file format (Cox et al., 2004).

Two individuals demonstrated sole right hemisphere damage, and those images were flipped to provide a mirror image and included in the analyses with the other left hemisphere damaged brains.

Lesion Identification

Lesions were drawn manually on the T1-weighted brain image (aided by observation of lesion extent from the T2-weighted images) using MRIcron (version 6 June 2013; Chris Rorden, Columbia, SC, USA; www.mricro.com) software (Rorden and Brett, 2000). Tracing was created by two double-blinded practicing neurosurgeons who worked together to develop a consensus for the lesion extent within each individual. The T1 images and corresponding lesion maps were normalized using the unified segmentation and normalization routines of the Clinical Toolbox in SPM8 (Wellcome Trust Centre for Neuroimaging, London, England) (Ashburner and Friston, 2005), which uses lesion cost function masking (Brett et al., 2001) which has been validated by Andersen et al. (2010) The Clinical Toolbox uses a template brain from older adults, created by Rorden et al. (2012). This template is ideal for studies of older adults, as it models normal age related atrophy resulting in less image distortion (Brett et al., 2001).

Voxel-Based Lesion Symptom Mapping (VLSM)

MRIcron (version 6 June 2013; Chris Rorden, Columbia, SC, USA; www.mrico.com) was used to show lesion locations and examine overlap of the lesioned voxels across participants. The normalized images and lesion masks were used in the VLSM analysis along with the measures of motor impairment and mobility. We used the Non-parametric mapping (NPM) software (version 6 June 2013; Chris Rorden, Columbia, SC, USA) included with the MRIcron software distribution to generate nonparametric tests with false-discovery rate (FDR) corrections at $P \leq 0.05$ to determine significant relationships between the lesioned areas and motor behavioral measure scores. Due to the non-normal distribution of the data, comparisons were made using Z-scores derived from the Brunner-Munzel test to determine significant differences between voxels of damaged tissue versus non-damaged tissue. Modern versions of NPM precisely calculate the statistical probability for small samples using permutation allowing this test to be applied to small sample sizes (Medina et al., 2010).

Statistical analysis

Comparisons were made using Z-scores derived from the

Brunner-Munzel test. We used the Non-parametric mapping (NPM) software module included with the MRIcron software (version 6 June 2013; Chris Rorden, Columbia, SC, USA; www.mricro.com) to generate nonparametric tests with False Discovery Rate (FDR) corrections at $P \leq 0.05$ to determine significant relationships between lesioned areas and motor behavioral scores. Medina et al. (2010) noted that early implementations of NPM were explicitly designed not to be used with small samples; however, version 6 June 2013 utilizes permutation analysis to appropriately estimate probabilities for small sample sizes.

Results

Motor Behavioral Measures

As expected, the TUG scores (M = 21.08 s, SD = 12.12 s) were greater than the value associated with an increased risk for falls (14 s) (Shumway-Cook et al., 2000). Although the average BBS score (M = 47.75, SD = 5.76) was slightly higher than the cut-off associated with a high risk of falls, it is consistent with an increased risk of falls (Blum and Korner-Bitensky, 2008; Muir et al., 2008).

The LEFM scores (M = 23.47, SD = 4.97) were below normal, signifying increased lower extremity motor impairment. One participant was not assessed using the LEFM due to time constraints. Gait speed, measured by the 3 Meter Walk, produced results (M = 0.47 m/s, SD = 0.21) indicative of low ambulatory stroke patients. Table 1 shows descriptive statistics and deficit cut-off scores for each behavioral test.

Lesion Overlap and VLSM

A lesion overlap map showing the frequency of injury across brain locations, regardless of motor impairment, is presented in Figure 1. Maximal overlap (red); the Talairach coordinations for the maximal overlap's center of mass were X = –29 mm, Y = –4 mm, Z = 18 mm, with this location injured in 7 of the 16 individuals we examined.

At an FDR of 0.05, the Brunner-Munzel test produced significant Z scores for the TUG scores (Z = 1.74) in relation to the lesion masks. Damage in the left postcentral gyrus, insular cortex, superior temporal pole, and inferior parietal lobule were related to TUG scores. Gait Speed assessment scores (Z = 2.37) were significant at an FDR of 0.01. Associations were found between Gait Speed assessment scores, measured by the 3 Meter Walk, and lesions in the corona radiata, caudate nucleus, striatum, middle frontal gyrus, inferior frontal operculum, and insular cortex. Statistical maps of lesioned locations and Z-scores for TUG and Gait Speed are shown in Figure 2.

At an FDR of 0.05, the Brunner-Munzel test produced significant Z scores for the BBS (Z = 1.91) in relation to the lesion masks. Damage to the caudate nucleus, precentral gyrus, putamen, pallidum, frontal inferior operculum, cuneus, and minimal damage in the thalamus was associated with BBS scores. LEFM scores (Z = 2.37) were significant at an FDR of 0.01. Damage to the corona radiata and left putamen was associated with the LEFM scores. Lesion locations associated with BBS and LEFM scores are shown in Figure 3.

VLSM – *Post Hoc* Analyses

Additional analyses were performed in only the participants who demonstrated deficits in each motor measure, in order to gain a clearer picture of brain injury in terms of specific motor deficits. Ten individuals demonstrated a gait speed of 0.50 m/s or less for the 3 Meter Walk, and the corresponding lesioned brains were reexamined using the same VLSM procedure. At an FDR of 0.01, the Brunner-Munzel test produced significant Z scores for the 3 Meter Walk test (Z = 2.64) in the VLSM analysis, with at least five individuals with lesions. Damage to descending motor tract in the corona radiata, extending from the putamen to the caudate nucleus (Figure 4) was associated with the 3 Meter Walk gait speed scores. The participants with deficits in the TUG (n = 10, scores ≥ 14), BBS (n = 6, scores ≤ 45), and LEFM (n = 13, scores ≤ 28) were also reexamined, although these data did not produce significant results.

Discussion

The relationship between neural damage due to stroke and motor impairment was examined in the present study. As hypothesized, behavioral measure scores corresponded with motor deficits expected after damage to motor systems, the areas of lesion location were consistent with systems involved in motor ability, and the lesion locations were predictive of motor impairment. However, the traditional motor systems, like primary motor cortex, were intact. TUG scores were associated with lesions in the postcentral gyrus, insular cortex, superior temporal pole, and inferior parietal lobule. Premotor injury in MCA strokes could lead to contralesional weakness and motor apraxia. Dovern et al. (2011) found that MCA strokes that caused dorsal premotor cortex lesions in individuals with apraxia resulted in impairments in the intentional retrieval of motor sequence knowledge. Commonly affected areas, such as the superior temporal gyrus, may cause motor aphasia or auditory receptive aphasia (Augustine, 2008).

BBS scores were associated with damage in the precentral gyrus, putamen, caudate nucleus, cuneus, pallidum, frontal inferior operculum, and minimal damage in the thalamus. LEFM scores were associated with damage in the corona radiata and left putamen was associated with LEFM scores. These results are consistent with previous studies; Lo et al. (2010) and Shelton and Reding (2001) also demonstrated that damage to the corona radiata was related to increased deficits in motor function.

Lesions in the middle frontal gyrus, inferior frontal operculum, insular cortex, caudate nucleus, striatum, and corona radiata predicted poorer gait speed times. *Post hoc* analyses of the participants demonstrating deficits in gait speed produced significant associations between decreased gait speed and damage to descending motor tract in the corona radiata, extending from the putamen to the caudate nucleus. For participants with gait speed impairments, the overlapping damage may be in striatal bridge cells within the internal capsule, although the resolution of the structural images was not sufficient to test this hypothesis (Tachibana et al., 2004).

DTI studies of this region suggest that it is a part of the corticospinal tract originating in the lower limb and trunk motor and supplementary motor region (Chen and Schlaug, 2013). This finding echoes findings in upper limb studies which noted damage in the corona radiate (Shelton and Reding, 2001; Lo et al., 2010) and putamen (Alexander et al., 2009). Furthermore, damage to the inferior portion of the posterolateral putamen has been associated with temporal gait asymmetry (Alexander et al., 2009). Injury to the S1 has been shown to lead to the loss of proprioception and tactile sensation on the contralateral side to the injury (Augustine, 2008). Individuals with MCA strokes may present with contralateral hemiplegia when damage involves the precentral gyrus, and contralesional weakness and motor apraxia may be effects of premotor involvement (Augustine, 2008). It is expected that individuals with loss of proprioception and tactile sensation, along with hemiplegia and motor apraxia after stroke, would present with impairment in walking and balance.

While there were individual lesions directly involved in motor areas across participants, such as corona radiata, premotor cortex and putamen (Figure 1), the significant lesion locations corresponded to some areas that are not directly involved in mobility. However, the limited damage found in the sensorimotor area is associated with MCA stroke (Ameli et al., 2009). MCA strokes are known to spare the motor cortex (M1), yet they are still involved with motor impairment (Gharbawie et al., 2005). Additionally, Gharbawie et al. (2005) occluded the MCA in rats to produce strokes, which led to primary somatosensory damage with motor impairment without M1 damage.

VLSM is a useful analysis technique that provides more information on brain trauma due to stroke and consequential behavioral deficit. The Brunner-Munzel test has provided a platform for analyzing fewer participants, particularly when employing multiple permutations in the NPM VLSM software. However, studying additional participants would ideally provide more statistical power. VLSM may serve as a diagnostic and prognostic tool to aid physicians and researchers in order to provide better care for individuals who experience stroke, and should be used in association with other analyses. Shedding more light on the relationship between neural injury and motor recovery will allow for quicker and more detailed development of motor training techniques, and ultimately provide more accurate prognosis of motor recovery. Additionally, more evidence on the associations between neural injury and motor recovery at different time points of injury may provide specific knowledge of neural regeneration and its impact on prognosis. VLSM has great potential for many other areas, such as improving psychiatric neurosurgical lesioning procedures (Yang et al., 2013) and improving therapy and day-to-day functioning of individuals with traumatic brain injury (Knutson et al., 2013).

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Author contributions: *Reynolds AM, Vendemia JM, Baylis GC, Krotish D and Fritz SL co-designed this study. Reynolds AM, Peters DM, Vendemia JM, Baylis GC, Krotish D and Fritz SL were responsible for definition of intellectual content. Reynolds AM, Peters DM, Vendemia JM, Baylis GC, Krotish D and Fritz SL researched the literatures. Reynolds AM, Peters DM, Baylis GC, Krotish D and Fritz SL were responsible for data acquisition. Reynolds AM, Smith LP and Sweet RC were responsible for data analysis. Reynolds AM was in charge of statistical analysis. Reynolds AM, Peters DM, Vendemia JM and Fritz SL were responsible for manuscript preparation. Reynolds AM, Peters DM, Vendemia JM, Krotish D and Fritz SL edited the manuscript. Baylis GC, Krotish D and Fritz SL were the guarantors of this paper. All authors participated in study concept and experimental studies, reviewed the manuscript and approved the final version of this paper.*

Conflicts of interest: *None declared.*

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