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Neural substrates of reduced walking activity after supratentorial stroke: A voxel-based lesion symptom mapping study

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ABSTRACT

Background: Most stroke patients exhibit low levels of walking activity, a key component of secondary stroke prevention. The predictors of walking activity may be multifactorial and are thus far partially understood. We aimed to study the neuroanatomic correlates of low levels of daily walking activity following hemispheric stroke.

Methods: In this cross-sectional study, 33 community-dwelling stroke survivors (age: 63.9 ± 12.9 years; % female: 36.4%; NIHSS at admission: 3.3 ± 4.0) were prospectively recruited at least 3 months after a first ever, unilateral, supratentorial stroke confirmed by brain magnetic resonance imaging. Walking activity was measured by daily step counts (steps·day^{-1}), recorded using an Actigraph GT3x+ triaxial accelerometer over 7 consecutive days. Voxel-based lesion-symptom mapping was performed to identify brain areas associated with walking activity following stroke.

Results: Participants presented 4491.9 ± 2473.7 steps·day^{-1}. Lower levels of walking activity were related to lesions of the posterior part of the putamen, of the posterior limb of the internal capsule and of the anterior part of the corona radiata. No cortical region was associated with walking activity.

Conclusions: Our preliminary results identify subcortical neuroanatomical correlates for reduced walking activity following stroke. If confirmed, these results could serve as a rationale for the development of targeted rehabilitative strategy to improve mobility after stroke.

1. Introduction

Physical activity is a key component of secondary stroke prevention (Billinger et al., 2014). Functional limitations experienced by post stroke patients often result in reduced physical activity, far below the recommended 10,000 daily steps required for health benefits (Mahendran, Kuys, & Brauer, 2016; Tudor-Locke et al., 2011) and can lead to sedentariness (English, Manns, Tucak, & Bernhardt, 2014). If the degree of physical impairment may be an important factor driving sitting and physical activity time in people post stroke, the determinants and predictors of low levels of walking activity (WA) may be multifactorial and are not well studied

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Table 1
Clinical characteristics of the population (n = 33).

Clinical characteristics		
	Females, n (%)	12 (36.4%)
	Age, mean (SD) (years)	63.9 (12.9)
	BMI, mean (SD) ($kg{\cdot}m^{-2}$)	27.4 (5.2)
	Modified Charlson Comorbidity Index Score, mean (SD)	3.7 (2.1)
	Montreal Cognitive Assessment (MoCA), mean (SD)	26.9 (2.0)
Severity of stroke on admission		
	NIHSS score, n (%)	
	(Range 0–42)	
	No stroke symptom (score 0)	6 (18.2%)
	Mild (score 1–4)	18 (54.5%)
	Moderate (score 5–15)	8 (24.2%)
	Moderate to severe (score 16–20)	1 (3.1%)
MRI stroke characteristics		
	Delay between stroke and MRI, mean (SD) (days)	2.9 (2.7)
	Lesion lateralization	
	Left, n (%)	19 (57.6%)
	Right, n (%)	14 (42.4%)
	Type	
	Ischemic, n (%)	33 (100%)
	Hemorrhagic, n (%)	0 (0%)
	Lesion volume, mean (SD) (cm^3)	18.4 (32.4)
	ARWMC total score [14], mean (SD)	5.7 (5.1)
	(Range 0–30)	

Data are reported as mean (1 standard deviation (SD)) or number of observations and percentages when appropriate. ARWMC: Age-Related White Matter Changes; BMI: Body Mass Index; L: Left; MoCA: Montreal Cognitive Assessment; MRI: Magnetic Resonance Imagery; NIHSS: National Institute of Health Stroke Scale; R: Right; SD: Standard Deviation.

(English et al., 2016). Thus, depression, fatigue and altered quality of life are negatively correlated with post-stroke physical activity (Thilarajah et al., 2018).

Walking requires the complex interaction of several brain structures and functions that goes far beyond voluntary motor control (Takakusaki, 2017). Studying the relationship between neuroimaging and mobility impairments can lead to a better understanding of the underlying pathophysiology of those impairments and can serve as biomarkers of recovery (Stinear, Byblow, & Ward, 2014). Thus, initial damage to the corticospinal tract (CST) can predict decreased gait speed, even after a chronic delay following stroke (Jones et al., 2016; Reynolds et al., 2014). Lesions involving the posterolateral putamen are associated with temporal gait asymmetry after a chronic delay following stroke (Alexander et al., 2009). When combined with lesions of neighbouring structures, lesions to the putamen are associated with poor recovery of gait post-stroke (Jones et al., 2016; Lee et al., 2017). The association between lesion location and reduced WA following stroke has never been studied. We hypothesized that a cluster of different lesion locations related to motor and non-motor determinants of gait control will be associated with lower WA levels. This study aims to identify the neuroanatomic correlates of low levels of WA following stroke, based on a voxel-based lesion-symptom mapping (VLSM) approach.

2. Material and methods

2.1. Participants

Thirty-three community-dwelling stroke survivors (age: 63.9 ± 12.9 years; % female: 36.4%; NIHSS at admission: 3.3 ± 4.0) were recruited in this cross-sectional study, at least 3 months after stroke onset (mean ± 1SD = 182.4 ± 74.9 days) from the Department of Neurology of the Geneva University Hospital between November 2012 and January 2016. Clinical characteristics are presented in Table 1. Inclusion criteria were: i) first ischemic, unilateral, supratentorial stroke (to overcome specific balance and gait impairments linked with brainstem or cerebellar lesions), ii) brain magnetic resonance imaging (MRI) confirming stroke diagnosis, iii) a Rivermead Mobility Index (Antonucci, Aprile, & Paolucci, 2002) score of level 7 or above, ensuring participants with sufficient mobility skills, and iv) absence of other neurological condition. Participants with contraindications to exercise participation, unable to walk, with language impairments including aphasia or who had an acute medical condition interfering with gait (except stroke) were not included in the study.

The protocol was approved by the Ethic Committee of the Geneva University Hospitals and each participant provided a signed informed consent.

2.2. Clinical data and measurements

Participants underwent a complete medical examination at least 3 months after stroke onset, performed by a certified neurologist, including the evaluation of their cognitive status using the Montreal Cognitive Assessment (MoCA). Clinical acute stroke characteristics, including score on the National Institute of Health Stroke Scale (NIHSS) at admission were retrieved in patients' medical records. The Modified Charlson Comorbidity Index was used to quantify comorbidity (Goldstein, Samsa, Matchar, & Horner, 2004).

Functional independence and mobility for activities of daily living were assessed using the Barthel Index (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013). Rivermead Mobility Index (Antonucci et al., 2002), a sub-scale of the Rivermead Motor Assessment was used to evaluate mobility skills (*i.e.* gait, balance and transfers). For both scales, higher scores reveal higher functional status and mobility skills. As a major determinant of post stroke walking ability (Fulk, He, Boyne, & Dunning, 2017), gait speed was determined in the Willy Taillard Kinesiology Laboratory of the Geneva University Hospital using a GAITRite walkway system® (GAITRite Gold, CIR Systems, PA, USA) (Bilney, Morris, & Webster, 2003). Participants were asked to walk at their comfortable gait speed. Each participant performed one evaluation trial at steady-state walking speed on a 10-meter walkway.

The main outcome for WA was the daily step counts (DSC) (Fulk et al., 2017) measured with an Actigraph GT3x+ triaxial accelerometer (ActiGraph, LLC, Pensacola, FL, USA). This device accurately discriminates movement over a broad range of gait speeds, including low gait speeds (Bassett & John, 2010) and is recognized as a valid step-count monitor for free-living condition (J. A. Lee, Williams, Brown, & Laurson, 2015). The accelerometer was worn over the fifth lumbar vertebra 24 h a day during 7 consecutive days and removed only for water-based activities. Accelerometers were initialized and data downloaded using software provided by the manufacturer (v5.2.0, ActiLife, ActiGraph). Data were included if the participant had accumulated at least 10 h of valid activity recordings per day for a minimum of 4 days (mean ± SD duration of recording: 7 ± 0 days).

2.3. MRI processing and lesion analysis

MRI scans were performed according to standard stroke protocols at the Radiology Department of Geneva University Hospitals on average within 3 days following stroke onset (2.9 ± 2.7 days). MRI protocol included T1, T2 and fluid attenuated inversion recovery (FLAIR) images, obtained with standard parameters on a 1.5 T apparatus (Intera, Philips Medical Systems).

MRI images were first processed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) for Matlab (Mathworks, Natick, MA). T1 native images were spatially normalized into Montreal Neurological Institute (MNI) space. The T2-weighted images were then co-registered to the spatially normalized T1 images.

Lesion delineation was performed by the same trained clinician (SB) blinded for all clinical data, onto axial slices of the processed T2-weighted images using the MRIcron software package (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Age-related white matter changes were rated by the same trained clinician on T2-weighted native images following the methodology proposed by Wahlund et al. (2001). All right-sided lesion maps (n = 14) were flipped onto the left hemisphere as reported before (Cheng et al., 2014).

VLSM is a voxel-by-voxel statistical method dedicated to the analysis of brain lesion-behavior relationship (Bates et al., 2003). VLSM analyses were performed using the nonparametric mapping (NPM) software (http://www.mccauslandcenter.sc.edu/mricro/mricron/) included in the MRICron toolset. In each voxel, a T-test was conducted to compare the behavioral score of patients with or without a lesion in that voxel. Analyses were only conducted on voxels damaged in ≥5 subjects. All 3D lesion maps were fed into NPM along with the corresponding participant performance in terms of DSC. Age, body mass index, and age-related white matter changes, three variables linked with impaired walking skills, were used as covariates. The resulting statistical maps were thresholded voxelwise at conventional statistical values ($p < 0.01$ uncorrected, with a cluster threshold of $p < 0.05$).

Results were displayed using MRIcron in radiological convention, with Montreal Neurological Institute coordinates provided in mm. To accurately describe the anatomical affected structures, the Automated Anatomic Labeling and the John Hopkins University white matter labels-1 mm atlases were overlaid with the significant VLSM clusters.

2.4. Statistical analysis

All variables are reported as mean ± 1 standard deviation (SD) or number of observations and percentages when appropriate. All statistical analyses were performed using SPSS 23 (IBM SPSS Statistics, Version 23.0. Armonk, NY).

3. Results

3.1. Clinical and walking activity assessment

We included patients without significant cognitive impairment, as reflected by scores from the MoCA. Scores from the Barthel Index revealed high functional independence and mobility for activities of daily living. Consistently, scores from the Rivermead Mobility Index revealed high functional mobility skills (Forlander & Bohannon, 1999) (Table 2). According to gait speed values, one participant (3%) was considered as home ambulator (gait speed $< 0.4\,m{\cdot}s^{-1}$), seven (21%) as limited community ambulators ($0.4 \leq$ gait speed $\leq 0.8\,m{\cdot}s^{-1}$) and 25 (76%) as full community ambulators (gait speed $> 0.8\,m{\cdot}s^{-1}$) (Fulk et al., 2017).

All participants had valid accelerometer recordings with a mean ± 1SD DSC of 4491.9 ± 2473.7 steps·day^{-1} (Table 2).

Table 2
Functional and mobility performances of the patients, assessed at least 3 months after stroke onset.

Performances on functional scales		
	Barthel Index, mean (SD) (Range 0–100)	94.9 (10.2)
	Rivermead Mobility Index, mean (SD) (Range 0–15)	14.6 (1.3)
Gait speed		
	Comfortable gait speed, mean (SD) ($m \cdot s^{-1}$)	0.98 (0.26)
Daily walking activity		
	Valid accelerometers recordings, n (%)	33 (100%)
	Daily steps count, mean (SD) (steps/day)	4491.9 (2473.7)

Data are reported as mean ± 1 standard deviation (SD) or number of observations and percentages when appropriate.

3.2. Imaging assessment – VLSM analysis

Stroke characteristics and quantification of age-related white matter changes are presented in Table 1. The highest frequency of lesions was observed in the middle cerebral artery territory as shown in Fig. 1. VLSM analyses showed that 3 subcortical brain regions, the posterior part of the putamen, the posterior limb of the internal capsule and the anterior part of the corona radiata were associated with low DSC (Fig. 2, MNI coordinates of peak value, −29, −10, 6, corresponding to the posterior part of the putamen). No cortical region was associated with WA levels.

4. Discussion

We found that daily WA, a major health outcome in terms of secondary prevention following stroke, measured three months after stroke onset was negatively associated with a cluster of subcortical lesions in a group of patients with high functional independence and mobility skills. The reported DSC of 4491.9 ± 2473.7 steps·day^{-1} is consistent with previous stroke studies (English et al., 2014; Mahendran et al., 2016).

Consistent with our hypothesis, a cluster of lesions found in the posterior part of the putamen, the posterior limb of the internal capsule and the anterior part of the corona radiata were associated with lower daily WA after controlling for age, body mass index and age-related white matter changes. The strongest association was observed in the posterior part of the putamen, a key structure involved in sub-cortico-cortical motor loops, and in particular in fronto-striatal connections, that span motor, cognitive and limbic cortical areas (Leh, Ptito, Chakravarty, & Strafella, 2007). From a motor point of view, stroke lesions involving the putamen are associated with gait impairments, such as gait asymmetry (Alexander et al., 2009) and negatively affect gait recovery post-stroke

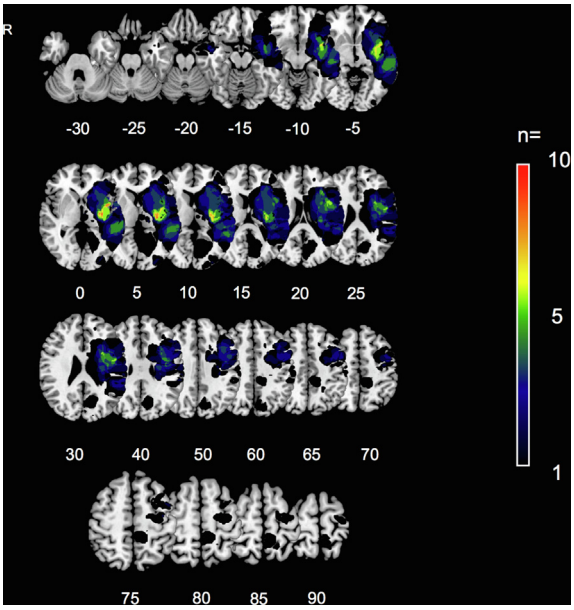

Fig. 1. Lesion overlap map from the 33 participants. All right-sided lesions (n = 14) are flipped onto the left hemisphere (Cheng et al., 2014). The color bar indicates number of overlapping lesions, that range from 1 (black) to 10 overlapping lesions (red). Montreal Neurological Institute coordinates of each transverse section (z axis) are given. R indicates the right side of brain MRI. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

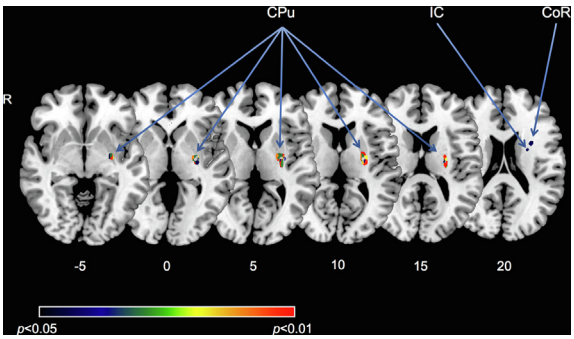

Fig. 2. Voxel-based lesion symptom mapping study: cerebral correlates of the daily walking activity evaluated by daily steps count (DSC) three months after stroke onset. Mapping of the DSC reveal an involvement of the posterior part of the putamen, the posterior limb of the internal capsule and the anterior part of the corona radiata. All lesions are flipped onto the left hemisphere. The color bar indicates t-tests values, that range from $p < 0.05$ (black) to $p < 0.01$ (red). Montreal Neurological Institute coordinates of each transverse section (z axis) are given. R indicates the right side of brain MRI. CoR = corona radiata; CPu = caudal putamen; IC = internal capsule. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Jones et al., 2016; Lee et al., 2017). Stroke lesions involving the putamen can also be associated with parkinsonism (Mehanna & Jankovic, 2013; Suri et al., 2018). We did not include patients with other neurological conditions but stroke. However, we did not quantify the presence of parkinsonism or mild parkinsonian signs that may have contribute to the observed WA limitation.

Other relevant structures were the internal capsule and the corona radiata, both part of the CST, previously described as being associated with lower gait speed (Reynolds et al., 2014) and poor gait recovery (Cheng et al., 2014; Jones et al., 2016) after stroke. In the study by Jones et al., higher lesion loads of the CST assessed by volumetric measurement were significantly associated with lower scores of gait and everyday functions of general mobility (Jones et al., 2016). Beyond anatomical lesion, the relevance of CST functional integrity on predicting functional outcomes post-stroke such as walking remains unclear (Stinear, 2017). Recent results suggest that the absence of hemiparetic lower limb motor evoked potential from the ipsilesional hemisphere induced by transcranial magnetic stimulation did not affect walking speed in chronic stroke survivors (Sivaramakrishnan & Madhavan, 2018). Authors further suggest that walking recovery may rely on the recruitment of redundant motor pathways, such as reticulospinal tract or could arise from the development of rehabilitation-induced motor compensations (Sivaramakrishnan & Madhavan, 2018). The anatomical-functional discrepancies regarding the role of CST in predicting walking recovery post-stroke reinforce the statement that walking recovery post-stroke is a complex process at least partially understood.

We found no association between cortical lesion and WA levels. This result is supported by two interventional studies highlighting the strong subcortical contribution to rehabilitation-induced recovery of lower limb and walking function after stroke (Enzinger et al., 2009; Luft et al., 2008). However, other authors observed cortical activation changes (bilateral primary sensorimotor cortex, bilateral supplementary motor area) in rehabilitation-associated walking improvements (Enzinger et al., 2009). These discrepancies could be explained by the design of the studies (observational *vs.* interventional) and by the outcome chosen to evaluate walking performance. Thus, Enzinger et al. (Enzinger et al., 2009) evaluated their patients with a walking endurance test (2-minute timed walking test) after 4 weeks of treadmill training while we assessed spontaneous WA in free-living condition over seven days in a cross-sectional manner. The small sample size may prevent us to report cortical lesions associated with WA. Our results, together with those of the two aforementioned studies underpinned the involvement of widespread sub-cortico-cortical motor loops in functional walking recovery post-stroke. Thus, WA may be the result of a 'cross-talk' between several motor and non-motor brain functions including gait and postural control, cognitive functions as well as volitional behaviour. We thus hypothesize that the outlined lesions, found as being negatively associated with WA represent key nodes of a wider WA-related connectome. The main limitation of this preliminary work was the inclusion of minor strokes, preventing the generalization of our findings for all stroke patients. Moreover, as MRI scans were performed at least three months before evaluation, we could have overestimated the stroke size due to initial edema. Finally, we included patients with high functional and mobility skills, as reflected by Barthel Index and Rivermead Mobility Index scores. Unfortunately, while focusing on motor skills and mobility impairments, our work did not include comprehensive cognitive and behavioural evaluations. Future work should investigate the contribution of cognition and behaviour to WA levels, while controlling for mobility skills.

5. Conclusions

Our results highlight that daily WA measured three months after stroke onset was negatively associated with a cluster of sub-cortical lesions. If confirmed, these results could serve as a rationale for the development of targeted rehabilitative strategies to improve mobility after stroke, especially when affecting the CST and the posterior part of the putamen. Future studies should confirm these findings in a larger population while performing the MRI at the same time of the physical activity measurement.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sébastien Baillieul was supported by a grant of the SOFMER (Société Française de Médecine Physique et de Réadaptation).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humov.2019.102517.

References

Alexander, L. D., Black, S. E., Patterson, K. K., Gao, F., Danells, C. J., & McIlroy, W. E. (2009). Association between gait asymmetry and brain lesion location in stroke patients. *Stroke, 40*(2), 537–544. https://doi.org/10.1161/STROKEAHA.108.527374.

Antonucci, G., Aprile, T., & Paolucci, S. (2002). Rasch analysis of the rivermead mobility index: A study using mobility measures of first-stroke inpatients. *Archives of Physical Medicine and Rehabilitation, 83*(10), 1442–1449.

Bassett, D. R., & John, D. (2010). Use of pedometers and accelerometers in clinical populations: Validity and reliability issues. *Physical Therapy Reviews, 15*(3), 135–142. https://doi.org/10.1179/1743288X10Y.0000000004.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience, 6*(5), 448–450. https://doi.org/10.1038/nn1050.

Billinger, S. A., Arena, R., Bernhardt, J., Eng, J. J., Franklin, B. A., Johnson, C. M., ... Council on Clinical Cardiology (2014). Physical activity and exercise recommendations for stroke survivors: A statement for healthcare professionals from the American heart association/american stroke association. *Stroke, 45*(8), 2532–2553. https://doi.org/10.1161/STR.0000000000000022.

Bilney, B., Morris, M., & Webster, K. (2003). Concurrent related validity of the gaitrite walkway system for quantification of the spatial and temporal parameters of gait. *Gait Posture, 17*(1), 68–74.

Cheng, B., Forkert, N. D., Zavaglia, M., Hilgetag, C. C., Golsari, A., Siemonsen, S., ... Thomalla, G. (2014). Influence of stroke infarct location on functional outcome measured by the modified rankin scale. *Stroke, 45*(6), 1695–1702. https://doi.org/10.1161/STROKEAHA.114.005152.

Duffy, L., Gajree, S., Langhorne, P., Stott, D. J., & Quinn, T. J. (2013). Reliability (inter-rater agreement) of the barthel index for assessment of stroke survivors: Systematic review and meta-analysis. *Stroke, 44*(2), 462–468. https://doi.org/10.1161/STROKEAHA.112.678615.

English, C., Healy, G. N., Coates, A., Lewis, L. K., Olds, T., & Bernhardt, J. (2016). Sitting time and physical activity after stroke: Physical ability is only part of the story. *Topics in Stroke Rehabilitation, 23*(1), 36–42. https://doi.org/10.1179/1945511915Y.0000000009.

English, C., Manns, P. J., Tucak, C., & Bernhardt, J. (2014). Physical activity and sedentary behaviors in people with stroke living in the community: A systematic review. *Physical Therapy, 94*(2), 185–196. https://doi.org/10.2522/ptj.20130175.

Enzinger, C., Dawes, H., Johansen-Berg, H., Wade, D., Bogdanovic, M., Collett, J., ... Matthews, P. M. (2009). Brain activity changes associated with treadmill training after stroke. *Stroke, 40*(7), 2460–2467. https://doi.org/10.1161/STROKEAHA.109.550053.

Forlander, D. A., & Bohannon, R. W. (1999). Rivermead mobility index: A brief review of research to date. *Clinical Rehabilitation, 13*(2), 97–100. https://doi.org/10.1191/026921599675502264.

Fulk, G. D., He, Y., Boyne, P., & Dunning, K. (2017). Predicting home and community walking activity poststroke. *Stroke, 48*(2), 406–411. https://doi.org/10.1161/STROKEAHA.116.015309.

Goldstein, L. B., Samsa, G. P., Matchar, D. B., & Horner, R. D. (2004). Charlson index comorbidity adjustment for ischemic stroke outcome studies. *Stroke, 35*(8), 1941–1945. https://doi.org/10.1161/01.STR.0000135225.80898.1c.

Jones, P. S., Pomeroy, V. M., Wang, J., Schlaug, G., Tulasi Marrapu, S., Geva, S., Rowe, P. J., Chandler, E., Kerr, A., Baron, J. C., & Investigators, S. W.-C. (2016). Does stroke location predict walk speed response to gait rehabilitation? *Human Brain Mapping, 37*(2), 689–703. https://doi.org/10.1002/hbm.23059.

Lee, K. B., Kim, J. S., Hong, B. Y., Sul, B., Song, S., Sung, W. J., ... Lim, S. H. (2017). Brain lesions affecting gait recovery in stroke patients. *Journal Brain and Behavior, 7*(11), e00868. https://doi.org/10.1002/brb3.868.

Lee, J. A., Williams, S. M., Brown, D. D., & Laurson, K. R. (2015). Concurrent validation of the actigraph gt3x+, polar active accelerometer, omron hj-720 and yamax digiwalker sw-701 pedometer step counts in lab-based and free-living settings. *Journal of Sports Sciences, 33*(10), 991–1000. https://doi.org/10.1080/02640414.2014.981848.

Leh, S. E., Ptito, A., Chakravarty, M. M., & Strafella, A. P. (2007). Fronto-striatal connections in the human brain: A probabilistic diffusion tractography study. *Neuroscience Letters, 419*(2), 113–118. https://doi.org/10.1016/j.neulet.2007.04.049.

Luft, A. R., Macko, R. F., Forrester, L. W., Villagra, F., Ivey, F., Sorkin, J. D., ... Hanley, D. F. (2008). Treadmill exercise activates subcortical neural networks and improves walking after stroke: A randomized controlled trial. *Stroke, 39*(12), 3341–3350. https://doi.org/10.1161/STROKEAHA.108.527531.

Mahendran, N., Kuys, S. S., & Brauer, S. G. (2016). Recovery of ambulation activity across the first six months post-stroke. *Gait and Posture, 49*, 271–276. https://doi.org/10.1016/j.gaitpost.2016.06.038.

Mehanna, R., & Jankovic, J. (2013). Movement disorders in cerebrovascular disease. *Lancet Neurology, 12*(6), 597–608. https://doi.org/10.1016/S1474-4422(13)70057-7.

Reynolds, A. M., Peters, D. M., Vendemia, J. M., Smith, L. P., Sweet, R. C., Baylis, G. C., ... Fritz, S. L. (2014). Neuronal injury in the motor cortex after chronic stroke and lower limb motor impairment: A voxel-based lesion symptom mapping study. *Neural Regeneration Research, 9*(7), 766–772. https://doi.org/10.4103/1673-5374.131589.

Sivaramakrishnan, A., & Madhavan, S. (2018). Absence of a transcranial magnetic stimulation-induced lower limb corticomotor response does not affect walking speed in chronic stroke survivors. *Stroke, 49*(8), 2004–2007. https://doi.org/10.1161/STROKEAHA.118.021718.

Stinear, C. M. (2017). Prediction of motor recovery after stroke: Advances in biomarkers. *Lancet Neurology, 16*(10), 826–836. https://doi.org/10.1016/S1474-4422(17)30283-1.

Stinear, C. M., Byblow, W. D., & Ward, S. H. (2014). An update on predicting motor recovery after stroke. *Annals of Physical and Rehabilitation Medicine, 57*(8), 489–498. https://doi.org/10.1016/j.rehab.2014.08.006.

Suri, R., Rodriguez-Porcel, F., Donohue, K., Jesse, E., Lovera, L., Dwivedi, A. K., & Espay, A. J. (2018). Post-stroke movement disorders: The clinical, neuroanatomic, and demographic portrait of 284 published cases. *The Journal of Stroke and Cerebrovascular, 27*(9), 2388–2397. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.04.028.

Takakusaki, K. (2017). Functional neuroanatomy for posture and gait control. *Journal of Movement Disorders, 10*(1), 1–17. https://doi.org/10.14802/jmd.16062.

Thilarajah, S., Mentiplay, B. F., Bower, K. J., Tan, D., Pua, Y. H., Williams, G., ... Clark, R. A. (2018). Factors associated with post-stroke physical activity: A systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation, 99*(9), 1876–1889. https://doi.org/10.1016/j.apmr.2017.09.117.

Tudor-Locke, C., Craig, C. L., Brown, W. J., Clemes, S. A., De Cocker, K., Giles-Corti, B., ... Blair, S. N. (2011). How many steps/day are enough? For adults. *International Journal of Behavioral Nutrition and Physical Activity, 8*, 79. https://doi.org/10.1186/1479-5868-8-79.

Wahlund, L. O., Barkhof, F., Fazekas, F., Bronge, L., Augustin, M., Sjögren, M., ... European Task Force on Age-Related White Matter Changes (2001). A new rating scale for age-related white matter changes applicable to mri and ct. *Stroke, 32*(6), 1318–1322. https://doi.org/10.1161/01.STR.32.6.1318.