

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

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- 1 Title: Neural substrates of reduced walking activity after supratentorial stroke: a voxel-based
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#### 1 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<sup>-1</sup>), 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<sup>-1</sup>. 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.

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

21

**Keywords:** Stroke; Secondary prevention; Walking; Magnetic resonance imaging; Physical
activity; Rehabilitation.

#### 1 1. INTRODUCTION

2

3 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 4 5 physical activity, far below the recommended 10,000 daily steps required for health benefits 6 (Mahendran, Kuys, & Brauer, 2016; Tudor-Locke et al., 2011) and can lead to sedentariness 7 (English, Manns, Tucak, & Bernhardt, 2014). If the degree of physical impairment may be an 8 important factor driving sitting and physical activity time in people post stroke, the 9 determinants and predictors of low levels of walking activity (WA) may be multifactorial and are not well studied (English et al., 2016). Thus, depression, fatigue and altered quality of life 10 11 are negatively correlated with post-stroke physical activity (Thilarajah et al., 2018).

Walking requires the complex interaction of several brain structures and functions that 12 13 goes far beyond voluntary motor control (Takakusaki, 2017). Studying the relationship 14 between neuroimaging and mobility impairments can lead to a better understanding of the 15 underlying pathophysiology of those impairments and can serve as biomarkers of recovery 16 (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; 17 Reynolds et al., 2014). Lesions involving the posterolateral putamen are associated with 18 19 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 20 21 with poor recovery of gait post-stroke (Jones et al., 2016; K. B. Lee et al., 2017). The 22 association between lesion location and reduced walking activity (WA) following stroke has 23 never been studied. We hypothesized that a cluster of different lesion locations related to 24 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.

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## 4 2. MATERIAL AND METHODS

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## 2.1. Participants

7 Thirty-three community-dwelling stroke survivors (age: 63.9±12.9 years; % female: 8 36.4%; NIHSS at admission: 3.3±4.0) were recruited in this cross-sectional study, at least 3 9 months after stroke onset (mean±1SD=182.4±74.9 days) from the Department of Neurology 10 of the Geneva University Hospital between November 2012 and January 2016. Clinical 11 characteristics are presented in Table 1. Inclusion criteria were: i) first ischemic, unilateral, supratentorial stroke (to overcome specific balance and gait impairments linked with 12 13 brainstem or cerebellar lesions), ii) brain magnetic resonance imaging (MRI) confirming 14 stroke diagnosis, iii) a Rivermead Mobility Index (Antonucci, Aprile, & Paolucci, 2002) 15 score of level 7 or above, ensuring participants with sufficient mobility skills, and iv) and absence of other neurological condition. Participants with contraindications to exercise 16 participation, unable to walk, with language impairments including aphasia or who had an 17 acute medical condition interfering with gait (except stroke) were not included in the study. 18

19 The protocol was approved by the Ethic Committee of the Geneva University20 Hospitals and each participant provided a signed informed consent.

Insert Table 1 about here

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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).

7 Functional independence and mobility for activities of daily living were assessed using the Barthel Index (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013). Rivermead 8 9 Mobility Index (Antonucci et al., 2002), a sub-scale of the Rivermead Motor Assessment was 10 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 11 12 walking ability (Fulk, He, Boyne, & Dunning, 2017), gait speed was determined in the Willy 13 Taillard Kinesiology Laboratory of the Geneva University Hospital using a GAITRite 14 walkway system® (GAITRite Gold, CIR Systems, PA, USA) (Bilney, Morris, & Webster, 2003). Participants were asked to walk at their comfortable gait speed. Each participant 15 performed one evaluation trial at steady-state walking speed on a 10-meter walkway. 16

17 The main outcome for WA was the daily step counts (DSC) (Fulk et al., 2017) 18 measured with an Actigraph GT3x+ triaxial accelerometer (ActiGraph, LLC, Pensacola, FL, 19 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 20 21 monitor for free-living condition (J. A. Lee, Williams, Brown, & Laurson, 2015). The accelerometer was worn over the fifth lumbar vertebra 24 hours a day during 7 consecutive 22 23 days and removed only for water-based activities. Accelerometers were initialized and data 24 downloaded using software provided by the manufacturer (v5.2.0, ActiLife, ActiGraph). Data were included if the participant had accumulated at least 10 hours of valid activity recordings
 per day for a minimum of 4 days (mean±SD duration of recording: 7±0 days).

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## 2.3. MRI processing and lesion analysis

5 MRI scans were performed according to standard stroke protocols at the Radiology 6 Department of Geneva University Hospitals on average within 3 days following stroke onset 7 (2.9±2.7 days). MRI protocol included T1, T2 and fluid attenuated inversion recovery 8 (FLAIR) images, obtained with standard parameters on a 1.5 T apparatus (Intera, Philips 9 Medical Systems).

10 MRI images were first processed using SPM12 (Wellcome Trust Centre for 11 Neuroimaging, London, United Kingdom) for Matlab (Mathworks, Natick, MA). T1 native 12 images were spatially normalized into Montreal Neurological Institute (MNI) space. The T2-13 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. (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 lesionbehavior 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*<.01</li>
uncorrected, with a cluster threshold of *p*<.05).</li>

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-1mm atlases were overlaid with the significant VLSM clusters.

10

11 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).

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#### 16 **3. RESULTS**

17 *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</li>
m·s<sup>-1</sup>), seven (21%) as limited community ambulators (0.4≤gait speed≤0.8 m·s<sup>-1</sup>) and 25

24 (76%) as full community ambulators (gait speed> $0.8 \text{ m} \cdot \text{s}^{-1}$ ) (Fulk et al., 2017).

All participants had valid accelerometer recordings with a mean±1SD DSC of 1 4491.9±2473.7 steps·day<sup>-1</sup> (Table 2). 2 3 Insert Table 2 about here 4 5 6 3.2. Imaging assessment – VLSM analysis 7 Stroke characteristics and quantification of age-related white matter changes are 8 presented in Table 1. The highest frequency of lesions was observed in the middle cerebral 9 artery territory as shown in Figure 1. VLSM analyses showed that 3 subcortical brain regions, 10 the posterior part of the putamen, the posterior limb of the internal capsule and the anterior 11 part of the corona radiata were associated with low DSC (Figure 2, MNI coordinates of peak 12 value, -29, -10, 6, corresponding to the posterior part of the putamen). No cortical region was 13 associated with WA levels. 14 Insert Figure 1 about here 15 Insert Figure 2 about here 16 17 18 4. **DISCUSSION** 19 We found that daily WA, a major health outcome in terms of secondary prevention 20 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 21 mobility skills. The reported DSC of  $4491.9 \pm 2473.7$  steps day<sup>-1</sup> is consistent with previous 22 23 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 24 25 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-1 2 related white matter changes. The strongest association was observed in the posterior part of 3 the putamen, a key structure involved in sub-cortico-cortical motor loops, and in particular in 4 fronto-striatal connections, that span motor, cognitive and limbic cortical areas (Leh, Ptito, 5 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., 6 7 2009) and negatively affect gait recovery post-stroke (Jones et al., 2016; K. B. Lee et al., 8 2017). Stroke lesions involving the putamen can also be associated with parkinsonism 9 (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 10 parkinsonism or mild parkinsonian signs that may have contribute to the observed WA 11 limitation. 12

13 Other relevant structures were the internal capsule and the corona radiata, both part of 14 the CST, previously described as being associated with lower gait speed (Reynolds et al., 15 2014) and poor gait recovery (Cheng et al., 2014; Jones et al., 2016) after stroke. In the study 16 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 17 (Jones et al., 2016). Beyond anatomical lesion, the relevance of CST functional integrity on 18 19 predicting functional outcomes post-stroke such as walking remains unclear (Stinear, 2017). 20 Recent results suggest that the absence of hemiparetic lower limb motor evoked potential 21 from the ipsilesional hemisphere induced by transcranial magnetic stimulation did not affect 22 walking speed in chronic stroke survivors (Sivaramakrishnan & Madhavan, 2018). Authors 23 further suggest that walking recovery may rely on the recruitment of redundant motor 24 pathways, such as reticulospinal tract or could arise from the development of rehabilitationinduced motor compensations (Sivaramakrishnan & Madhavan, 2018). The anatomical-25

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.

4 We found no association between cortical lesion and WA levels. This result is supported by two interventional studies highlighting the strong subcortical contribution to 5 6 rehabilitation-induced recovery of lower limb and walking function after stroke (Enzinger et 7 al., 2009; Luft et al., 2008). However, other authors observed cortical activation changes 8 (bilateral primary sensorimotor cortex, bilateral supplementary motor area) in rehabilitation-9 associated walking improvements (Enzinger et al., 2009). These discrepancies could be 10 explained by the design of the studies (observational vs. interventional) and by the outcome 11 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 12 13 weeks of treadmill training while we assessed spontaneous WA in free-living condition over 14 seven days in a cross-sectional manner. The small sample size may prevent us to report 15 cortical lesions associated with WA. Our results, together with those of the two 16 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 17 'cross-talk' between several motor and non-motor brain functions including gait and postural 18 19 control, cognitive functions as well as volitional behaviour. We thus hypothesize that the 20 outlined lesions, found as being negatively associated with WA represent key nodes of a 21 wider WA-related connectome. The main limitation of this preliminary work was the 22 inclusion of minor strokes, preventing the generalization of our findings for all stroke 23 patients. Moreover, as MRI scans were performed at least three months before evaluation, we 24 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 25

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

#### 6 5. CONCLUSIONS

Our results highlight that daily WA measured three months after stroke onset was negatively associated with a cluster of subcortical 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.

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19

## 20 DECLARATION OF CONFLICTING INTERESTS

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- 25

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**3 Table 1:** Clinical characteristics of the population (n=33)

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

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Figure 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.

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14 Figure 2: Voxel-based lesion symptom mapping study: cerebral correlates of the daily 15 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 16 limb of the internal capsule and the anterior part of the corona radiata. All lesions are flipped 17 onto the left hemisphere. The color bar indicates t-tests values, that range from p<0.05 (black) 18 19 to p<0.01 (red). Montreal Neurological Institute coordinates of each transverse section (z 20 axis) are given. R indicates the right side of brain MRI. CoR = corona radiata; CPu = caudal 21 putamen; IC = internal capsule.



R

-30 -25 -20 -15 -10 -5



0 5 10 15 20 25





75 80 85

90

n=

10

5



*p*<0.05

*p*<0.01

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%)			
Туре				
Ischemic, n (%)	33 (100%)			
Hemorrhagic, n (%)	0 (0%)			
Lesion volume, mean (SD) (cm <sup>3</sup> )	18.4 (32.4)			
ARWMC total score [14], mean (SD)	5.7 (5.1)			
(Range 0-30)				

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

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.

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

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

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