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1 **Title:** Neural substrates of reduced walking activity after supratentorial stroke: a voxel-based
2 lesion symptom mapping study

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1 **ABSTRACT**

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

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

13 **Results:** Participants presented 4491.9 ± 2473.7 $\text{steps} \cdot \text{day}^{-1}$. Lower levels of walking activity
14 were related to lesions of the posterior part of the putamen, of the posterior limb of the
15 internal capsule and of the anterior part of the corona radiata. No cortical region was
16 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

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

24

1 1. INTRODUCTION

2

3 Physical activity is a key component of secondary stroke prevention (Billinger et al.,
4 2014). Functional limitations experienced by post stroke patients often result in reduced
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
10 are not well studied (English et al., 2016). Thus, depression, fatigue and altered quality of life
11 are negatively correlated with post-stroke physical activity (Thilarajah et al., 2018).

12 Walking requires the complex interaction of several brain structures and functions that
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
17 predict decreased gait speed, even after a chronic delay following stroke (Jones et al., 2016;
18 Reynolds et al., 2014). Lesions involving the posterolateral putamen are associated with
19 temporal gait asymmetry after a chronic delay following stroke (Alexander et al., 2009).
20 When combined with lesions of neighbouring structures, lesions to the putamen are associated
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.

1 This study aims to identify the neuroanatomic correlates of low levels of WA following
2 stroke, based on a voxel-based lesion-symptom mapping (VLSM) approach.

3

4 **2. MATERIAL AND METHODS**

5

6 *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 \pm 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,
12 supratentorial stroke (to overcome specific balance and gait impairments linked with
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
16 absence of other neurological condition. Participants with contraindications to exercise
17 participation, unable to walk, with language impairments including aphasia or who had an
18 acute medical condition interfering with gait (except stroke) were not included in the study.

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

21

22 [Insert Table 1 about here](#)

23

24 *2.2. Clinical data and measurements*

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

7 Functional independence and mobility for activities of daily living were assessed
8 using the Barthel Index (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013). Rivermead
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
11 reveal higher functional status and mobility skills. As a major determinant of post stroke
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,
15 2003). Participants were asked to walk at their comfortable gait speed. Each participant
16 performed one evaluation trial at steady-state walking speed on a 10-meter walkway.

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,
20 including low gait speeds (Bassett & John, 2010) and is recognized as a valid step-count
21 monitor for free-living condition (J. A. Lee, Williams, Brown, & Laurson, 2015). The
22 accelerometer was worn over the fifth lumbar vertebra 24 hours a day during 7 consecutive
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

1 were included if the participant had accumulated at least 10 hours of valid activity recordings
2 per day for a minimum of 4 days (mean±SD duration of recording: 7±0 days).

3

4 *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.

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

20 VLSM is a voxel-by-voxel statistical method dedicated to the analysis of brain lesion-
21 behavior relationship (Bates et al., 2003). VLSM analyses were performed using the
22 nonparametric mapping (NPM) software
23 (<http://www.mccauslandcenter.sc.edu/mricro/mricron/>) included in the MRICron toolset. In
24 each voxel, a T-test was conducted to compare the behavioral score of patients with or
25 without a lesion in that voxel. Analyses were only conducted on voxels damaged in ≥ 5

1 subjects. All 3D lesion maps were fed into NPM along with the corresponding participant
2 performance in terms of DSC. Age, body mass index, and age-related white matter changes,
3 three variables linked with impaired walking skills, were used as covariates. The resulting
4 statistical maps were thresholded voxelwise at conventional statistical values ($p < .01$
5 uncorrected, with a cluster threshold of $p < .05$).

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

10

11 *2.4. Statistical analysis*

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

15

16 **3. RESULTS**

17 *3.1. Clinical and walking activity assessment*

18 We included patients without significant cognitive impairment, as reflected by scores
19 from the MoCA. Scores from the Barthel Index revealed high functional independence and
20 mobility for activities of daily living. Consistently, scores from the Rivermead Mobility Index
21 revealed high functional mobility skills (Forlander & Bohannon, 1999) (Table 2). According
22 to gait speed values, one participant (3%) was considered as home ambulator (gait speed < 0.4
23 $\text{m}\cdot\text{s}^{-1}$), seven (21%) as limited community ambulators ($0.4 \leq \text{gait speed} \leq 0.8 \text{ m}\cdot\text{s}^{-1}$) and 25
24 (76%) as full community ambulators (gait speed $> 0.8 \text{ m}\cdot\text{s}^{-1}$) (Fulk et al., 2017).

1 All participants had valid accelerometer recordings with a mean \pm 1SD DSC of
2 4491.9 \pm 2473.7 steps·day⁻¹ (Table 2).

3
4 [Insert Table 2 about here](#)

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
15 [Insert Figure 1 about here](#)

16 [Insert Figure 2 about here](#)

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
21 cluster of subcortical lesions in a group of patients with high functional independence and
22 mobility skills. The reported DSC of 4491.9 \pm 2473.7 steps·day⁻¹ is consistent with previous
23 stroke studies (English et al., 2014; Mahendran et al., 2016).

24 Consistent with our hypothesis, a cluster of lesions found in the posterior part of the
25 putamen, the posterior limb of the internal capsule and the anterior part of the corona radiata

1 were associated with lower daily WA after controlling for age, body mass index and age-
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
6 putamen are associated with gait impairments, such as gait asymmetry (Alexander et al.,
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
10 neurological conditions but stroke. However, we did not quantify the presence of
11 parkinsonism or mild parkinsonian signs that may have contribute to the observed WA
12 limitation.

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
17 significantly associated with lower scores of gait and everyday functions of general mobility
18 (Jones et al., 2016). Beyond anatomical lesion, the relevance of CST functional integrity on
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 rehabilitation-
25 induced motor compensations (Sivaramakrishnan & Madhavan, 2018). The anatomical-

1 functional discrepancies regarding the role of CST in predicting walking recovery post-stroke
2 reinforce the statement that walking recovery post-stroke is a complex process at least
3 partially understood.

4 We found no association between cortical lesion and WA levels. This result is
5 supported by two interventional studies highlighting the strong subcortical contribution to
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)
12 evaluated their patients with a walking endurance test (2-minute timed walking test) after 4
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
17 motor loops in functional walking recovery post-stroke. Thus, WA may be the result of a
18 ‘cross-talk’ between several motor and non-motor brain functions including gait and postural
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
25 with high functional and mobility skills, as reflected by Barthel Index and Rivermead

1 Mobility Index scores. Unfortunately, while focusing on motor skills and mobility
2 impairments, our work did not include comprehensive cognitive and behavioural evaluations.
3 Future work should investigate the contribution of cognition and behaviour to WA levels,
4 while controlling for mobility skills.

5

6 **5. CONCLUSIONS**

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

13

14

15

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19

20 **DECLARATION OF CONFLICTING INTERESTS**

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25

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1 **LEGENDS**

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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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8 **Figure 1: Lesion overlap map from the 33 participants.** All right-sided lesions (n=14) are
9 flipped onto the left hemisphere (Cheng et al., 2014). The color bar indicates number of
10 overlapping lesions, that range from 1 (black) to 10 overlapping lesions (red). Montreal
11 Neurological Institute coordinates of each transverse section (z axis) are given. R indicates the
12 right side of brain MRI.

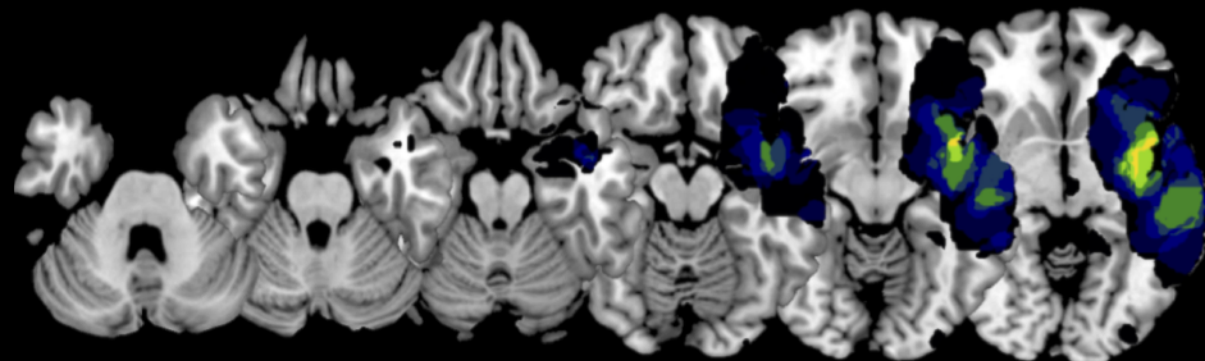
13

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.**

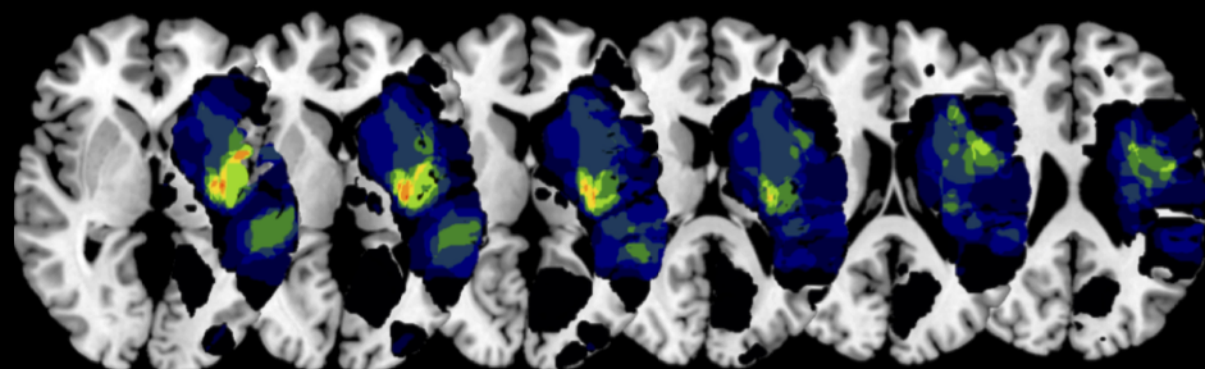
16 Mapping of the DSC reveal an involvement of the posterior part of the putamen, the posterior
17 limb of the internal capsule and the anterior part of the corona radiata. All lesions are flipped
18 onto the left hemisphere. The color bar indicates t-tests values, that range from $p < 0.05$ (black)
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.

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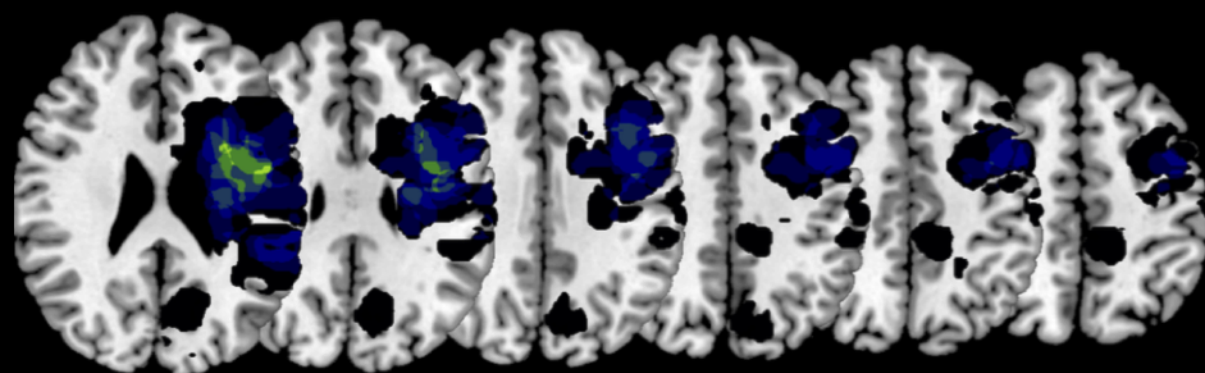
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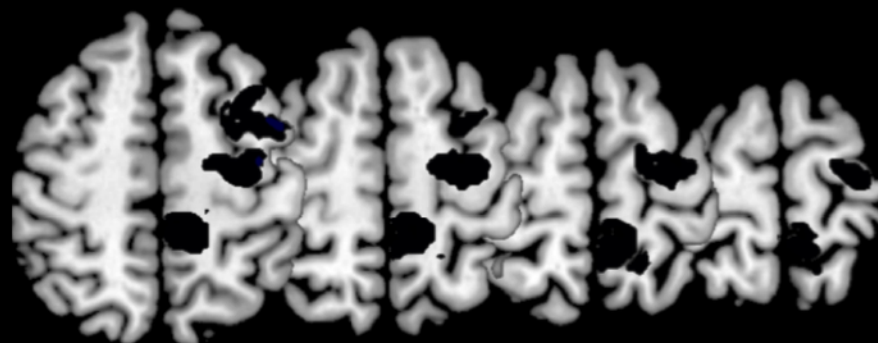
-30 -25 -20 -15 -10 -5



0 5 10 15 20 25



30 40 50 60 65 70



75 80 85 90

n=

10



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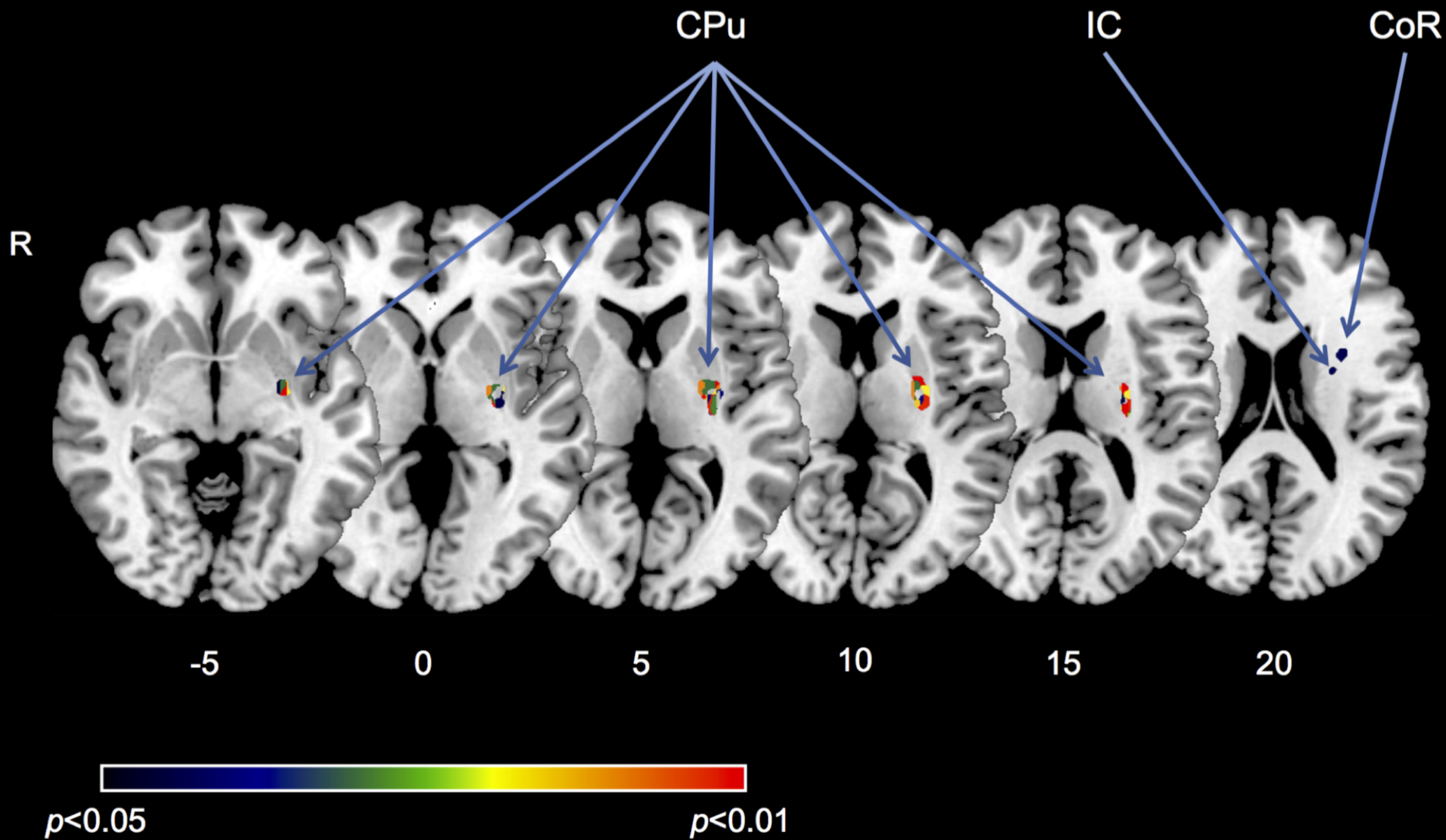


Table 1: Clinical characteristics of the population (n=33)

Clinical characteristics	
Females, n (%)	12 (36.4%)
Age, mean (SD) (years)	63.9 (12.9)
BMI, mean (SD) (kg·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.

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·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.