### Title

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RESEARCH ARTICLE

# Lower extremity long-latency reflexes differentiate walking function after stroke

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## Abstract

The neural mechanisms of walking impairment after stroke are not well characterized. Specifically, there is a need for understanding the mechanisms of impaired plantarflexor power generation in late stance. Here, we investigated the association between two neurophysiologic markers, the long-latency reflex (LLR) response and dynamic facilitation of antagonist motor-evoked responses, and walking function. Fourteen individuals with chronic post-stroke hemiparesis and thirteen healthy controls performed both isometric and dynamic plantarflexion. Transcranial magnetic stimulation (TMS) assessed supraspinal drive to the tibialis anterior. LLR activity was assessed during dynamic voluntary plantarflexion and individuals post-stroke were classified as either LLR present (LLR+) or absent (LLR−). All healthy controls and nine individuals post-stroke exhibited LLRs, while five did not. LLR+ individuals revealed higher clinical scores, walking speeds, and greater ankle plantarflexor power during walking compared to LLR− individuals. LLR− individuals exhibited exaggerated responses to TMS during dynamic plantarflexion relative to healthy controls. The LLR− subset revealed dysfunctional modulation of stretch responses and antagonist supraspinal drive relative to healthy controls and the higher functioning LLR+ individuals post-stroke. These abnormal physiologic responses allow for characterization of individuals post-stroke along a dimension that is clinically relevant and provides additional information beyond standard behavioral assessments. These findings provide an opportunity to distinguish among the heterogeneity of lower extremity motor impairments present following stroke by associating them with responses at the nervous system level.

**Keywords** Stroke · Walking · Long-latency reflex · Transcortical reflex · Reciprocal inhibition

## Introduction

Following stroke, many individuals face lifelong walking impairments that restrict community participation (Jorgensen et al. 1995; Grau-Pellicer et al. 2019). Most rehabilitation strategies intended to improve walking function report success only in approximately 50% of cases (Nadeau et al. 2013; Awad et al. 2016). This limited success could be due in part to physiologic heterogeneity among individuals with stroke (Duncan et al. 2011; Banks et al. 2017), which is recognized but poorly understood. Unlike the underlying physiology, the biomechanical deficits in walking following stroke are better characterized (Wonsetler and Bowden 2017). Here, we investigated the association between known clinical and biomechanical deficits and two neurophysiologic markers in the paretic lower extremity of individuals with chronic stroke.

One key biomechanical deficit present in many individuals with chronic stroke is impaired plantarflexor power generation in late stance (Jonkers et al. 2009; Kitatani et al. 2016b). In normal walking, the ankle is the primary energy generator, producing the necessary propulsion to advance the limb during swing (Winter 1983; Little et al. 2014). It is currently unclear what limits the ability of individuals with stroke to produce plantarflexion, but three potential contributors include weakness, excessive co-contraction, and spasticity. Weakness, one of the

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cardinal sequelae of stroke, arises from central factors and prevents sufficient and appropriate muscle activation patterns (Nadeau et al. 1999; Clark et al. 2006). Excessive co-contraction increases joint stiffness, is energetically inefficient, and is assumed to be a common manifestation in post-stroke gait impairment (Lamontagne et al. 2000; Kitatani et al. 2016a). Spasticity manifests in the forms of hypertonia and hyperreflexia, and is a common treatment target in the paretic ankle musculature (Malhotra et al. 2009; Thibaut et al. 2013). Impaired plantarflexion during gait could arise from any combination of these factors, but all are worth exploring to understand walking impairment within this population.

We originally designed an experiment to assess the neurophysiologic correlates of plantarflexor dysfunction following stroke (Patten et al. 2017). Here we report results from a secondary analysis of that study. Because paretic leg propulsion requires coordination of both plantar- and dorsiflexor muscle activity (Roelker et al. 2019), the role of the antagonist dorsiflexors also remains to be explored. Assessing the dorsiflexors can provide particular insights into the roles of co-contraction and, potentially, spasticity during plantarflexion. This is possible because plantarflexor power generation stretches the dorsiflexors, producing stretch-mediated reflex activity. Here, a reflex will be defined as an electromyographic (EMG) response of a consistent duration exceeding background activity occurring at a consistent delay after stretch (Hof and Duysens 2018). Muscle stretch produces reflex responses of varying latencies, but here we will focus on the long-latency reflex (LLR) because evidence suggests that it has a strong cortical component (Jones and Watt 1971; Petersen et al. 1998a). There are several common characteristics of the LLR between the upper and lower limbs and across muscles. The latency of this response is too long for a monosynaptic spinal pathway, but too short to be volitionally mediated (Marsden et al. 1983). This time window is ideal for integration with sensory information from all modalities and modification in response to a perturbation (Pruszynski and Scott 2012). These stretch-mediated responses can be highly informative regarding central nervous system gating and integration of information (Scott et al. 2015), leading to new understanding of the control of walking and lower extremity movement.

The goal of this secondary analysis is to investigate the association between neurophysiologic responses in the antagonist muscle during plantarflexion and walking function following stroke. We hypothesize that these neuromarkers will allow differentiation of a clinically heterogeneous group of individuals with chronic stroke. Specifically, the presence or absence of the LLR will differentiate high- and low-functioning individuals, allowing for further study of the underlying mechanisms of dysfunction within low-functioning individuals.

## Methods

### Subjects

Of the 39 individuals that participated in the larger study, 14 individuals with chronic stroke (age $63 \pm 8$ years, 12 male) and 13 healthy age-matched controls (age $61 \pm 8$ years, 6 male) met the criteria for inclusion in this analysis. Demographic data for the stroke cohort, reported in Table 1, illustrate a diverse group of individuals with mild-to-moderate motor impairment. Overall inclusion criteria for the stroke group included: a diagnosis of unilateral cortical or subcortical stroke at least six months prior to date of enrollment, ability to follow three-step commands, and ability to walk at least ten meters without assistance. CT or MR imaging results in medical records confirmed stroke diagnosis. All participants were free of any contraindications for transcranial magnetic stimulation (TMS), including implanted metal above the chest, seizure disorders, or pregnancy (Rossini et al. 2015). In addition to overall inclusion criteria, this secondary analysis was restricted to participants with adequate ankle range of motion and volitional movement velocities to measure LLRs during the dynamic plantarflexion task, as well as measurable motor evoked responses (MEPs) to TMS in the tibialis anterior. We excluded nine individuals due to insufficient range of motion during the task, two for lack of measurable MEPs, and one control who was determined neurologically unhealthy.

Testing occurred at the Brain Rehabilitation Research Center in the Malcom Randall VA Medical Center in Gainesville, FL. Isolated plantarflexion, instrumented gait analysis, and clinical assessments spanned 2–3 days for each participant. The University of Florida Health Science Center Institutional Review Board approved all procedures and all participants gave written informed consent prior to participation. Testing was conducted in accordance with the Declaration of Helsinki.

### Instrumentation

Isolated plantarflexion movements were tested using a commercially available dynamometer (Biodex System 3.2, Shirley, NY, USA) and controlled by a Power1401 data acquisition system (Cambridge Electronic Design Limited, Cambridge, England). We collected surface electromyography (EMG) using a commercially available system (MA300-28, Motion Lab Systems, Baton Rouge, LA, USA) from the medial gastrocnemius (MG), soleus (SOL), and tibialis anterior (TA) muscles using gel surface electrodes (Cleartrace 2, ConMed, Utica, NY, USA) and snap-on preamplifiers (MA-420, Motion Lab Systems, Baton

**Table 1** Subjects' demographics

| Subject | Age (yrs) | Sex | Paretic side | Chronicity (mos) | Stroke type | Lesion location | LE FMA | SPPB | DGI | AFO/device | LLR status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke 01 | 80 | M | R | 97 | Hemorrhagic | L temporal lobe | 32 | 11 | 23 | – | LLR+ |
| Stroke 02 | 53 | M | R | 25 | Ischemic | L parietal lobe | 34 | 12 | 24 | – | LLR+ |
| Stroke 03 | 61 | M | R | 35 | Ischemic | L ICA occlusion with striatocapsular involvement | 24 | 10 | 16 | Aircast® | LLR+ |
| Stroke 04 | 61 | M | R | 87 | Ischemic | L temporal, parietal, and frontal lobes | 12 | 5 | 8 | Custom AFO | LLR− |
| Stroke 05 | 73 | M | R | 62 | Ischemic | L parietal lobe | 34 | 11 | 22 | – | LLR+ |
| Stroke 06 | 67 | M | R | 86 | Ischemic | L parietal with basal ganglia involvement | 34 | 8 | 22 | – | LLR+ |
| Stroke 07 | 69 | M | L | 267 | Hemorrhagic | R internal capsule | 17 | 6 | 10 | Walk Aide® | LLR− |
| Stroke 08 | 73 | M | L | 93 | Ischemic | R posterior limb of internal capsule | 26 | 8 | 15 | Custom AFO | LLR− |
| Stroke 09 | 55 | F | L | 25 | Ischemic | R temporal lobe | 34 | 12 | 23 | – | LLR+ |
| Stroke 10 | 57 | M | R | 59 | Ischemic | L frontal and temporal lobes with basal ganglia involvement | 13 | 5 | 10 | Custom AFO | LLR− |
| Stroke 11 | 62 | M | L | 65 | Ischemic | R parietal and temporal lobes | 34 | 12 | 21 | – | LLR+ |
| Stroke 12 | 56 | F | R | 131 | Ischemic | L occipital and parietal lobes | 19 | 7 | 9 | Custom AFO | LLR+ |
| Stroke 13 | 54 | M | L | 7 | Hemorrhagic | R putamen | 22 | 7 | 14 | Custom AFO | LLR− |
| Stroke 14 | 66 | M | R | 131 | Ischemic | L insula and basal ganglia | 34 | 12 | 24 | – | LLR+ |

Additional subject characterization is included in Fig. 5

*yrs* years, *M* male, *F* female, *L* left, *R* right, *mos* months, *ICA* internal carotid artery, *LE FMA* Lower Extremity Fugl-Meyer Motor score, *SPPB* Short Physical Performance Battery, *DGI* Dynamic Gait Index, *AFO* ankle foot orthosis, *LLR* long-latency reflex

Rouge, LA, USA). Electrodes were placed according to SENIAM guidelines (Freriks et al. 1999). We applied single-pulse TMS using a Magstim 200$^2$ stimulator with a 110 mm double-cone coil (Whitland, UK). A Brainsight TMS neuronavigation system (Rogue Resolutions Ltd, Montreal, CA, USA) was used to maintain coil placement.

Analog signals from the dynamometer (torque, position, and velocity) were low-pass filtered using an analog hardware filter (100 Hz cutoff). All data were recorded in Signal 6.0 (Cambridge Electronic Design Limited, Cambridge, England) at a sampling rate of 2000 Hz.

## Protocol

Dynamometer testing took place in a single session. Each participant was seated with the seatback fully upright and the paretic leg (or test leg in healthy controls) extended, with approximately 90° of hip flexion, 20° of knee flexion, and the ankle positioned against the footplate at neutral plantar/dorsiflexion, as shown in Fig. 1. All joints were positioned so movement would occur only through the sagittal plane at the ankle. This configuration minimizes contributions of the hip muscles to plantarflexion while simultaneously positioning the medial gastrocnemius and soleus muscles within the optimal operating ranges (Winter and Challis 2008; Rubenson et al. 2012). We assessed maximum voluntary contractions (MVCs) at the beginning of the session in both neutral and dorsiflexed (approximately 5°) ankle positions. MVCs were determined in real time as the best of 3–5 trials involving 2–4 s contractions, with at least 60 s of rest between trials. Participants received visual torque feedback and verbal encouragement from study personnel. Trials in which participants contracted thigh muscles in addition to ankle musculature were excluded. The test leg was randomized across healthy control participants. The original study assessed corticospinal efficacy to the plantarflexors, so TMS was localized to generate MEPs in the MG and SOL. Due to the close relationship between the ankle musculature within the cerebral architecture, TA MEPs are almost always elicited when targeting the plantarflexors (Brouwer and Ashby 1990; Bawa et al. 2002), a phenomenon we observed during our study. Soleus resting motor threshold (rMT) was the minimum stimulus level required to elicit a response $\geq 50$ μV peak-to-peak amplitude in at least 50% of trials (Rossini et al. 2015).

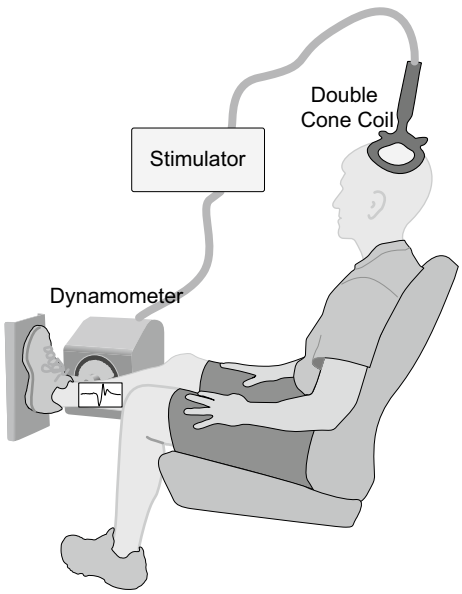


**Fig. 1** Illustration of experimental setup. Participant positioned with test leg extended and foot resting against dynamometer footplate, with ankle aligned to axis of rotation. Transcranial magnetic stimulation (TMS) was delivered through a double cone coil positioned above contralateral hemisphere motor cortex

During testing, participants were instructed to generate and hold 10–20% of their measured MVC torque against the dynamometer footplate. Participants were provided real-time visual feedback of torque output to ensure consistent effort and task attention. Following a one-second hold of 10–20% measured MVC torque, a magnetic stimulus was applied at 120% of SOL rMT. The mean stimulus intensity was 63% of maximum stimulator output for healthy controls and 84% for individuals with chronic stroke. In the isometric condition, the footplate remained stationary in the neutral position during stimulation. In the dynamic condition, the footplate started in approximately 5° of dorsiflexion. Following the 1-second hold, the footplate released, allowing the participant to plantarflex, "as hard and as fast as possible", up to a maximum velocity of 90° per second through their available range of motion (Fig. 2). This rate is comparable to, or slower than, angular velocities that occur at the ankle during normal walking, and comparable to stretch velocities employed in another lower extremity reflex study (Thilmann et al. 1991). Magnetic stimulation was triggered when the ankle moved through the neutral position. After each trial, the participant had 2–3 s of rest before the footplate passively returned to the starting position and the next trial began. A minimum of six trials were performed in each test condition.

## Data analysis

Data were processed offline using Matlab R2015a (The MathWorks, Natick, MA, USA). TA EMG was filtered using a fourth order bandpass filter (10–450 Hz cutoff range). In the isometric condition, background EMG was measured 100 ms prior to the magnetic stimulus to determine an activity threshold for each trial (mean ± 1 standard deviation). In the dynamic condition, the length and position of the activity threshold window were adjusted manually for each

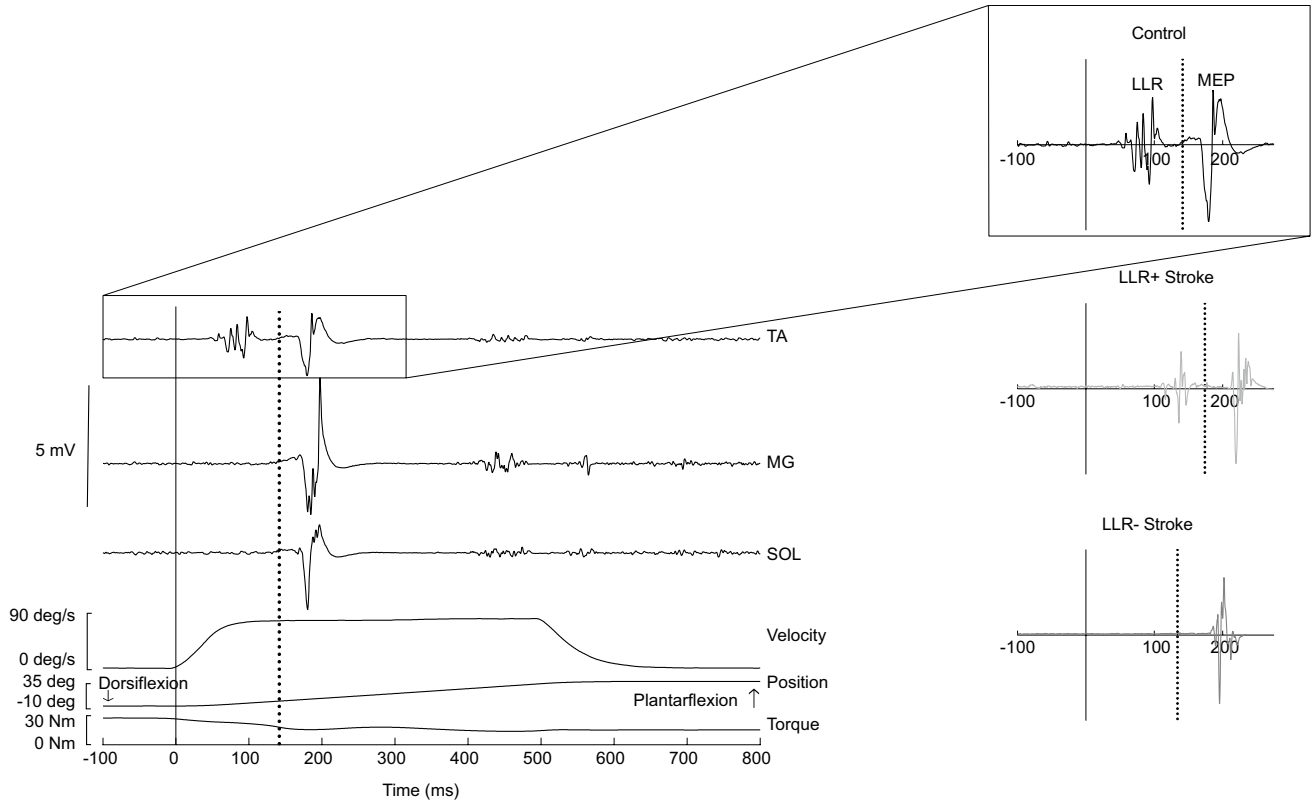


**Fig. 2** Experimental data from a representative healthy control (main panel), and tibialis anterior (TA) EMG from the same control and two representative individuals post-stroke (right side). EMG from TA, medial gastrocnemius (MG), and soleus (SOL), respectively, are shown in the top three traces of the left image. The bottom three traces display the dynamometer velocity, position, and torque, respectively. The solid line indicates the time when the dynamometer head began to move (time = 0), while the dotted line indicates the time of delivery of the TMS pulse. On the right side, TA EMG from the same control, as well as an individual post-stroke with long-latency reflex (LLR) activity (LLR+) and an individual with absent LLR responses (LLR−) are shown. Following delivery of the TMS pulse, a motor-evoked response (MEP) is seen in all individuals

participant to include only the period prior to movement onset (range of 50–100 ms). This difference in establishing duration of the activity threshold window for the dynamic condition was to exclude LLR activity from the background EMG calculation.

## Study variables

Primary variables of interest include LLR presence and TA $MEP_{area}$ change. LLR presence was quantified as the percentage of trials in which the amplitude of an EMG burst in TA within 100–170 ms after movement initiation exceeded 2.5 times the average background EMG (Petersen et al. 1998b). Given that all controls showed LLRs, the threshold criteria were determined using a detection algorithm developed on the healthy control data (Fig. 3). LLR presence was measured only during dynamic plantarflexion. TA $MEP_{area}$ is the area under the rectified and background-normalized motor-evoked response elicited by TMS measured in the tibialis anterior muscle. We have expressed TA $MEP_{area}$ change as the ratio between the isometric and dynamic conditions using the following equation:

$$MEP_{area}\text{change }(\%) = \frac{\text{Dynamic } MEP_{area} - \text{Isometric } MEP_{area}}{\text{Isometric } MEP_{area}} \times 100.$$

Secondary clinical variables for this analysis include: Lower Extremity Fugl-Meyer Motor Function score, Short Physical Performance Battery (SPPB) score, Dynamic Gait Index (DGI), self-selected walking speed (SSWS), and fastest comfortable walking speed (FCWS). The Lower Extremity Fugl-Meyer Motor Function score is a subscale of the Fugl-Meyer Assessment of Motor Recovery After Stroke, a widely used assessment of motor impairment with a maximum value of 34 points (Fugl-Meyer et al. 1975). The SPPB measures mobility and balance performance on a twelve-point scale and demonstrates robust predictive capacity for all-cause morbidity and mortality in older adults (Guralnik et al. 1994; Volpato et al. 2011). The DGI evaluates functional stability during walking with a maximum score of 24

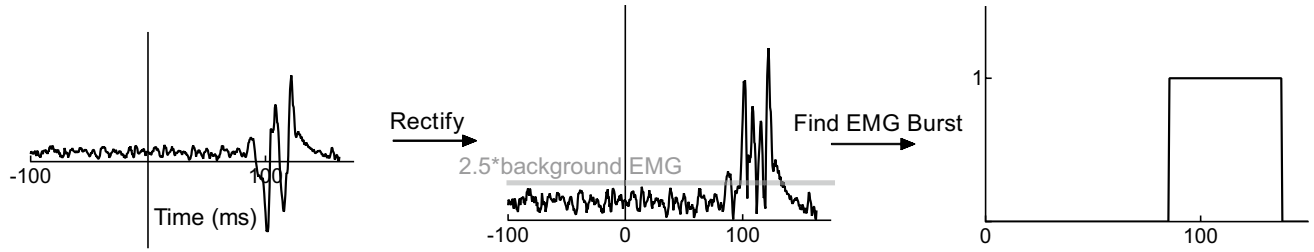


**Fig. 3** LLR detection algorithm. Developed using TA EMG from healthy controls, LLRs were detected by rectifying the EMG and then searching for a burst that exceeds 2.5 times the background EMG prior to the onset of movement. Once this threshold is achieved for a minimum of 10 ms, the burst is transformed into a step function, allowing for consistent identification of LLRs

points and is validated for use in chronic stroke (Shumway-Cook and Woollacott 1995; Jonsdottir and Cattaneo 2007). SSWS and FCWS were measured as the average speed from 3 to 5 passes over a 16-foot pressure-sensitive walkway (GaitRite Platinum Plus System, Version 3.9, Havertown, PA, USA). For SSWS, participants walked at their casual, comfortable pace. FCWS was assessed as the fastest speed the participant could safely attain when walking, "as if you are crossing the street and the walk signal changes to a red hand". Clinical measures were administered within a single session by a licensed physical therapist (VLL).

Our secondary biomechanical variable for this analysis is peak ankle plantarflexor power (A2). A2, the second peak in the sagittal plane ankle power profile, corresponds to plantarflexor power generation (Winter 2009). A2 was derived from inverse dynamics using motion analysis performed while participants walked at their self-selected speed on an instrumented split-belt treadmill (Bertec, Columbus, OH, USA). Marker data were obtained with a 12-camera Vicon motion capture system (Vicon MX, Vicon Motion Systems Ltd., Oxford, UK) using a modified Helen Hayes marker set sampled at 200 Hz. One healthy control and one individual post-stroke did not complete the instrumented gait assessment. Ankle power data during gait are not available for one additional participant with stroke due to dependence on a rigid ankle foot orthosis during gait assessments. All other participants walked on the treadmill with either an Aircast® or without a brace and produced valid kinetics.

### Statistical analysis

Data were assessed for normality using the Shapiro–Wilk $W$ test and were not normally distributed ($p$'s $< 0.05$). Therefore, TA $MEP_{area}$ change and walking speeds were assessed for group differences using Kruskal–Wallis ANOVA and a significance level of $\alpha = 0.05$. Post-hoc analyses were carried out using the Steel–Dwass method to correct for multiple comparisons. Clinical assessments were compared between subgroups of individuals stratified by LLR presence using Mann–Whitney $U$ tests with Bonferroni correction, and significance assessed using $\alpha = 0.017$. One-tailed Spearman correlations assessed the relationships between $MEP_{area}$ change and A2, using $\alpha = 0.05$. All tests were carried out in JMP Pro 11 (SAS Institute, Cary, NC, USA).

## Results

All thirteen healthy controls revealed LLRs in response to rapid stretch of the TA during voluntary plantarflexion. Nine individuals post-stroke, herein referred to as LLR present (LLR+), also showed this stretch-mediated EMG. Five individuals post-stroke, referred to herein as LLR absent (LLR−), lacked long-latency EMG activity in response to TA stretch. These three patterns are exemplified on the right-hand side of Fig. 2. 21 of the 27 individuals tested showed facilitation of TA $MEP_{area}$ in the dynamic, relative to the isometric, condition (Fig. 4). There was a significant effect of group ($p = 0.017$) on TA $MEP_{area}$ change. The post hoc tests revealed significant

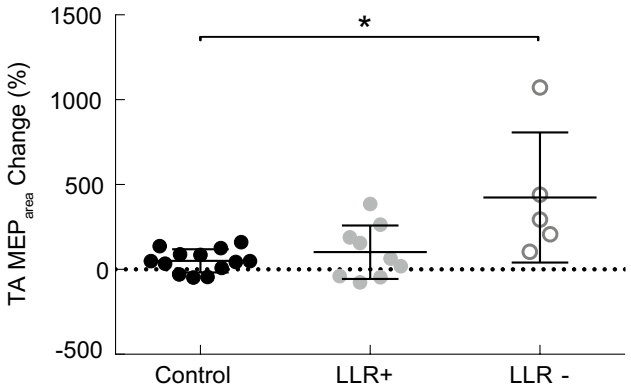


**Fig. 4** LLR− individuals ($n = 5$) show exaggerated TA $MEP_{area}$ change relative to healthy controls ($n = 13$). LLR+ individuals ($n = 9$) are not different from healthy controls or LLR− individuals. Bars represent median ± interquartile range. Asterisk indicates significance at $p < 0.05$ using Kruskal–Wallis ANOVA and Steel–Dwass post hoc analysis

facilitation of TA $MEP_{area}$ ($p = 0.012$) in LLR− individuals, with a median (IQR) of 295% (156–757) relative to controls, with a median of 49% (−10 to 108).

LLR− individuals revealed lower clinical scores and walking speeds than LLR+ individuals and healthy controls (Fig. 5). Fugl-Meyer Motor Function score was lower in LLR− individuals, with a median (IQR) score of 17 (12.5–24), than LLR+ individuals with a median score of 34 (28–34; $p = 0.007$). SPPB score was also lower in LLR− individuals, with a median score of 6 (5–7.5), than LLR+ individuals with a median score of 11 (9–12; $p = 0.006$). DGI score was lower in LLR− individuals, with a median score of 10 (9–14.5), than LLR+ individuals, with a median score of 22 (18.5–23.5; $p = 0.013$). Kruskal–Wallis ANOVA detected differences across groups for SSWS ($p = 0.0002$) and FCWS ($p = 0.001$, Fig. 5b). Post hoc analyses revealed that SSWS was higher in healthy controls, with a median speed of 1.3 m/s (1.2–1.5), than both LLR+, with a median speed of 1.1 m/s (0.96–1.2; $p = 0.01$), and LLR−, with a median speed of 0.37 m/s (0.24–0.64; $p = 0.005$), and higher in LLR+ than LLR− individuals ($p = 0.021$). FCWS was higher in healthy controls, with a median speed of 2.0 m/s (1.7−2.3) than LLR+, with a median speed of 1.6 m/s (1.2–1.9, $p = 0.03$), and LLR− with a median speed of 0.48 m/s (0.34–0.95; $p = 0.01$), but was not significantly different between LLR+ and LLR− individuals ($p = 0.053$).

TA $MEP_{area}$ change was not associated with A2 magnitude in healthy controls ($p = 0.29$, Fig. 6), however, the stroke group revealed a significant correlation ($p = 0.03$). The scatterplot in Fig. 6 illustrates an unambiguous gap between low and high ankle power. It is worth noting that all LLR− individuals produce low ankle power, although not all individuals that produce low power are LLR−.

## Discussion

Our primary findings are that the most impaired individuals show a dysregulation of TA MEPs and lack LLRs in TA during voluntary, dynamic plantarflexion. Healthy individuals had relatively unchanged TA responses to dynamic plantarflexion, and all showed LLRs. Because the majority of individuals with chronic stroke in this sample were not physiologically distinct from the healthy controls, our discussion will focus primarily on the subset of lower-functioning individuals. These individuals appear to have difficulty sensing and integrating appropriate sensorimotor information within the context of this plantarflexion task. Importantly, there is not one-to-one correspondence between the dysregulation of TA MEPs and lack of LLRs. This, in combination with a review of the literature, leads us to conclude that these phenomena arise from distinct mechanisms.

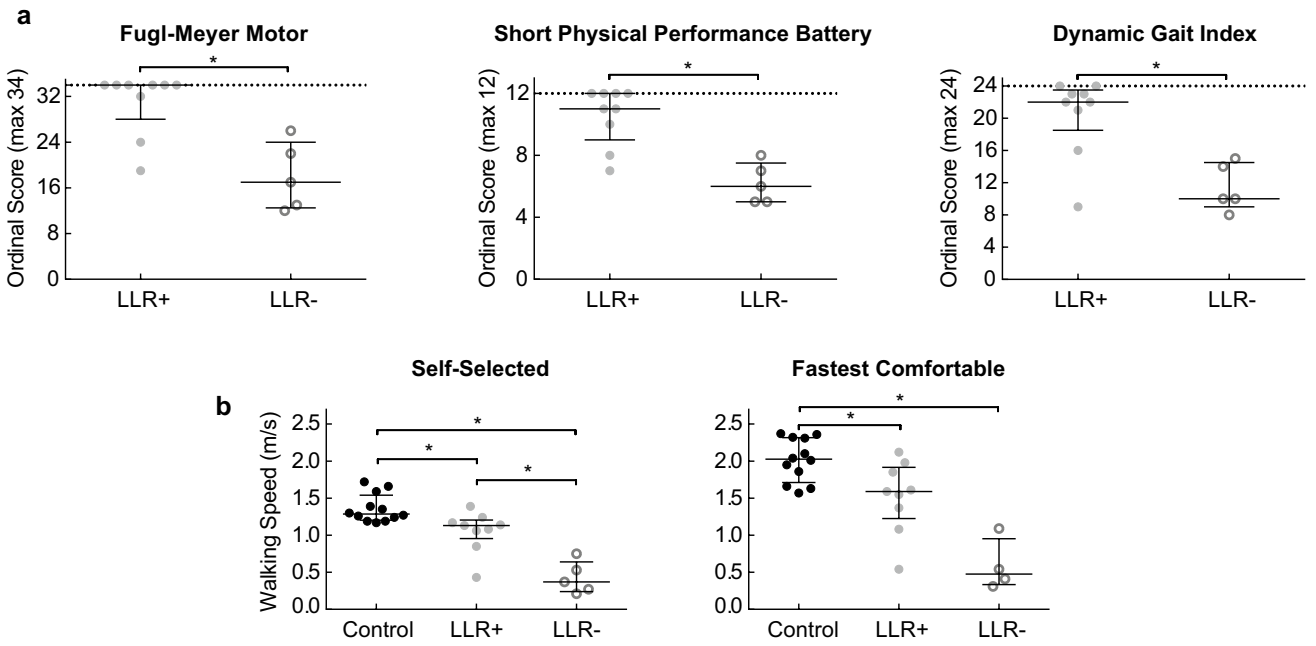


**Fig. 5** **a** Clinical scores are markedly lower for LLR− individuals ($n = 5$) than LLR+ individuals ($n = 9$) post-stroke. From left to right, scores include: Lower Extremity Fugl-Meyer Motor Function score, Short Physical Performance Battery, and Dynamic Gait Index. **b** Walking speed was different between all groups for self-selected walking speed (left) and between controls ($n = 12$) and each LLR group (LLR+ $n = 9$; LLR− $n = 4$) for fastest comfortable walking speed (right). One healthy control did not complete the walking speed assessment, while one LLR− individual completed only the self-selected walking speed measurement. Bars represent median ± interquartile range. Asterisk indicates significance at $p < 0.017$ for clinical scores or $p < 0.05$ for walking speeds

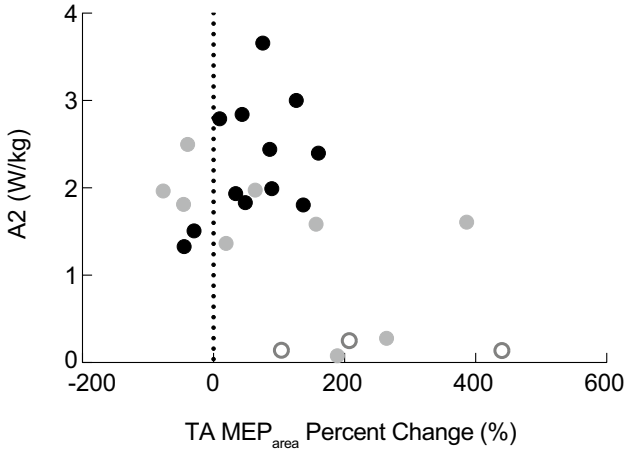


**Fig. 6** $MEP_{area}$ change predicts ankle plantarflexor power (A2) post-stroke, but not in healthy individuals. In healthy controls ($n=12$), the two variables are not correlated (Spearman $\rho=0.34$, $p>0.05$ black), however, in individuals post-stroke, there is a significant negative correlation between tibialis anterior $MEP_{area}$ change and A2 ($\rho=-0.64$, $p=0.03$). LLR+ individuals are indicated in light gray circles ($n=9$), while LLR− individuals are indicated with gray open circles ($n=3$), for illustrative purposes only. One LLR− individual relied on a rigid AFO for safe ambulation, and one LLR− individual and one healthy control did not complete the instrumented gait analysis, therefore their A2 could not be calculated

The lower extremity LLR may serve as a first line of defense in response to a perturbation (Sozzi et al. 2016; Hof and Duysens 2018). Although we are unable to mechanistically confirm that our observations represent the same LLR recorded in other muscles and tasks, the latency of the measured response and the absence of LLRs within a subset of individuals with central nervous system injury leads us to believe that the measured LLR arises from a transcortical pathway (Conrad and Aschoff 1977; Petersen et al. 1998a). The detection algorithm we designed assessed responses within 100–170 ms of movement initiation, a window that is comfortably late enough for transcortical involvement (Zuur et al. 2009). With that said, we cannot conclude that we are exclusively measuring a transcortical reflex within this dataset. There is a convergence of pathways that can contribute to the response at this latency, and we do not have the experimental control necessary to ascribe a particular mechanism to the data from this secondary analysis (Marsden et al. 1983; Shemmell et al. 2010). Overall, the idea that sensory information alters motor output dates back to the work of Sherrington, Evarts, and others (Sherrington 1910; Evarts 1979). However, the LLR could represent a simple, clinically accessible probe of sensorimotor function for individuals with chronic stroke. Individuals who lack LLRs could be missing key components of normal motor control, but further study is necessary to draw conclusions about the functional consequences of this phenomenon.

The underlying mechanism responsible for the exaggerated facilitation of TA MEPs also remains unclear. Given the dynamic condition instructions, it is not unreasonable that the controls exhibited a small facilitation in TA MEP size due to a generalized increase in motor excitability during volitional plantarflexion. However, the excessive facilitation present in some individuals post-stroke warrants further consideration. Diminished reciprocal inhibition, and even a reversal pattern termed reciprocal facilitation have been observed in some neuropathologies, including: cerebral palsy, spinal cord injury, and stroke (Gottlieb et al. 1982; Myklebust et al. 1982; Crone et al. 2003). The appearance of reflex reversals is inconsistent and poorly understood, but may be attributable to the disynaptic reciprocal inhibitory circuit (Okuma and Lee 1996; Crone et al. 2003; Bhagchandani and Schindler-Ivens 2012). In addition to spinal circuitry, supraspinal inputs to inhibitory interneurons contribute to the reciprocal inhibitory pathway (Lundberg 1970). Lesions in the motor cortex may, therefore, interrupt normal patterns of inhibitory control, allowing for pathologic disinhibition with dynamic movement. Our observation that the magnitude of TA MEP facilitation during plantarflexion is negatively correlated with the magnitude of ankle plantarflexor power may be indicative of over-excitable dorsiflexor activity, inhibiting plantarflexion vital to gait. The mechanism of this dysregulation warrants further investigation. The finding that all LLR− individuals and some LLR+ individuals within this sample exhibited excessive facilitation indicates that this facilitation is likely driven by a different mechanism than the LLR; the interaction between these two responses would require further investigation within a larger sample.

The three potential contributors to plantarflexor dysfunction mentioned earlier are weakness, excessive co-contraction, and spasticity. The clinical outcomes and the LLR− group, coupled with their reduced ankle power, demonstrate that these individuals are weak (Table 1). The dysregulation of dynamic dorsiflexor MEPs in some individuals points to impaired antagonist control, another indicator of central nervous system impairment. Whether in the control or stroke groups, there was no evidence of excessive co-contraction during the isolated plantarflexion movements in this sample (Fig. 2). Previously, we assessed co-contraction during gait in most of the individuals from this sample and found that co-contraction is not a common strategy employed by individuals with chronic stroke (Banks et al. 2017). Spasticity is also an unlikely contributor to impairments in dynamic plantarflexion within this sample. Although a small portion of individuals within this sample had measurable hyperreflexia in response to faster passive stretches, reflex responses were absent during active stretches of the dorsiflexors, the opposite of an expected finding in the case of spasticity. Although

definitive conclusions cannot be drawn from this small dataset, weakness appears to be the most likely source of these impairments in motor control. Strength training can improve both central and peripheral weakness, and it produces no exacerbation of spasticity in the process, thus these LLR− individuals have the potential to benefit from strength training (Patten et al. 2004; Clark and Patten 2012).

The primary limitation of this study was that the methods were not designed to assess LLRs. All plantarflexor stretches employed in this study were followed by TMS pulses. For some individuals in the larger sample, there was insufficient time for the LLR to occur prior to the TMS response, and these cases were therefore excluded from this secondary analysis. Despite our focus on dorsiflexor excitability in this study, TMS was targeted to the plantarflexors. Two individuals who were unable to produce measurable soleus MEPs had consistent TA MEPs in both conditions, a finding that is not surprising due to the relative ease of eliciting TA MEPs when either the TA or SOL is the primary target (Charalambous et al. 2019). One control and one LLR− individual did not complete the gait analysis portion of the study, and therefore we were unable to calculate A2 for these individuals and compare between LLR subgroups. The remaining sample size and methods employed preclude the ability to draw definitive conclusions regarding the role of these neurophysiologic outcomes in walking deficits. However, these preliminary findings offer the opportunity for theoretical discussion. Future work is indicated to replicate and elucidate the mechanisms and functional significance of LLR absence in chronic stroke.

The two neurophysiologic phenomena assessed in this study are both associated with impaired walking function following stroke, but likely stem from different mechanisms. Not all individuals who exhibited exaggerated dorsiflexor excitability were LLR−, and the majority of LLR− individuals showed exaggerated TA MEPs in the dynamic condition. It is possible that the LLR+ individuals with exaggerated TA MEPs possess a more segmental deficit, while LLR− individuals possess a supraspinal impairment, but it is too early to draw definitive conclusions from a mechanistic perspective. What can be concluded is that the LLR− individuals were clinically and biomechanically lower functioning than LLR+ individuals and healthy controls. Work must be done to gain a better approximation of the prevalence of these deficits among individuals with stroke, including assessment of a larger sample and measurement of individuals in the acute stages of recovery. Due to the ease of measurement and the unambiguous presence or absence of response, the LLR appears to be a promising physiologic marker of motor dysfunction in chronic stroke.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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