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Role of the premotor cortex in leg selection and anticipatory postural adjustments associated with a rapid stepping task in patients with stroke

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ABSTRACT

The premotor cortex (PMC) plays an important role in selecting and preparing for movement. This study investigates how stroke-induced PMC lesions affect stepping leg selection and anticipatory postural adjustments (APAs) preparation. Fifteen hemi-paretic patients (eight with PMC lesions (PMC_{Lesion}) and seven PMC spared (PMC_{Spared})) and eight age- and sex-matched healthy adults participated in the study. The subjects performed rapid forward stepping with the right or left leg under simple and choice reaction time conditions. The percentage of trials in which the subject showed the correct initial vertical ground reaction force pattern before lift-off of the stepping leg indicated the accuracy in selecting the designated stepping leg. The latency of bilateral contractions in the tibialis anterior (TA) and the reaction time (RT) of the stepping leg represented the time needed to prepare for stepping-related APAs and stepping movement, respectively. All three groups demonstrated a similar rate of accuracy of the stepping leg selection under both conditions. However, in both conditions, the PMC_{Lesion} group exhibited a longer RT and TA contraction latency of the affected leg than the healthy and PMC_{Spared} groups. The PMC_{Lesion} group also presented a longer TA contraction latency of the unaffected leg than the healthy group in both conditions. These results suggest that the PMC is involved in APAs associated with leg stepping movement and that a PMC lesion in one hemisphere impairs APAs of both the contralateral and ipsilateral legs during stepping.

1. Introduction

Studies in monkeys [1–4] and humans [5–7] suggest that the premotor cortex (PMC) plays an important role in selecting and preparing for visuomotor movements of the upper extremities. After a PMC lesion, monkeys show an increase in direction selection error when performing a choice reaction time task [2]. The neuronal activity of the PMC has been found to be direction-related, magnitude-related, and time-locked to the intended movement [1,8–11]. These characteristics of PMC neuronal activity are similar to those of anticipatory postural adjustments (APAs), as both relate to an intended voluntary movement [12].

However, it remains unclear whether the PMC is involved in leg selection or in the APAs associated with leg movement. The purpose of this study was to investigate whether PMC lesions influence stepping leg selection and stepping-related APAs in patients with a PMC lesion following a stroke (PMC_{Lesion}). Results were compared to age- and sex-matched controls as well as patients with strokes that spared the PMC (PMC_{Spared}). A rapid stepping task was selected, as this task requires intricate coordination between postural preparation and movement initiation. When a healthy adult voluntarily steps forward, the bilateral tibialis anterior (TA) muscles anticipatorily activate, and the vertical ground reaction force (Fz) underneath the stepping leg momentarily increases before initiating foot lift-off [13]. Thus, TA muscles are considered to be the primary anticipatory postural muscles for stepping. The contraction latency of the bilateral TA muscles indicates the time needed to prepare for stepping-related

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Table 1
Fugl-Meyer Assessment lower extremity (FMA-LE) scores, lesion hemisphere, lesion areas, and neurological symptoms and signs of all patients with stroke.

Subject	FMA-LE motor (0–34)	FMA-LE sensory (0–24)	Lesion hemisphere	Lesion area of the PMC	Other brain lesion areas	Neurological symptoms and signs
PMC_{Lesion} group						
1	29	24	L	PMd	DLPf, M1, S1, CR, BG, IC	ROM limitation, spasticity, hemiparesis
2	26	21	R	PMd, PMv	DLPf, BG	ROM limitation, hemiparesthesia, hemiparesis
3	31	14	R	PMv	DLPf, M1, S1, PPC, O, T	ROM limitation, hemiparesthesia, hemiparesis
4	32	24	L	PMd, PMv	PPC, Broca area, O	Hemiparesis
5	31	22	R	PMd, PMv	O, IC	ROM limitation, hemiparesthesia, hemiparesis
6	27	22	R	PMv	M1, PPC, CR, BG, IC	ROM limitation, hemiparesthesia, spasticity, hemiparesis
7	32	22	L	PMv	Broca area, T, BG, IC	Hemiparesthesia, hemiparesis
8	33	22	L	PMd, PMv	M1, S1, PPC, Broca area, Wernicke area, O, T, CR	ROM limitation, hemiparesthesia, visual field deficit, hemiparesis
PMC_{Spared} group						
1	34	22	R	–	T, CR, BG, IC	ROM limitation, hemiparesthesia, hemiparesis
2	31	17	L	–	M1, S1	Hemiparesthesia, hemiparesis
3	32	20	L	–	M1, O	Hemiparesthesia, hemiparesis
4	32	24	R	–	DLPf, M1, S1, SMA	Hemiparesis
5	34	22	R	–	DLPf, M1, S1, PPC, O	Hemiparesthesia, visual field deficit
6	32	22	L	–	BG, IC	Hemiparesthesia, hemiparesis
7	32	24	R	–	DLPf, M1, SMA	Hemiparesis

Left (L); right (R); basal ganglia (BG); corona radiata (CR); dorsal lateral prefrontal cortex (DLPf); internal capsule (IC); primary motor cortex (M1); occipital lobe (O); dorsal premotor cortex (PMd); ventral premotor cortex (PMv); posterior parietal cortex (PPC); primary somatosensory cortex (S1); supplementary motor area (SMA); temporal lobe (T).

APAs, while changes in initial Fz under both feet indicate whether stepping leg selection is correct. We hypothesized that the PMC is involved in both leg selection and APAs associated with stepping.

2. Methods

2.1. Subjects

Eight PMC_{Lesion} patients, seven PMC_{Spared} patients, and eight age- and sex-matched healthy adults (Tables 1 and 2) participated in this study. All patients were (1) diagnosed with a single-onset ischemic cortical stroke by a neurologist and a radiologist using clinical and neuroimaging (CT or MRI) data, (2) able to step forward with either leg without assistance from a person or device, (3) able to contract the affected ankle dorsiflexors while sitting, and (4) scored ≥24 on the Mini-Mental State Examination [14]. Participants had no other neurological diseases and were without musculoskeletal or cardiopulmonary diseases that could affect stepping ability. All participants signed informed consent forms approved by the institutional review board.

Clinical assessments were conducted before the stepping experiment. The lower extremity motor section of the Fugl-Meyer Assessment [15] was used to examine the sensorimotor function and passive range-of-motion of the affected lower extremity in patients with stroke. The Mini-Mental State Examination and Berg Balance Scale [16] were used to examine cognitive and balance functions, respectively, for all subjects.

Table 2
Demographic data of all three subject groups.

Characteristics/tests	PMC_{Lesion} group ($n=8$)	PMC_{Spared} group ($n=7$)	Healthy group ($n=8$)
Age (y)	66.6 ± 13.6 (48–80)	65.1 ± 11.9 (47–75)	65.9 ± 7.5 (52–75)
Gender			
Male	6	5	7
Female	2	2	1
Pre-stroke footedness			
Right	4	5	4
Left	0	0	1
Mixed	4	2	3
Hemi-paretic side			
Left	4	4	–
Right	4	3	–
Post-stroke onset days (d)	161.9 ± 72.6 (63–276)	294.9 ± 475.9 (24–1357)	–
Fugl-Meyer Assessment			
Motor (0-34)	30.1 ± 2.5	32.4 ± 1.1	–
Range-of-motion (0–20)	18.9 ± 1.0*	19.9 ± 0.4	–
Sensation (0–20)	21.4 ± 3.2	21.6 ± 2.4	–
Mini-Mental State Examination (0–30)	27.5 ± 2.3	28.6 ± 1.7	29.0 ± 1.0
Berg Balance Scale (0–56)	53.3 ± 2.3†	54.9±1.2	55.6 ± 0.7

Values indicate the mean ± SD (or range). A one-way analysis of variance (ANOVA) was used to compare age differences among the three groups. χ^2 tests were used to compare differences in the distribution of sex and footedness among the three groups and differences in the distribution of lesion side between the two patient groups. The Mann–Whitney U test was used to compare differences in post-onset days and Fugl-Meyer Assessment lower extremity motor, sensory, and range-of-motion sub-scores between the two patient groups. The Kruskal–Wallis test was used to compare Mini-Mental State Examination and Berg Balance Scale scores among the three groups.

* Significantly different from the PMC_{Spared} group ($p < 0.05$).

† Significantly different from the healthy group ($p < 0.05$).

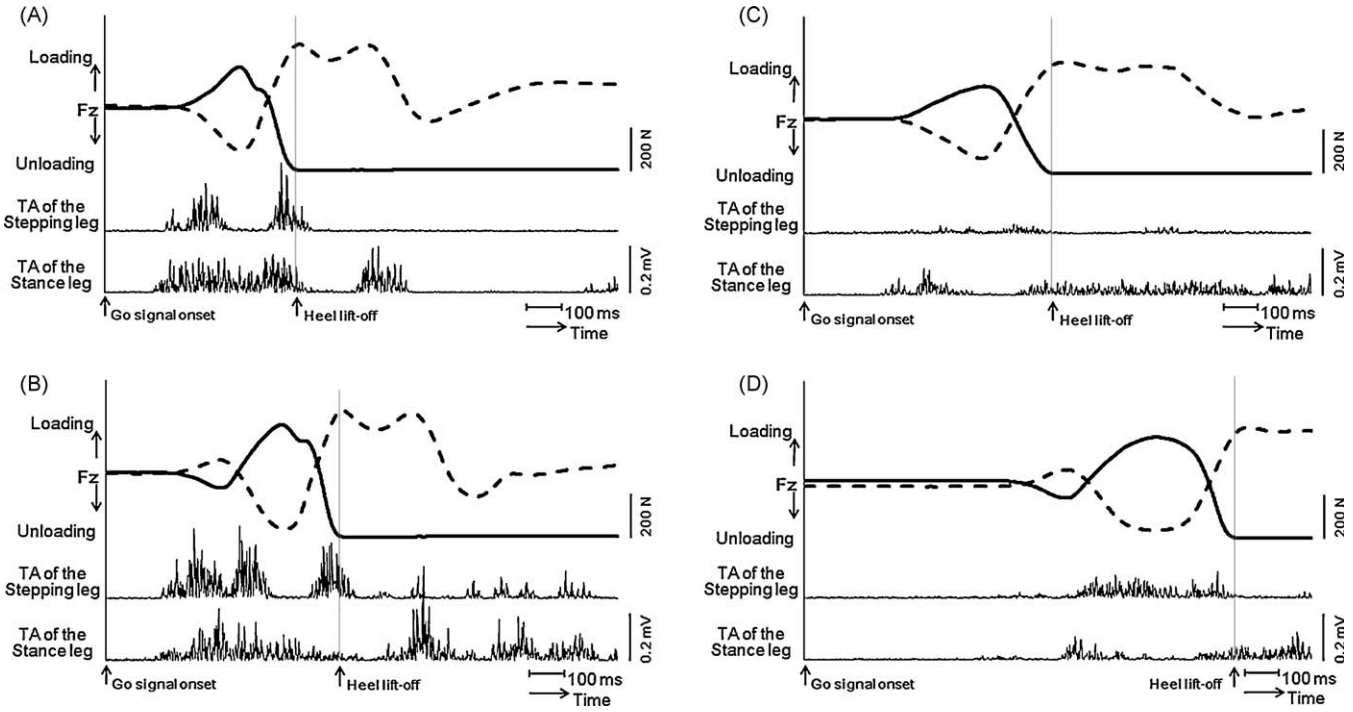

Fig. 1. Illustrations of the vertical ground reaction force (Fz) patterns and EMG signals of bilateral TA muscles obtained while a healthy subject ((A) and (B)) was stepping with his left leg and a PMC_{Lesion} subject ((C) and (D)) was stepping with her affected leg under the CRT condition. (A) and (C) show Fz and TA contraction patterns of trials with correct leg selection. (B) and (D) show Fz and TA contraction patterns of trials with incorrect leg selection. The solid and dashed curves indicate the Fz trajectories of the stepping and stance leg, respectively.

2.2. Apparatus

The Multi-stimuli Generator System (Advance Instrument Inc., Taipei, Taiwan) was used to generate stimuli signals in the stepping experiment. Two force plates (AMTI OR6-7, Advanced Mechanical Technology, Inc., Watertown, MA, USA) were used to measure the Fz exerted by the legs. An eight-channel surface EMG system (Bagnoli-8 EMG System, DelSys Inc., Boston, MA, USA) was used to collect data on muscle activity from bilateral TA muscles. The electrodes were placed over the TA muscle bellies, approximately two finger widths from the tibial tuberosity [17]. A foot-switch (MA-153, Motion Lab Systems, Inc., Baton Rouge, LA, USA), which can respond reliably to 200 g of pressure, was attached beneath the mid-calcaneus of each foot to detect the heel lift-off instant of the stepping leg. The heel lift-off instant was when the pressure on the switch starts to fall below 200 g. Data were simultaneously sampled from all apparatuses at 1000 Hz and converted into digital signals using the DATAPAC 2000 Data Acquisition Module (Run Technologies, Mission Viejo, CA, USA). Data were then analyzed using the DATAPAC 2000 Data Analysis Module.

2.3. Procedures

In the stepping experiment, subjects stood facing a monitor. Each foot was placed on one force plate with feet 25 cm apart and 15° externally rotated. The monitor was raised to each subject's eye level and positioned 1.5 m in front. All subjects were asked to prepare to react to an upcoming "go" signal (a green circle) after a red warning signal was observed on the monitor. The interval between the warning and "go" signals varied from 1 to 5 s to prevent subjects from predicting the onset of the "go" signal. The "go" signal lasted 150 ms.

Two testing conditions were used, namely, simple (SRT) and choice reaction time (CRT) conditions. Each subject underwent six right- and six left-leg-stepping trials in each condition. In the SRT condition, the "go" signal was presented in the center of the monitor. The right-leg-stepping and left-leg-stepping trials were carried out in blocks, and block order was counterbalanced among subjects in each group. Clear instructions concerning which leg should step were given prior to each block in the SRT condition. In the CRT condition, the right- and left-leg-stepping trials were randomized, and the instructions were as follows: "If the green circle is presented on the left side of the monitor, step as fast as possible with the left leg and vice versa." The testing condition order was counterbalanced among subjects in each group. All subjects stepped independently without using any device. Between conditions, subjects rested for at least 2 min to avoid fatigue. Data collection from all apparatuses began 0.8 s before the onset of the "go" stimulus and lasted for 3 s.

2.4. Data analysis

The force signals were low-pass filtered at 30 Hz. The EMG signals were band-pass filtered at 20–250 Hz and full-wave rectified. The initial Fz patterns before the heel lift-off of the stepping leg were used to determine whether the initial selection of the designated stepping leg was correct. Three criteria must be met for a correct trial: (1) an initial increase in stepping leg Fz, (2) a concomitant decrease in stance leg Fz, and (3) an Fz difference between legs (i.e., stepping leg Fz – stance leg Fz) >5% of body weight and lasting for at least 50 ms (Fig. 1). These criteria were modified from a previous study [18]. Incorrect trials were discarded. The accuracy rate was the number of correct trials presented as a percentage of the total number of trials in the SRT or CRT condition. We calculated the contraction latency of the bilateral TA muscles and the reaction time (RT) of the stepping leg to quantify the preparation time for stepping-related APAs and stepping movement, respectively. The TA contraction latency was defined as the time interval between the "go" signal onset and the time for the TA activity to exceed two standard deviations above baseline activity [19]. RT was defined as the time interval between the "go" signal onset and heel-off instant of the stepping leg detected by the foot-switch.

2.5. Statistical analyses

The normality and homogeneity of variance in the demographic data and dependent measures (i.e., accuracy rate, TA contraction latency of the affected and unaffected legs, and RT) were first tested by the Shapiro–Wilk and Levene's tests, respectively. When these assumptions were met, parametric statistics were applied; otherwise, nonparametric statistics were used (Table 2).

One PMC_{Lesion} subject did not activate the TA of the affected leg in the unaffected-leg-stepping trials. Thus, the TA contraction latency data of the affected leg in these trials were treated as missing. Data for all of the dependent measures met the normality and homogeneity assumptions. Due to the small sample size, we chose to perform one-way ANOVA to compare the accuracy rate, TA contraction latency, and RT among the three groups for the SRT and CRT conditions separately. Because there was no difference in the TA contraction latency of the right and left legs among healthy adults, we compared the right leg data from healthy adults with the unaffected leg data from the stroke patients and the left leg data from healthy adults with the affected leg data from stroke patients. For patient groups, data from the affected legs were pooled from the left- and right-leg-stepping trials, and the same was done for data from the unaffected leg. The significance level was set at $p < 0.05$ for all statistical analyses. Significant one-way ANOVA results were followed by post hoc tests with Bonferroni's adjustments.

3. Results

3.1. Subjects

Table 1 summarizes the lesion locations and clinical symptoms and signs from all stroke subjects. Fig. 2 presents the brain images

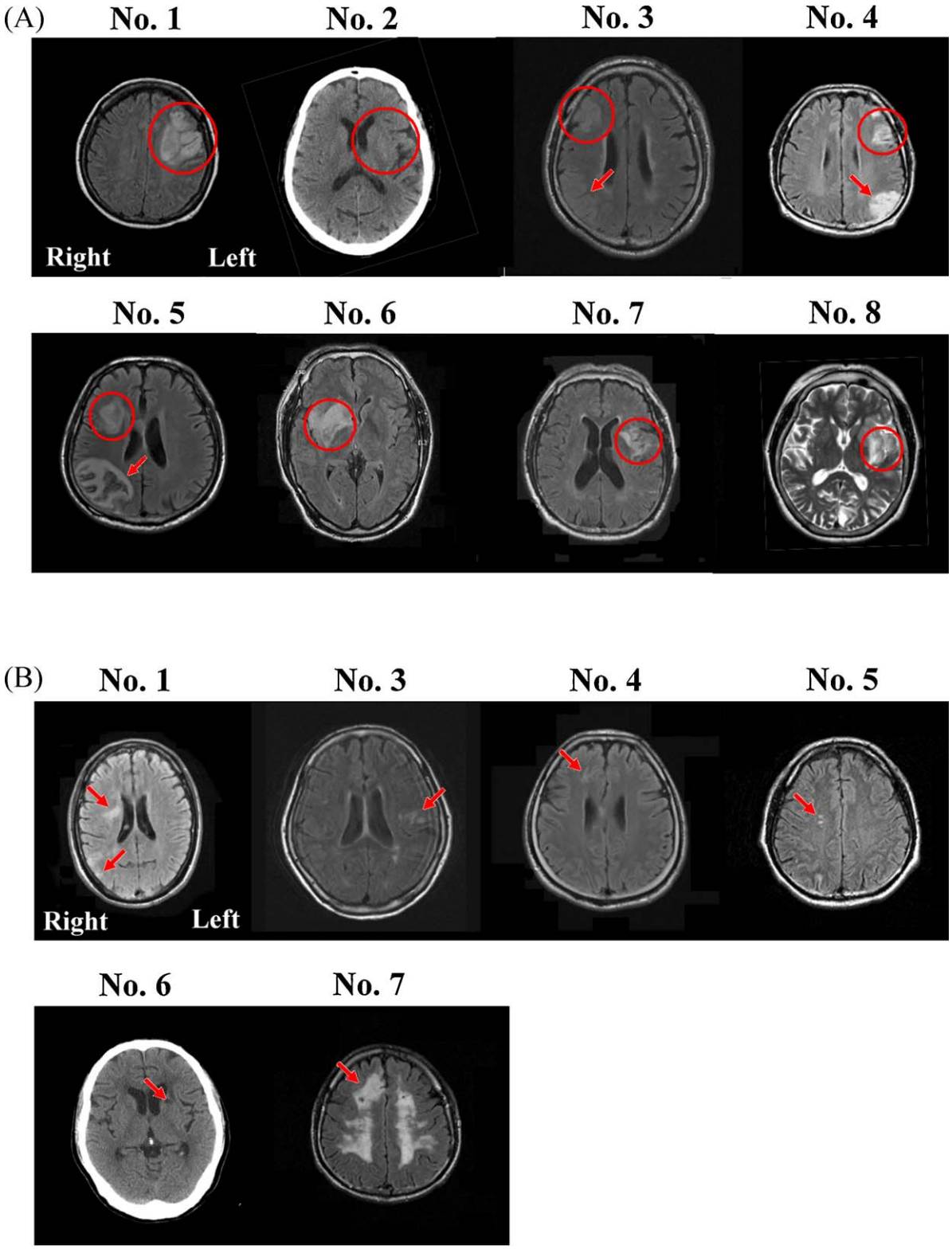

Fig. 2. Brain images of (A) PMC_{Lesion} subjects and (B) PMC_{Spared} subjects. All patients had T2 magnetic resonance images except that subject No. 2 of the PMC_{Lesion} group and subject No. 6 of the PMC_{Spared} group had CT images only. Subject No. 2 of the PMC_{Spared} group only has hardcopy images and does not have digital image file available. Therefore, her brain image is not presented here. The involved PMC areas are marked with circles, while other brain lesion areas are marked with arrows. The image slices selected for the PMC_{Spared} subjects are to demonstrate that the PMC is intact in patients in this group.

of patients. These images revealed that the PMC area was involved in the PMC_{Lesion} group, but not in the PMC_{Spared} group. The three subject groups did not show significant differences in age, gender, or cognitive function (Table 2). The two stroke patient groups presented similar clinical characteristics, except the PMC_{Lesion} group had lower range-of-motion scores ($p = 0.021$) than the PMC_{Spared} group. The PMC_{Lesion} group also presented significantly lower balance scores than the healthy group ($p = 0.011$).

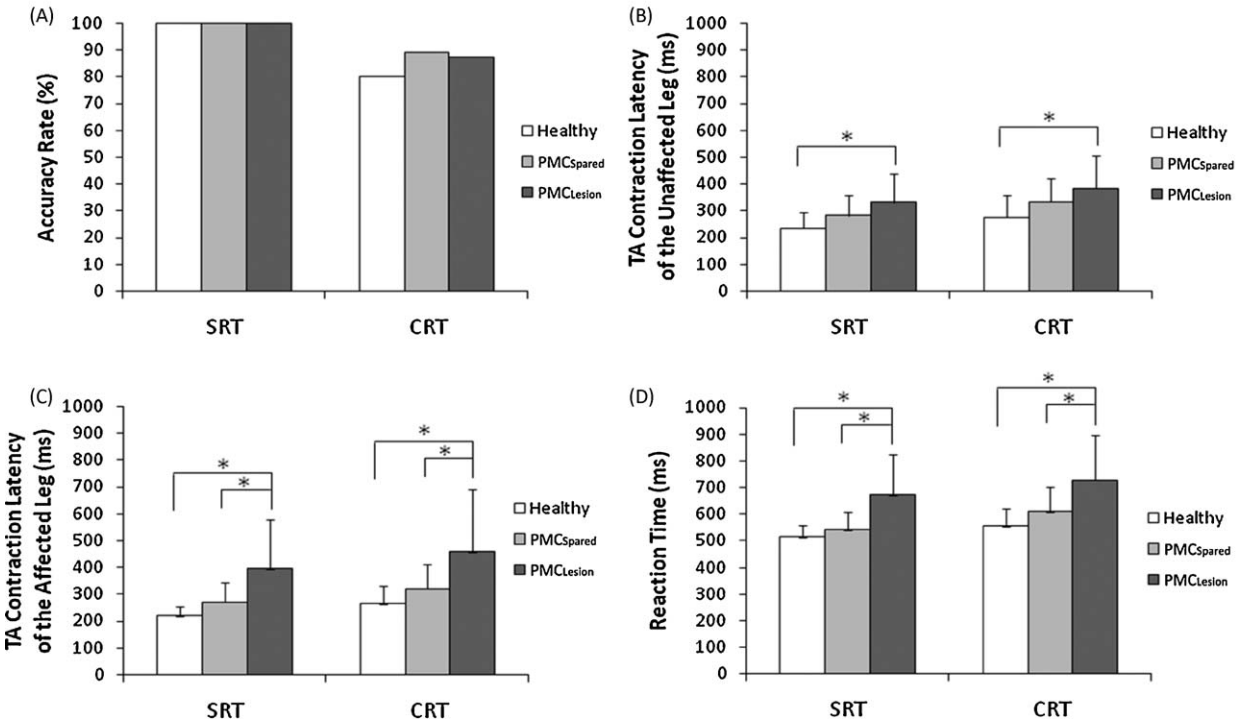

Fig. 3. The (A) accuracy rate, (B) TA contraction latency of the unaffected leg, (C) TA contraction latency of the affected leg, and (D) RT of the three subject groups in the SRT and CRT conditions. *Significant difference between groups ($p < 0.05$).

3.2. The effect of condition on the accuracy of leg selection

In the SRT condition, all three groups performed with 100% accuracy in selecting the designated stepping leg, as determined by their initial Fz patterns. In the CRT condition, there were also insignificant group differences in leg selection accuracy ($F_{2,20} = 1.878$, $p = 0.179$). Each group showed an accuracy of 80–89% (Fig. 3A).

3.3. Group effects on TA contraction latency of unaffected and affected legs and RT

In the SRT condition, there were significant between-group differences in TA contraction latency of the unaffected leg ($F_{2,43} = 5.187$, $p = 0.01$), TA contraction latency of the affected leg ($F_{2,42} = 9.923$, $p < 0.0005$), and RT ($F_{2,43} = 10.912$, $p < 0.0005$) (Fig. 3B–D). The post hoc analyses revealed that the PMC_{Lesion} group had a significantly longer TA contraction latency of the unaffected ($p = 0.007$) and affected ($p < 0.0005$) legs, as well as a longer RT ($p < 0.0005$), as compared to the healthy group. The PMC_{Lesion} group also showed a significantly longer TA contraction latency of the affected leg ($p = 0.015$) and RT ($p = 0.004$) as compared to the PMC_{Spared} group (Fig. 3B–D).

In the CRT condition, there were also significant group differences in TA contraction latency of the unaffected leg ($F_{2,43} = 4.840$, $p = 0.013$), TA contraction latency of the affected leg ($F_{2,42} = 7.006$, $p = 0.002$), and RT ($F_{2,43} = 8.767$, $p = 0.001$) (Fig. 3B–D). The post hoc analyses revealed that the PMC_{Lesion} group presented a significantly longer TA contraction latency of the unaffected ($p = 0.01$) and affected ($p = 0.002$) legs, as well as a longer RT ($p = 0.001$), as compared to the healthy group. The PMC_{Lesion} group also presented a significantly longer TA contraction latency of the affected leg ($p = 0.048$) and RT ($p = 0.025$) as compared to the PMC_{Spared} group (Fig. 3B–D).

4. Discussion

4.1. Role of PMC in the preparation of stepping-related APAs

Our main finding that the PMC_{Lesion} group presented the longest TA contraction latency for both legs among the three groups supports our hypothesis that PMC_{Lesion} patients have poorer leg movement-related APAs than PMC_{Spared} patients. We speculated that poorer APA control in the PMC_{Lesion} group was probably not due to greater deficits in sensorimotor functions or lesions in well-known APA-related brain areas, as the two patient groups had similar demographics, clinical characteristics, and levels of sensorimotor impairment. None of the patients had strokes affecting areas known to contribute to APAs, such as the thalamus, brain stem, or cerebellum [20–23]. All PMC_{Lesion} subjects had spared SMA, whereas two of the PMC_{Spared} subjects had lesions in the SMA.

The majority of subjects in both patient groups had lesions in the primary motor cortex (M1) or the internal capsule, which are areas supplied by the same anterior cerebral circulation system that supplies the PMC. The M1 and its descending pathways are known to contribute to the control of APAs [24]. Analysis of our data showed significant correlations ($r = -0.58$ to -0.79, $p < 0.05$) between the Fugl-Meyer lower extremity motor score of the affected leg and TA contraction latency of both legs in all patient subjects. However, we suggest that that the severity of the M1 or internal capsule lesions was not the primary reason for the longer TA contraction latency in the PMC_{Lesion} group, as the PMC_{Lesion} and PMC_{Spared} groups had similar lower extremity motor scores.

We suggest that the PMC lesion was primarily responsible for the longer TA contraction latency of both legs in the PMC_{Lesion} group. Indeed, five of the eight PMC_{Lesion} patients had lesions involving the dorsal aspect of the PMC, an area known to be important for movement preparation [1,3]. Our findings also suggest that PMC lesions, in either the right or left hemisphere,

affect the APAs of bilateral lower extremities. These findings are consistent with the so-called parallel model of APA control originally proposed by Massion [12,25], with the exception that our data suggest that the PMC be added to the model. When using this model to explain the control of stepping movements and the associated APAs, the M1 of one hemisphere is considered to primarily control postural or leg movement of the contralateral leg, and the SMA is thought to be involved in initiating activity of the neural substrates in the brain stem that are responsible for generating the APAs of bilateral lower extremities [12,23,25]. Our findings suggest that the function of each PMC is similar to that of the SMA in Massion's model [12,25]. Therefore, when a lesion occurs at the PMC of one hemisphere, as in our PMC_{Lesion} group, TA contraction latency for both affected and unaffected legs is delayed due to impaired descending input from the PMC to initiate the execution of APAs. We speculate that the PMC is in this model because our task was an externally triggered stepping activity. Although our subjects performed volitional stepping in this experiment, they began stepping only after receiving the "go" signal. Past research has suggested that the PMC is particularly involved with preparing for externally triggered movements, whereas the SMA is more involved in preparing internally generated movements [26–28].

Regarding the differences in APAs between the PMC_{Spared} and the healthy groups, we found that the PMC_{Spared} group showed a trend toward longer TA contraction latency for the unaffected and affected legs (Fig. 3B and C). However, these differences did not show statistical significance. This finding may be due to the role of the M1 in the postural control of the contralateral stance leg during stepping, as suggested by Massion's model [12,25]. Indeed, five of the seven PMC_{Spared} subjects had lesions in the M1 (Table 1).

4.2. Role of the PMC in the selection of the stepping leg

Results of the accuracy rate of stepping leg selection failed to support the hypothesis that PMC lesions would result in greater error in selecting the stepping leg. There are two possible explanations of our findings. First, all patients in our PMC_{Lesion} group had partial and unilateral PMC lesions, which may not result in noticeable selection difficulty. Previous studies on monkeys and humans have shown that larger or bilateral PMC lesions result in greater deficits in movement response selection than smaller or partial PMC lesions [2,29,30]. Second, we used two stimuli to indicate which leg should step in the CRT condition, which was fewer than the four or six stimulus-response pairs used in previous studies [6,29] and, thus, may not have been challenging enough for patients with partial PMC lesions.

4.3. Stepping movement initiation

In Massion's model [12,25], stepping movement onset is delayed until the APAs are executed to ensure the maintenance of a dynamic equilibrium during the stepping movement. Given that humans use a bipedal stance, the lift-off of stepping movement is impossible without the postural preparation of the stance leg. We found that the PMC_{Lesion} group had a significantly longer RT than the PMC_{Spared} and healthy groups in both the SRT and CRT conditions. The delayed RT can be ascribed to the delayed APAs of both legs [12,25].

4.4. Hemisphere dominance issues

Researchers have suggested that the left hemisphere may be specialized for upper extremity action [5]. Schluter et al. [5,6] used transcranial magnetic stimulation and positron emission tomography to investigate the differential roles of the left and right PMC in action among healthy adults. They showed that the left (dominant) PMC influenced action preparation and selection for both upper limbs, whereas the right (non-dominant) PMC only influenced action selection for the contralateral upper limb. In our study, the four subjects with left PMC lesions and the four subjects with right PMC lesions showed the same leg selection accuracy of 87.5%. Thus, these results do not demonstrate left hemisphere dominance in lower extremity stepping response selection. Our data also fail to support the left hemisphere dominance hypothesis insofar as the subjects with lesions to the right PMC presented a trend towards a longer TA contraction latency (mean = 379–541 ms) for both legs as compared to those with lesions to the left PMC (mean = 282–389 ms) in both the SRT and CRT conditions (effect size = 0.67–0.98). The differences between our findings and those of Schluter et al. [5,6] may be due to the different study methods used and the nature of the tasks performed. Unlike previous imaging or electrophysiological studies performed on healthy adults [5,6], this study was a lesion study in which subjects with right and left PMC lesions may have had different degrees of damage to the PMC. Furthermore, our task was a lower extremity movement task in which the APAs of the stance and stepping legs must be highly coupled to allow the stepping task to be carried out safely [12,13]. Thus, hemispheric dominance may have been less evident for this task in particular and/or for lower limb movement in general.

5. Conclusions

This study suggests that the PMC may be involved in stepping-specific APAs in humans and that a lesion in one PMC delays the contraction latency of the primary postural muscles of both lower extremities. However, because of the small sample size of this study, these findings should be tested further with a larger sample of subjects.

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Conflict of interest statement

None of the authors have any financial and personal relationships with other people or organizations that could inappropriately influence the work. The role of the National Health and Research Institutes was simply the funding supporters. The supporters did not have any involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

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