Identification of the laterality of motor unit behavior in female patients with parkinson's disease using high-density surface electromyography

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Graphical Abstract

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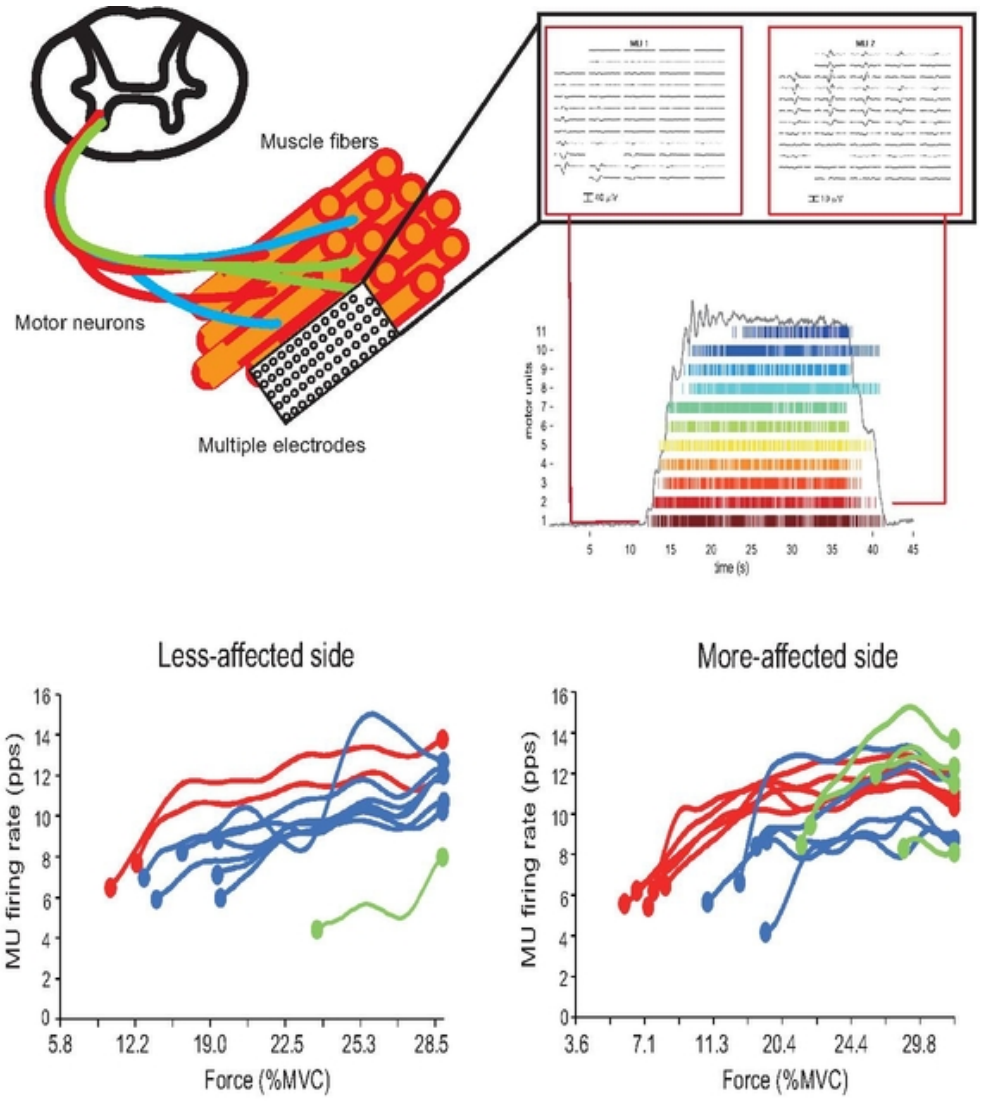

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Authors' full names

Yuichi Nishikawa, Ph.D.[1, 2*]; Kohei Watanabe, Ph.D.[3]; Aleš Holobar, Ph.D.[4]; Noriaki Maeda, Ph.D.[5]; Hirofumi, Maruyama, Ph.D.[6]; and Shinobu Tanaka, Ph.D.[1]

Author affiliations

1) Faculty of Frontier Engineering, Institute of Science & Engineering, Kanazawa University, Kanazawa, Japan
2) Division of Rehabilitation, Department of Clinical Practice and Support, Hiroshima University Hospital, Hiroshima, Japan
3) Laboratory of Neuromuscular Biomechanics, School of International Liberal Studies, Chukyo University, Nagoya, Japan
4) Faculty of Electrical Engineering and Computer Science, University of Maribor, Slovenia
5) Division of Sports Rehabilitation, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
6) Department of Clinical Neuroscience and Therapeutics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

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23 **Correspondence:**

24 Yuichi Nishikawa, Faculty of Frontier Engineering, Institute of Science & Engineering,

25 Kanazawa University, Kanazawa, Japan

26 Kakuma-machi, Kanazawa, 920-1192

27 Tel. & Fax.: +81-76-234-4790, Email: yuichi@se.kanazawa-u.ac.jp

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Abstract

Patients with Parkinson's disease (PD) have greater laterality of muscle contraction properties than other people with parkinsonian diseases. However, few studies have reported the laterality of MU activation properties of the lower extremity muscles in patients with PD. The aim of the present study was to identify the laterality of MU behavior in PD patients using high-density surface electromyography (HD-SEMG). Eleven female patients with PD (age, 69.2±6.2 years, disease duration, 2.7±0.9 years, Unified Parkinson's disease Rating Scale score, 13 (9-16)) and 9 control female subjects (age, 66.8±3.5 years) were enrolled in the present study. All subjects performed sustained isometric knee extension in a 30% maximal voluntary contraction (MVC) task for 20 s. HD-SEMG signals were used to record and extract single MU firing behavior in the vastus lateralis muscle during submaximal isometric knee extensor contractions with 64 electrodes and decomposed with the convolution kernel compensation technique to extract individuals MUs. Compared to the control subjects, the patients with PD exhibited laterality of the MU firing rate and an absence of a relationship between the mean MU firing rate and MU threshold. Patients with PD exhibit laterality of MU behavior and experience MU behavioral abnormalities even with mild symptoms such as Hoehn & Yahr stage ≤ 3 and disease duration=2.7±0.9. These findings suggest the importance

of considering the detection of abnormal muscle properties in PD patients beginning in the early phase of the disease.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders and is characterized by motor and cognitive dysfunction (Kalia & Lang, 2015). Motor dysfunction in PD can be partly attributed to impaired muscle contractions and force output due to central mechanisms (Stevens-Lapsley *et al.*, 2012). The central nervous system regulates force output through the recruitment of motor units (MUs) and the modulation of their discharge rates (De Luca *et al.*, 1982). Previous studies using intramuscular electromyography (EMG) have reported that PD patients show aberrant MU discharge patterns (Milner-Brown *et al.*, 1979; Dengler *et al.*, 1986). Glendinning and Enoka reported that PD patients exhibited more variable and intermittent MU discharge rates and a greater number of MUs recruited at lower force thresholds compared to healthy subjects in a submaximal voluntary contraction task (Glendinning & Enoka, 1994). Taken together, these studies demonstrate altered MU recruitment and rate coding in PD patients that may affect force output and regulation.

As measured clinically, PD is often an asymmetric condition whereby tremor, rigidity, and muscle weakness are often greater on one side versus another (Djaldetti *et al.*, 2006). This is unlike other parkinsonism diseases (e.g., Lewy body dementia, multiple system atrophy, and progressive supranuclear palsy) that have a more symmetric presentation (Cubo *et al.*, 2010;

68 Baumann *et al.*, 2014). Based on clinical presentation, it is plausible that PD patients have
69 greater laterality of muscle contraction properties than other people with parkinsonian diseases.
70 However, no report has compared the symmetry of MU activation properties limbs in PD
71 patients. A better understanding of the asymmetries in whole muscle activation in the lower
72 extremities may lead to the development of novel therapies. However, to the best of our
73 knowledge, few reports have examined the symmetry of MU behavior (e.g., neural drive to the
74 skeletal muscles) in patients with PD using the high-density surface electromyography (HD-
75 SEMG) method (Povalej Bržan *et al.*, 2017; Holobar *et al.*, 2018). In particular, no report has
76 identified the laterality of MU activation properties of lower extremity muscles in patients with
77 PD and the relationship to clinical measures of function.

78 The purpose of this study was to clarify the disease-specific changes in and
79 laterality of MU behavior during sustained isometric knee extensor contractions in patients
80 with PD using HD-SEMG. According to a previous study, healthy elderly people exhibited a
81 lower mean MU firing rate than young subjects (Watanabe *et al.*, 2016). In general, the firing
82 rates of earlier-recruited MUs are higher than later-recruited MUs at any time and force (e.g.,
83 onion skin). Watanabe *et al.* reported that for ramp-up contraction to 30% maximal voluntary
84 contraction (MVC), the MU firing rates of earlier-recruited MUs were generally higher than

later-recruited MUs at each torque level in both elderly and young adults, although these relationships were not observed in all MU pairs of elderly individuals (Watanabe *et al.*, 2016). Based on these findings the onion skin phenomenon is impaired in elderly people during force production at low to moderate force levels. Furthermore, a previous study reported that patients with PD exhibited a shift in the MU population to lower recruitment thresholds (Glendinning & Enoka, 1994).We hypothesized that compared with the less-affected side and age-matched control subjects, the more-affected side of patients with PD may display more variable MU firing rates, an abnormal recruitment threshold, and MU firing rates reflecting the degree of disease severity.

Materials and Methods

Subjects

Eleven female patients with PD and 9 control female subjects were enrolled in this study. Previous studies have reported sex-related differences among motor symptoms (Haaxma *et al.*, 2007; Solla *et al.*, 2012). In particular, Szewczyk-Krolikowski K *et al.* reported greater alterations in the symmetricity of motor function in male patients with PD than in female patients with PD (Szewczyk-Krolikowski *et al.*, 2014). Thus, female patients with PD may

exhibit greater laterality of motor function than male patients with PD. Therefore, we included only female subjects in the current study to detect the laterality of MU behavior. The exclusion criteria were as follows: Hoehn & Yahr stage > 3, injury to lower limb extremities, neurodegenerative disease (e.g., progressive supranuclear palsy, frontotemporal dementia, Alzheimer's disease, and dystonia), and diabetes mellitus. All procedures were in accordance with the Declaration of Helsinki and were approved by Hiroshima University's Committee on Ethics in Research (approved number No. E-53-2). All subjects signed an informed consent form prior to enrollment. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess physical function. The UPDRS characterizes impairments and functional ability using a rating scale from 0 to 4. The same neurologist performed the UPDRS assessments on all participants. PD patients were defined as left side- or right side-affected considering anamnesis and based on UPDRS scores. All measurements were performed during the on-medication period.

Motor testing and clinical evaluation protocols

For both legs, participants performed MVCs of the knee extensors, and the order of leg tested was randomized. Isometric knee extension was performed using a Biodex system (Biodex System 4; Biodex Medical Systems, Shirley, NY, USA). During contractions, both the

hip and knee extension angles were positioned at 90 degrees. The MVC involved a gradual increase in knee extension torque from 0 Nm to their maximal torque over 3 s, with the maximum torque held for 2 s. The participant performed at least two MVC trials with > 120 s of rest between trials and a warm-up for 10 min, including indoor walking and lower limb stretching before MVC measurements (Nishikawa *et al.*, 2019). The peak torque was used as the maximal effort and to calculate the target torque for the submaximal ramp-up contraction. After MVC measurements, participants were asked to perform submaximal isometric contractions at 30% MVC task, which were sustained for 20 sec, and rising phase and decline phase for 5 sec. The participant-generated torque and target torque were shown to the participants on a computer monitor. The participants practiced the MVC and submaximal contraction at least 10 min before the motor testing session began. We calculated the coefficient of variation (CV) of force (standard deviation (SD)/mean x 100, CV force) during the sustained submaximal isometric contraction and ramp-up contraction at 0–30% MVC.

EMG recording

During submaximal contraction, HD-SEMG signals were detected from the bilateral vastus lateralis (VL) muscles using a semidisposable grid of 64 electrodes (ELSCH064NM2, OT Bioelettronica, Torino, Italy) according to the same procedure used in previous studies

(Watanabe *et al.*, 2012; Nishikawa *et al.*, 2017a; Nishikawa *et al.*, 2017b; Nishikawa *et al.*, 2019). The grid consisted of 13 columns and 5 rows of electrodes (diameter, 1 mm; interelectrode distance, 8 mm in each direction), with one missing electrode at the upper left corner. The participants' hair was removed, and the skin was cleaned with alcohol. The electrode was attached to the skin with a bi-adhesive sheet (KITAD064, OT Bioelettronica) after applying conductive paste (Elefix Z-181BE, NIHONKOHDEN, Tokyo, Japan). The center of the electrode grid was positioned at the center of the line between the superior lateral edge of the patella and the greater trochanter protuberance. The columns of the electrode grid were placed parallel to the longitudinal axis of the VL muscle. A reference electrode was attached at the anterior superior iliac spine (Nishikawa *et al.*, 2017a).

Monopolar HD-EMG signals (64 channels) were amplified by a factor of 1,000, sampled at 2,048 Hz, and digitized by a 12-bit analog-to-digital converter (EMG-USB2+, OTBioelettronica). The recorded monopolar signals were off-line bandpass filtered (10–500 Hz) and transferred to analysis software (MTALAB 2019b, Math Works GK, MA, USA). Bipolar HD-SEMG signals (n = 59) along the columns were obtained from the 64 electrodes.

Data processing

Individual EMG channels were visually examined to remove noisy channels. The remaining channels were decomposed to attain information on a single MU. From high-density SEMG signals, individual MU firing patterns were decomposed using the Convolution Kernel Compensation technique (Figure 1) (Holobar & Zazula, 2004; Merletti *et al.*, 2008; Holobar *et al.*, 2009). We followed the decomposition procedure that was previously extensively validated on signals from various skeletal muscles (Holobar *et al.*, 2009; Farina *et al.*, 2010; Gallego *et al.*, 2015a; Gallego *et al.*, 2015b; Yavuz *et al.*, 2015; Watanabe *et al.*, 2016; Watanabe *et al.*, 2018). The pulse-to-noise ratio introduced by Holobar (Holobar *et al.*, 2014) was used as an indicator of the MU identification accuracy, and only MUs with a pulse-to-noise ratio > 30 dB (corresponding to an accuracy of MU firing identification > 90%) were used for further analysis, whereas all other MUs were discarded (Holobar *et al.*, 2014). After decomposition, the discharge patterns of individual MUs were inspected and correlated by two experienced investigators together. Discharge times for individual MUs were used for calculation of instantaneous MU firing rates. During this calculation, we excluded abnormal interspike intervals (<33.3 or >250 ms (30 and 4 Hz, respectively)) (Holobar *et al.*, 2009; Watanabe *et al.*, 2013; Watanabe *et al.*, 2016). The instantaneous firing rates (pulses per second, pps) of individual MUs were calculated by

169 taking the inverse of the interspike interval. The mean MU firing rate for each MU was
170 calculated as the average of the instantaneous firing rates during the submaximal voluntary
171 contraction task. The CV of the firing rates for each MU, which was defined as the ratio of its
172 SD to the mean, was computed. The mean MU firing rate with > 30% CV were excluded
173 from further analysis (Fuglevand *et al.*, 1993). Detected MUs were divided into three groups
174 by recruitment torque: MUs recruited at (1) MU10; <10%, (2) MU20; 10–20%, and (3)
175 MU30; 20–30% MVC. The three MU groups were used for further analysis.

176 *Statistical analyses*

177 Statistical analyses were performed using SPSS ver. 22.0 (SPSS, Inc., Chicago, IL, USA). The
178 continuous data are presented as the mean ± SD or the median (min–max). Before analysis, the
179 normal distribution of the data was confirmed using the Shapiro-Wilk test. The age, height, and
180 weight were compared between patients with PD and control subjects using unpaired *t*-tests.
181 The scores for subcomponents of UPDRS part III were compared between the more-affected
182 side and less-affected side using a Wilcoxon signed rank test. The MMSE was compared
183 between patients with PD and control subjects using the Mann-Whitney U test. A multiple
184 regression analysis was performed to estimate the influence of laterality on knee extensor torque,
185 the CV of force, the cross-correlation function, the mean MU firing rate, the number of MUs

in MU groups (MU10, MU20, and MU30), and MU firing rate with matched recruitment threshold (21.5 %MVC, a tolerance of ± 0.5 %MVC). The dependent variable was the difference between the less-affected side and more-affected side or between the dominant side and non-dominant side, and the explanatory variables is the group (PD or control) were adjusted according to the less-affected or dominant leg (based on kicking preference). Pearson's correlation coefficients were computed to assess bivariate correlations between the mean MU firing rate and MU threshold on both sides of patients with PD. The correlation coefficients were qualitatively interpreted according to the following thresholds: 0.2–0.4, small; 0.4–0.7, moderate; 0.7–0.9, strong; and 0.9–1.0, very strong. Analysis of covariance (ANCOVA) was performed to compare the slopes of the mean MU firing rate and MU threshold bilaterality in the limbs of patients with PD and control subjects. A mixed-effects model with a random intercept and a random slope was applied to analyze the mean MU firing rate. The explanatory variables were the group (PD or control), MU groups (MU10, MU20, and MU30), limb (more-affected side or less-affected side, dominant or non-dominant side), and their interaction terms, and the %MVC was included as a continuous variables. Significance was accepted for values of $p < 0.05$.

Results

The general characteristics of the subjects are shown in Table 1. Significant differences in age, height, and weight were not observed between patients with PD and control subjects ($p = 0.3166$, $p = 0.5215$, and $p = 0.8009$, respectively). The multiple regression analysis revealed that laterality of the knee extensor torque was associated with PD ($p < 0.0001$; Figure 2A). A significant difference in the MMSE score was not observed between patients with PD and control subjects ($p = 0.0760$). The scores for subcomponents of UPDRS part III (e.g., Finger tapping, Hand movements, Pronation-supination movements of hands, Toe tapping and Leg agility) were significantly higher on the more-affected side than on the less-affected side of patients with PD ($p < 0.0001$, respectively, Table 2).

Three hundred seventy MUs for the patients with PD (less-affected side = 109 and more-affected side = 105) and control subjects (left side = 77 and right side = 79) were accepted for data processing (Table 3). The multiple regression analysis revealed that laterality of the number of MU10, MU20, and MU30 was not associated with PD ($p = 0.901$, $p = 0.200$, and $p = 0.723$, respectively).

Submaximal isometric contraction at 30% MVC

The multiple regression analysis revealed that laterality of the CV of force, the mean

MU firing rate, and the cross-correlation function was associated with PD ($p = 0.013$, $p = 0.005$, and $p < 0.0001$, respectively; Figure 2B–D, Figure 3). Moderate to strong correlations were observed between the CV of force and mean MU firing rate on the more-affected and less-affected sides (r = 0.7527, $p = 0.0120$ and r = 0.6619, $p = 0.0371$, respectively). On the other hand, no correlations were observed between the CV of force and mean MU firing rate on the left and right sides of the control subjects (r = -0.5022, $p = 0.1683$ and r = -0.5164, $p = 0.1547$). Furthermore, strong correlations were observed between the UPDRS part III score and mean MU firing rate on the more-affected side (r = 0.7233, $p = 0.0119$; Figure 4B). On the other hand, the less-affected side did not show a correlation between the UPDRS part III score and mean MU firing rate (r = 0.2082, $p = 0.5390$; Figure 4A).

Relationship between the mean MU firing rate and MU threshold

When performing submaximal contractions on the less-affected side for patients with PD and the left and right sides for control subjects, significant negative correlations were observed between the MU threshold and mean MU firing rate (r = -0.3540, $p < 0.0001$, r = -0.4954, $p < 0.0001$, and r = -0.6871, $p < 0.0001$, respectively; Figure 4C and D). On the other hand, no significant correlations were observed between the MU threshold and mean MU firing rate on the more-affected side (r = -0.07806, $p = 0.4242$; Figure 4C). The slope of the mean

MU firing rate and MU threshold revealed a significant difference between the bilateral limbs of patients with PD ($F = 39.664$, $p < 0.0001$). On the other hand, no significant difference in the slope of mean MU firing rate and MU threshold between limb was observed in control subjects ($F = 2.644$, $p = 0.106$).

Ramp-up contraction at 0–30% MVC

The mean firing rate of each MU was plotted against contraction torque (y-axis: firing rates (pps) and x-axis: force (%MVC)) and smoothed with a Hanning window of length of 2.0 seconds for a patient with PD and a control subject (Figure 5). While the firing rates of individual MUs increased with the force levels on both sides of patients with PD and control subjects, the MU firing rate of MU20 and MU30 was higher on the more-affected side than on the less-affected side of patients with PD and on both sides of control subject (e.g., blue and green lines). For MU20, the more-affected side of patients with PD did not show a significant difference in the mean MU firing rate compared with MU10 ($p = 0.43$). On the other hand, the comparison of other adjacent MU groups (e.g., MU10 vs MU20 for control subjects, MU20 vs, MU30 for PD and control subjects) was significant ($p < 0.001$; Figure 6). The multiple regression analysis revealed that laterality of the MU firing rate with matched recruitment threshold (21.5 ± 0.5 %MVC) was associated with PD ($p = 0.018$). The MU firing rate was

254 higher on the more-affected side than on the less-affected side of patients with PD (9.63 ± 2.23
255 pps vs. 8.36 ± 1.96 pps, Figure 7).

256 **Discussion**

257 The present study compared the MU behavior between the less-affected side and the
258 more-affected side of individual patients with PD and bilateral sides of control subjects. The
259 primary novel results are described below. Compared to the control subjects, the patients with
260 PD exhibited (1) laterality of the MU firing rate; (2) an abnormal relationship between the
261 mean MU firing rate and MU threshold on the more-affected side; (3) the MU firing rate
262 reflected the degree of disease severity; and (4) a higher MU firing rate on the more-affected
263 side than on the less-affected side. These findings support our hypothesis that the more-
264 affected side of patients with PD showed abnormal MU activity compared with the less-
265 affected side of patients with PD and both sides of control subjects during the submaximal
266 voluntary contraction task.

267 The CV of force and mean MU firing rate were higher on the more-affected side of
268 patients with PD than on the less-affected side of patients with PD and both sides of control
269 subjects. Previous studies reported that PD patients exhibited more force fluctuations during
270 force production, more variable and intermittent MU firing rates and a greater number of

271 MUs recruited compared with age-matched healthy subjects (Glendinning & Enoka, 1994;
272 Nishikawa *et al.*, 2017b). Based on these findings, force control is more difficult on the more-
273 affected side of patients with PD than on the less-affected side of patients with PD and both
274 sides of control subjects. Our results agreed with these previous studies. Importantly, we
275 clarified that there is a laterality of MU behavior in PD patients. Previous studies reported that
276 abnormal and irregular MU activation in PD patients occurred by disinhibition of
277 reticulospinal pathways induced by degeneration of the substantia nigra pars compacta
278 (SNPc) (Chronister *et al.*, 1988; Delwaide *et al.*, 1991). The main pathological changes are
279 observed in the dopaminergic neurons of the SNPc (Fearnley & Lees, 1991), which show
280 greater damage on the side contralateral to the side of the body exhibiting more severe
281 symptoms (Tang *et al.*, 2010; Kwon *et al.*, 2012). Previous studies have investigated potential
282 neural asymmetries in the neocortex of patients with PD (Pollok *et al.*, 2012; Hall *et al.*,
283 2014). Heinrichs-Graham et al. reported that PD patients exhibited a relationship between
284 symptom asymmetry and neural activity laterality during movement (Heinrichs-Graham *et*
285 *al.*, 2017). Compared with control subjects, the patients with PD exhibited significant
286 laterality of the MU firing rate, suggesting that the asymmetrical MU activity patterns in
287 patients with PD are influenced by an asymmetrical change in dopaminergic neurons of the

SNPc (Kempster *et al.*, 1989). Furthermore, we found a correlation between the UPDRS part III score and mean MU firing rate of the more-affected side in patients with PD (Figure 4B). The degeneration of dopaminergic neurons progresses annually in patients with PD (Fearnley & Lees, 1991). Thus, the increase in MU firing rates reflects the degree of neurodegeneration. In the present study, clinical symptoms of PD reflected events of the MU behavior, and MU firing rates may infer the overall symptoms and laterality of PD.

Based on the results of the present study, the mean MU firing rate and MU threshold on the less-affected side and both sides of control subjects were inversely related (Figure 4C and D). The mean MU firing rate and MU thresholds show an "operating point" of the motor neuron pool that shifts in response to excitation, and the correlations between the MU firing rates and the MU threshold are achieved at a particular force that maintains a fixed relationship defined by the slope of the regression equations (De Luca & Hostage, 2010). Our results are consistent with a neural control scheme proposed in the literature known as the "onion skin" control scheme, which states that MUs that are recruited early achieve a mean MU firing rate that is greater than MUs recruited later, and earlier-recruited MUs maintain higher MU firing rates than later-recruited MUs (De Luca & Erim, 1994; De Luca & Hostage, 2010; de Souza *et al.*, 2018). On the other hand, the more-affected side of patients with PD

305 did not show correlations between the MU firing rates and MU thresholds and a lower cross-
306 correlation function than the less-affected side of patients with PD (Figure 3). A reasonable
307 explanation for this phenomenon is the abnormal discharge pattern and MU thresholds of the
308 more-affected side of patients with PD. Furthermore, higher MU firing rates with a matched
309 recruitment threshold were observed on the more-affected side compared with the less-
310 affected side in patients with PD. The MU firing rates during contraction are mainly
311 determined by synaptic excitatory input from the corticospinal tract to a motor neuron pool
312 (Sun *et al.*, 2000). Another previous study showed that reticulospinal pathways originating in
313 the reticularis gigantocellularis nucleus were disinhibited in PD as a result of abnormal
314 descending influences on spinal cord interneurons (Delwaide *et al.*, 1991). Furthermore,
315 patients with PD exhibited more variable and intermittent MU discharge rates than healthy
316 subjects in a submaximal voluntary contraction task (Glendinning & Enoka, 1994). Patients
317 with PD exhibit damage in the basal ganglia cells in the substantia nigra and the degeneration
318 of cells in the locus coeruleus, thalamus, brain stem, autonomic nuclei, and spinal cord
319 (Paulus & Jellinger, 1991). The spinal cord also receives dopaminergic projections from the
320 thalamus and hypothalamus (Lindvall *et al.*, 1983). Because motor neurons receive numerous
321 inputs from descending brain stem and cortical pathways, as well as from propriospinal and

322 sensory afferents, damage to many of these areas in patients with PD might disturb the normal
323 balance of excitatory and inhibitory synapses onto motor neurons. The results of such an
324 imbalance would be a change in the function of motor neurons. Grimby *et al.* reported that
325 recruitment order of MUs upon voluntary contraction changes according to proprioceptive
326 afferent activity (Grimby & Hannerz, 1968). Furthermore, patients with PD exhibit decreased
327 of Ib interneuron activity (Delwaide *et al.*, 1991) and increased Ia inhibitory activity (Nichols
328 & Koffler-Smulevitz, 1991). These findings suggest that spinal cord circuits behave
329 abnormally in PD patients and could alter motor neuron behavior. In addition to changes in
330 the central nervous system, a previous study reported that fast-twitch muscle fibers appear to
331 atrophy selectively in PD patients (Edstrom, 1970). The authors explained that this
332 phenomenon is the effect of selective disuse of high-threshold phasic MUs and increased
333 usage of low threshold MUs owing to rigidity. These previous findings are consistent with the
334 results of the present study showing that compared with the less-affected side of patients with
335 PD and both sides of control subjects, the more-affected side of patients with PD exhibits
336 lower muscle strength, higher MU firing rates, and an absence of a relationship between the
337 mean MU firing rate and MU threshold. Thus, the cause of the greater reduction in the mean
338 MU firing rate in patients with PD may be a change in central nervous system control that

339 results in neurophysiological adaptations related to changes in the contractile properties of the
340 muscle fibers.

341 In the present study, we applied HD-SEMG to clarify disease-specific MU
342 activation in PD patients. Many previous studies have performed analyses of MU behavior in
343 healthy conditions and in several diseases (e.g., stroke and diabetes mellitus) (Watanabe *et al.*,
344 2013; Hyngstrom *et al.*, 2018; Martinez-Valdes *et al.*, 2018). HD-SEMG can be used to
345 noninvasively investigate MU behavior in a large area of muscles during force production and
346 can thus be employed as a tool to test disease-specific MU behavior in several diseases.

347 The present study has several limitations. First, the small sample size of 11 patients
348 with PD is a study limitation, but the results of our study clearly show that the more-affected
349 side of patients with PD exhibited different MU behaviors compared with the less-affected
350 side. Second, the subjects in the present study only performed a low-intensity MVC task (e.g.,
351 30% MVC). Third, only patients with PD presenting mild to moderate motor symptoms, and
352 almost no non-motor symptoms (e, g, cognitive impairment and sleep disturbance) were
353 recruited for this study. Finally, we only recruited female patients with PD, and thus the
354 results of this study cannot be applied to male patients with PD. Therefore, future studies
355 (e.g., a large-sample study, studies testing different MVC tasks, studies recruiting patients

with PD presenting severe symptoms, and studies examining the effect of sex on MU behavior and laterality) are needed to clearly understand MU behavior in patients with PD.

In conclusion, we investigated disease-specific MU behavior in PD patients using HD-SEMG. Compared to the control subjects, the patients with PD exhibited laterality of MU recruitment behavior. Importantly, PD patients exhibited laterality of MU behavior and MU behavior abnormalities even when exhibiting only mild symptoms. These findings suggest the importance of considering the detection of abnormal muscle properties in PD patients beginning in the early phase of the disease.

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Competing Interests

The authors declare no conflicts of interest and that no companies or manufacturers will benefit from the results of this study.

Authors' Contributions

YN and KW conceived and designed the study; YN performed experiments; YN and KW analyzed data; YN, KW, AH, HM and ST interpreted the results of experiments; YN, KW and AH prepared figures; YN, KW, and AH drafted the manuscript; and YN, KW, AH, NM, HM and ST edited and revised the manuscript. YM, KW, AH, NM, HM, and ST approved the final version of the manuscript.

Data Accessibility

Data are available via request from the corresponding author.

Abbreviations

CV, coefficient of variation; EMG, electromyography; HD-SEMG, high-density surface electromyography; MU, motor unit; MVC, maximal voluntary contraction; PD, Parkinson's disease; pps, pulses per second; SD, standard deviation; SNPc, substantia nigra pars compacta;

390 UPDRS, Unified Parkinson's Disease Rating Scale; VL, Vastus lateralis

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583 **Figure and Table Legends**

584 **Table 1.** Characteristics of patients with PD and control subjects.

585

586 **Table 2.** Subcomponents of UPDRS Part III.

587

588 **Table 3.** Number of MUs in each MU group.

589

590 **Figure 1.** Representative image of the high-density surface electromyogram (SEMG)
591 decomposition of the less-affected side of a patient with PD (72 years old) during the
592 submaximal isometric contraction task. A: Motor unit action potential templates of 11 motor
593 units, identified by the Convolution Kernel Compensation technique from a high-density
594 surface electromyogram. B: Discharge pattern of the detected individual motor units and
595 performed force. MU action potential templates on discarded SEMG channels are left blank.

596

597 **Figure 2.** Comparison of laterality for the knee extensor torque (A), CV of force (B), cross-
598 correlation function, and (D) mean MU firing rate on both sides of patients with PD and
599 control subjects.

600 **Figure 3.** Cross-correlation functions computed between the MU firing rates of the less-
601 affected side (A) and more-affected side (B) for patients with PD and the left side (C) and
602 right side (D) of a control subject during submaximal isometric contraction.
603
604 **Figure 4.** Correlations between the mean MU firing rate and UPDRS part III score for the
605 less-affected side (A) and more-affected side (B) of patients with PD, and the MU threshold
606 for both sides of patients with PD (C) and control subjects (D). Strong correlations were
607 observed between the mean MU firing rate and UPDRS part III score on the more-affected
608 side (B). Moderate correlations were observed between the mean MU firing rate and threshold
609 on the less-affected side of patients with PD and both sides of control subjects (C and D).
610
611 **Figure 5.** Representative MU firing rates for the less-affected side (A) and more-affected side
612 (B) of a patient with PD (67 years old) and left side (C) and right side (D) of a control subject
613 (66 years old) during ramp-up contraction to 0–30% MVC. The red lines, blue lines, and
614 green lines indicate motor units recruited at < 10; MU10, 10–20; MU20, 20–30% MVC;
615 MU30.
616

617 **Figure 6.** Comparison of the mean MU firing rate for individual MU groups of control

618 subjects (A) and patients with PD (B) during submaximal ramp contraction to 30% MVC. * p

619 < 0.05.

620

621 **Figure 7.** Comparison of laterality for the MU firing rate with matched recruitment threshold

622 (21.5 % ± 0.5 %MVC) on both sides of patients with PD and control subjects.

Table 1. Characteristics of PD patients and control subjects

	Parkinson's disease patients, n = 11 More-affected side/Less-affected side	Control subjects, n = 9 Left side/Right side
Age, year	69.2 ± 6.2	66.8 ± 3.5
Height, cm	152.9 ± 4.0	151.8 ± 3.3
Weight, kg	51.2 ± 7.2	51.9 ± 4.9
Disease duration, year	2.7 ± 0.9	N/A
UPDRS part III	13 (9–16)	N/A
Knee extension torque, Nm	58.5 ± 11.1/70.0 ± 15.2	72.6 ± 13.1/73.9 ± 11.7
L-dopa, mg	200 (100–200)	N/A
Mini-Mental State Examination	28.8 ± 1.1	29.8 ± 0.4

UPDRS, Unified Parkinson's Disease Rating Scale

Table 2. Subcomponents of the Unified Parkinson's Disease Rating Scale Part III

	More-affected side	Less-affected side
Speech	1 (0–1)	
Facial expression	1 (1–2)	
Rigidity	0 (0–0)	0 (0–0)
Finger tapping	1 (1–1)	0 (0–0)*
Hand movements	1 (1–2)	0 (0–1)*
Pronation-supination movements of hands	1 (1–2)	0 (0–1)*
Toe tapping	1 (1–2)	0 (0–0)*
Leg agility	0 (0–1)	0 (0–0)*
Arising from chair	1 (0–2)	
Gait	1 (0–1)	
Freezing of gait	0 (0–0)	
Postural stability	1 (0–2)	
Posture	1 (0–1)	
Global spontaneity of movement	1 (0–2)	
Postural tremor of the hands	0 (0–0)	0 (0–0)
Kinetic tremor of the hands	0 (0–0)	0 (0–0)

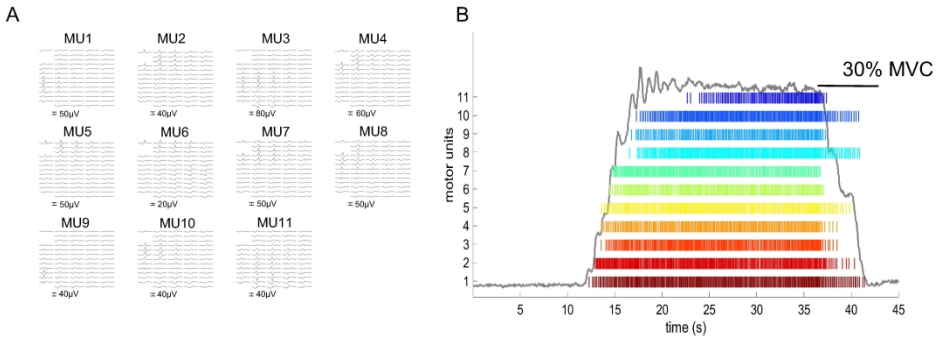
Rest tremor amplitude	0 (0–0)
Constancy of rest tremor	0 (0–0)

Data shown as the median (min–max).

* $p < 0.05$, compared with the more-affected side.

Table 3. Number of motor units in each MU group.

	Less-affected side	More-affected side	Left side	Right side
Total	10.82 ± 3.06	11.82 ± 2.99	8.56 ± 2.74	8.78 ± 3.11
MU10	2.82 ± 1.94	2.64 ± 2.01	2.00 ± 1.66	2.11 ± 1.36
MU20	5.36 ± 2.06	6.45 ± 2.16	3.67 ± 1.80	3.56 ± 1.81
MU30	2.64 ± 2.01	2.73 ± 1.79	2.89 ± 1.27	3.11 ± 0.93



Representative of the high-density surface electromyogram (SEMG) decomposition in a less-affected side Parkinson's disease patient (72 years old) during submaximal isometric contraction task. A: Motor unit action potential templates of 11 motor units, identified by the Convolution Kernel Compensation technique from a high-density surface electromyogram. B: Discharge pattern of the detected individual motor units and performed force. Motor unit action potential templates on discarded SEMG channels are left blank.

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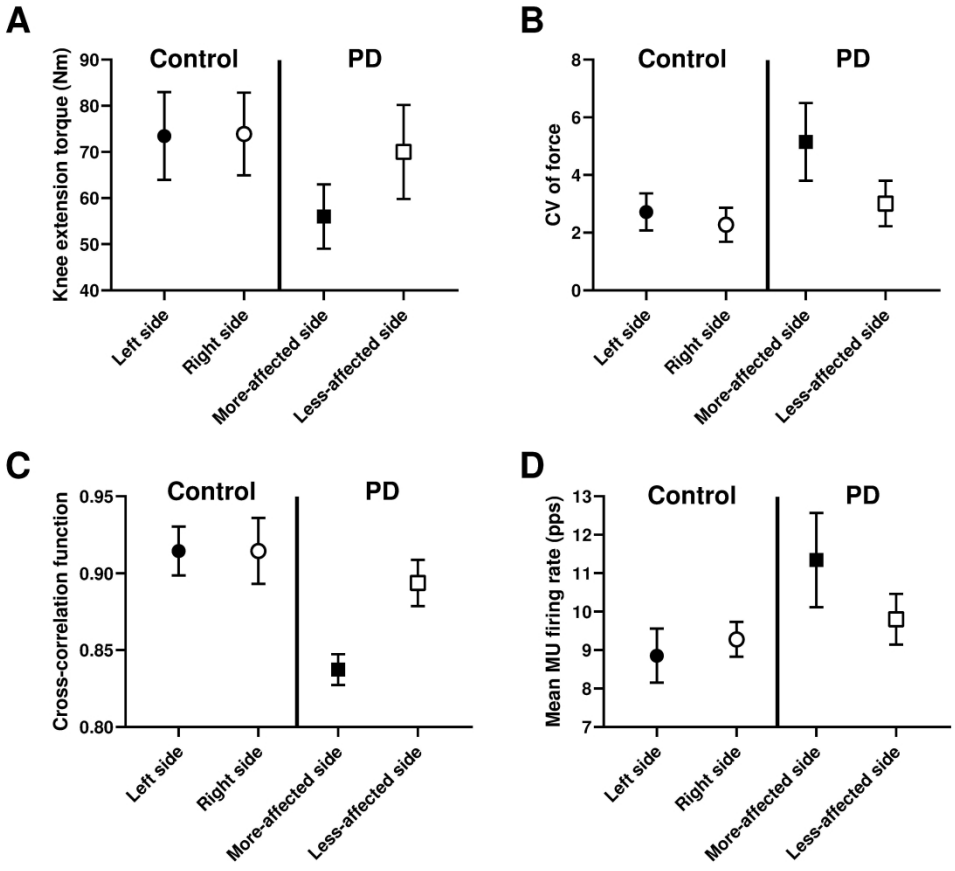

Figure 2. Comparison of laterality for the knee extensor torque (A), CV of force (B), cross-correlation function, and (D) mean MU firing rate on both sides of patients with PD and control subjects.

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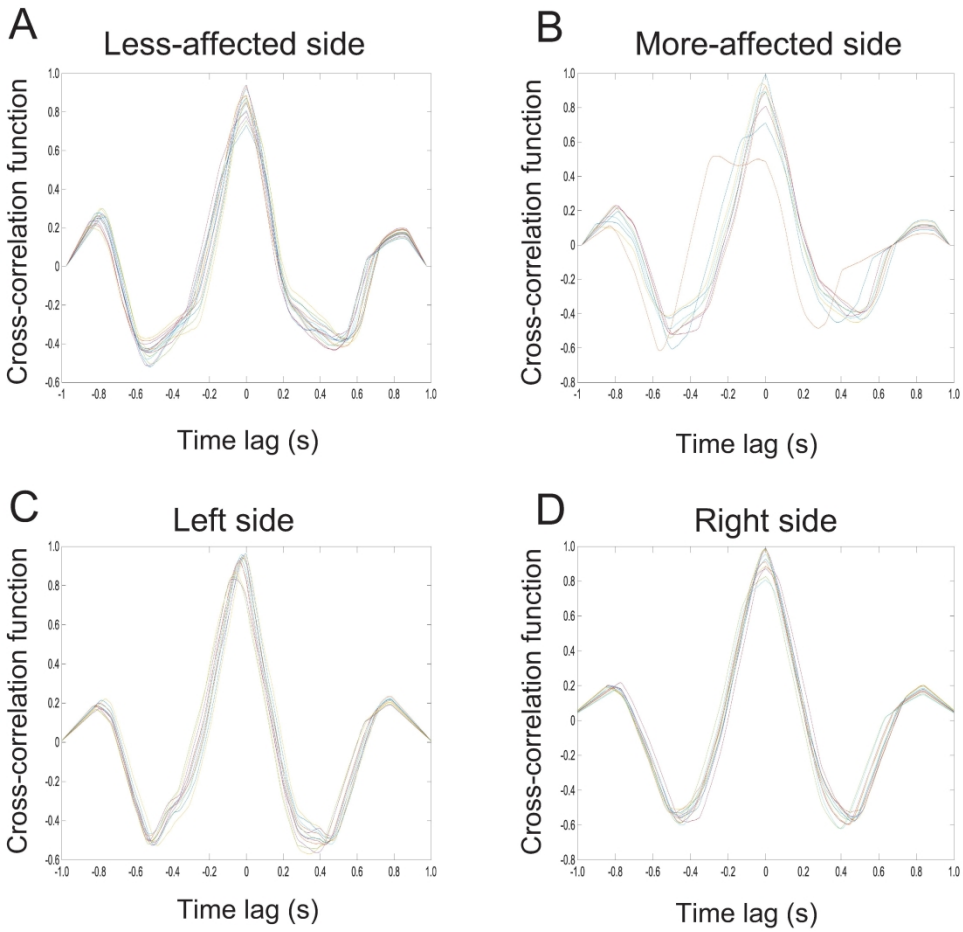

Figure 3. Cross-correlation functions computed between the MU firing rates of the less-affected side (A) and more-affected side (B) for patients with PD and the left side (C) and right side (D) of a control subject during submaximal isometric contraction.

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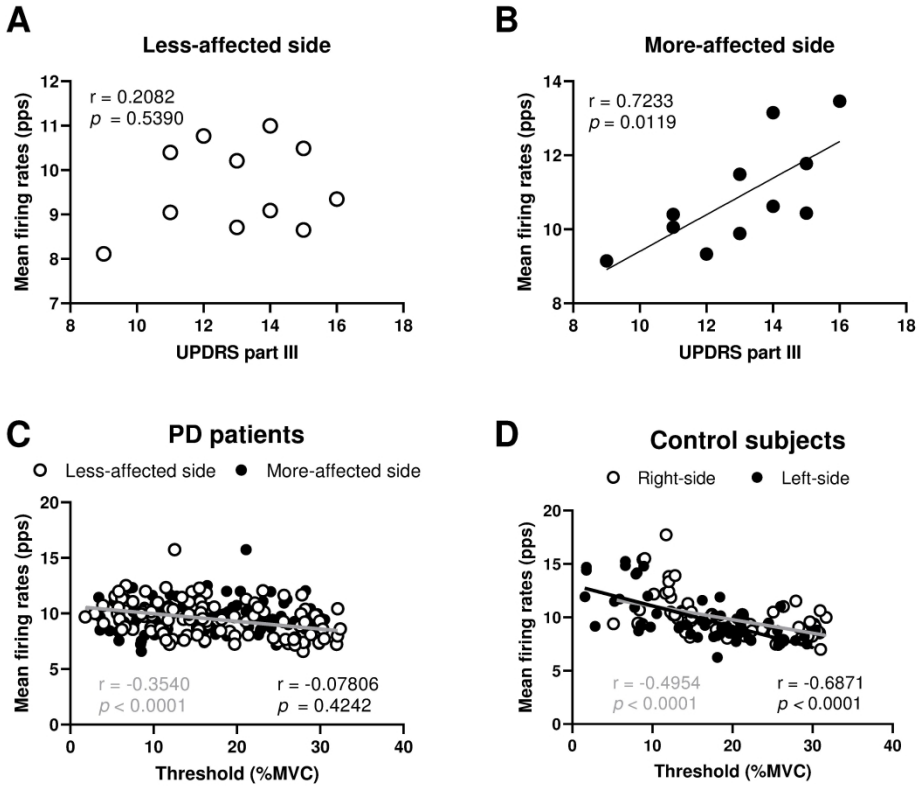

Figure 4. Correlations between the mean MU firing rate and UPDRS part III score for the less-affected side (A) and more-affected side (B) of patients with PD, and the MU threshold for both sides of patients with PD (C) and control subjects (D). Strong correlations were observed between the mean MU firing rate and UPDRS part III score on the more-affected side (B). Moderate correlations were observed between the mean MU firing rate and threshold on the less-affected side of patients with PD and both sides of control subjects (C and D).

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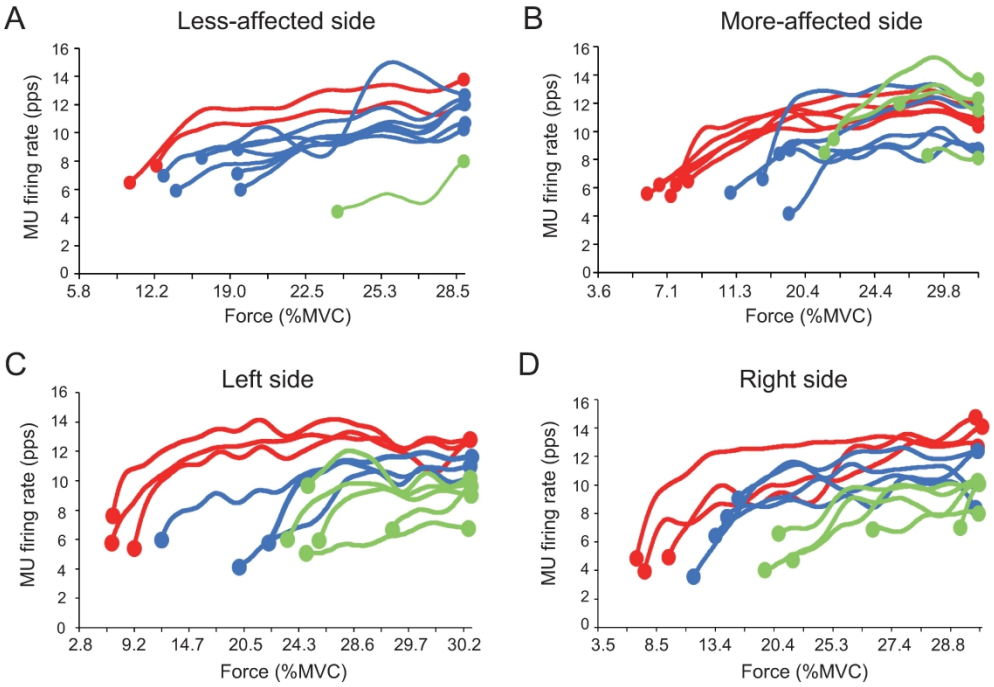

Figure 5. Representative MU firing rates for the less-affected side (A) and more-affected side (B) of a patient with PD (67 years old) and left side (C) and right side (D) of a control subject (66 years old) during ramp-up contraction to 0–30% MVC. The red lines, blue lines, and green lines indicate motor units recruited at < 10; MU10, 10–20; MU20, 20–30% MVC; MU30.

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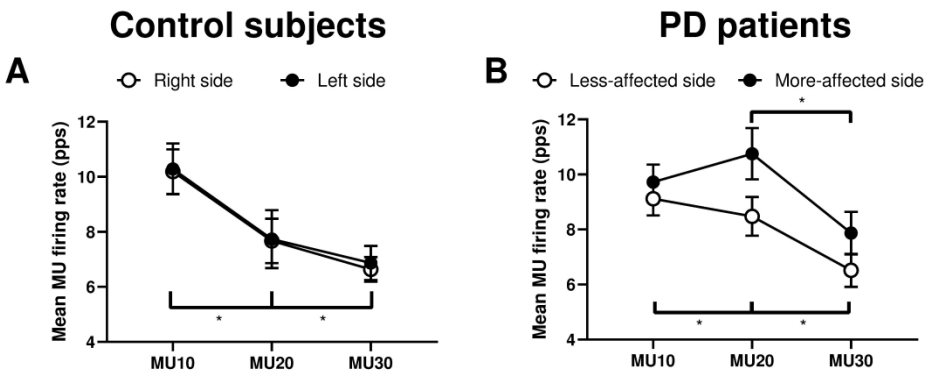

Figure 6. Comparison of the mean MU firing rate for individual MU groups of control subjects (A) and patients with PD (B) during submaximal ramp contraction to 30% MVC. * $p < 0.05$.

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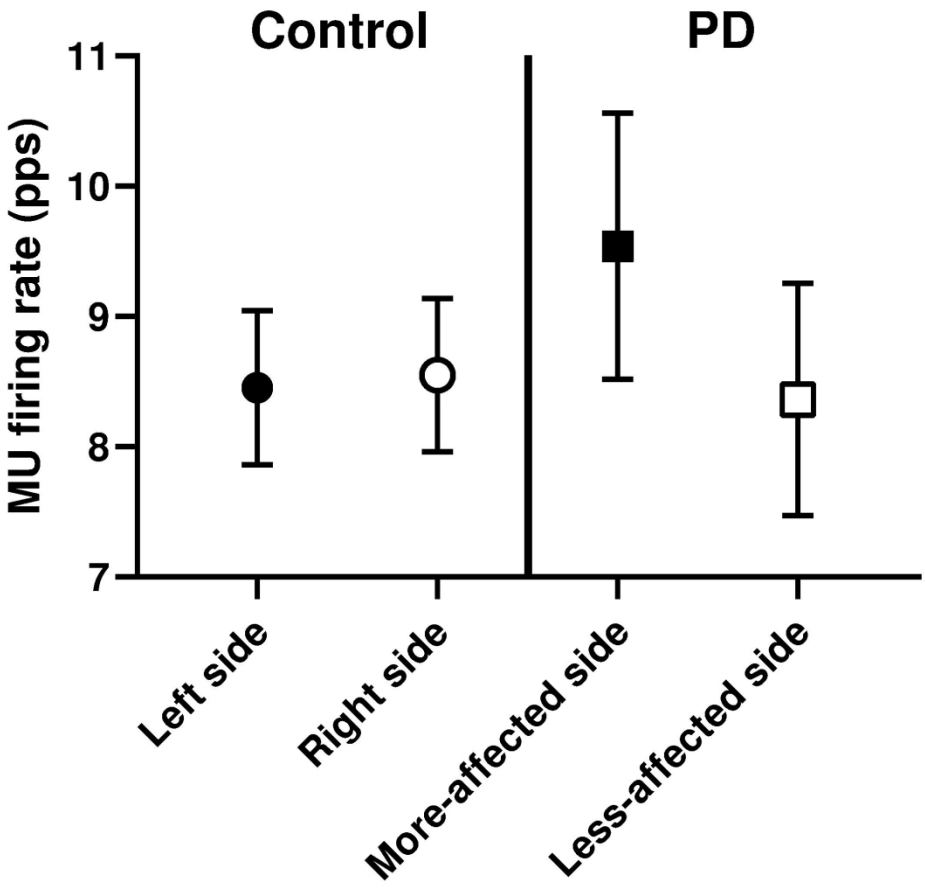

Figure 7. Comparison of laterality for the MU firing rate with matched recruitment threshold (21.5 % ± 0.5 %MVC) on both sides of patients with PD and control subjects.

97x92mm (600 x 600 DPI)