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1. **Title**

Spatial electromyography distribution pattern of the vastus lateralis muscle during ramp up contractions in Parkinson’s disease patients

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Abstract

Parkinson’s disease (PD) related decreases in muscle strength may result from both central and peripheral factors. However, the effect of PD on the neuromuscular system, such as motor unit activation properties, remains unclear. The purpose of the present study was to compare the spatial distribution pattern of electromyographic activity during sustained contractions in healthy subjects and PD patients. Twenty-five female PD patients and 25 healthy age-matched female control subjects performed ramp submaximal contractions during an isometric knee extension from 20% to 80% of the maximal voluntary contraction (MVC). To evaluate alterations in the spatial electromyography (EMG) potential distribution, normalized root mean square (RMS), modified entropy, coefficient of variation, and correlation coefficients were calculated from multi-channel surface electromyography at 10% force increments. The comparison between PD and healthy subjects revealed that, during increased force exertions, PD patients exhibited less change in normalized RMS, modified entropy, coefficient of variation, and pattern of spatial EMG distribution. These data showed that the heterogeneity and the changes in the activation pattern are smaller in the PD patients than in healthy subjects. This finding may be associated with central adaptation and/or peripheral changes in PD patients.
1. Introduction

Parkinson’s disease (PD) is one of the most common neurodegenerative disorders with a prevalence of 180.3 per 100,000 individuals in Japan (Yamawaki et al., 2009). Muscle weakness and fatigue are common symptoms associated with PD that have attracted attention and may have substantial functional consequences for individuals (Cano-de-la-Cuerda et al., 2010). The PD-related decreases in muscle strength may result from both central and peripheral factors (Stevens-Lapsley et al., 2012). One previous study reported that fast-twitch muscle fibers appeared to atrophy selectively in PD patients (Edstrom, 1970). Furthermore, a previous study reported that PD patients show lower muscle strength, higher antagonistic moments and higher activation deficits than healthy subjects (Moreno Catalá et al., 2013). A previous study reported that the reticulospinal pathways are disinhibited in PD patients, resulting in abnormal descending influences on spinal cord interneurons (Delwaide et al., 1991). Unbalanced influences on interneurons have been reported to change the gain of circuitry that mediates reciprocal activation and alter the tonic state of motor neurons, influencing the ability to maintain constant discharge (Glendinning and Enoka, 1994).
Moreover, several studies have reported that PD patients show aberrant patterns of discharge in motor units (MUs) using the intramuscular electromyography (EMG) method (Dengler et al., 1986; Milner-Brown et al., 1979; Petajan and Jarcho, 1975). One study reported that PD patients exhibit more activation of action potentials and inconsistent discharge rates of MUs than healthy subjects in the 20% maximum voluntary contraction (MVC) task (Glendinning and Enoka, 1994). However, these previous studies examined only muscle contraction at low force, and muscle activity during increasing force contraction was not evaluated.

Surface EMG (SEMG) has been used as a technique to evaluate regulation and adaptations in the neuromuscular system. Given that the SEMG signal is a summation of the action potentials of activated MUs under the electrodes, an increase in the SEMG amplitude is interpreted as reflecting a modification of MU activation (Merletti et al., 2001).

Neuromuscular functions, such as the recruitment of MUs within a muscle, have been recently assessed through the spatial distribution patterns of muscle activation using multi-channel SEMG (Farina et al., 2008; Holtermann et al., 2008; Merletti et al., 2008). These studies have demonstrated that the spatial SEMG potential distribution pattern within a muscle is altered by contractions or fatigue levels (Farina et al., 2008; Holtermann and Roeleveld, 2006). This phenomenon has been explained by a spatial inhomogeneity in the
location of different types of muscle fibers (Chanaud and Macpherson, 1991) and a clustering of muscle fibers innervated by one MU in a limited territory (Lexell and Downham, 1991).

Previous studies have demonstrated that alterations of the spatial distribution of multi-channel SEMG can be explained by the physiological phenomena of MU recruitment, which suggests that the spatial distribution of multi-channel SEMG can be used to study changes in MU recruitment (Holtermann et al., 2005; Holtermann et al., 2009). Although this technique is an indirect method of assessing MU behavior, multi-channel SEMG can be used to non-invasively investigate MU activation in a large area of the muscles during force production.

The purpose of the present study was to investigate the spatial distribution pattern of muscle activation during ramp up contractions in PD patients using a multi-channel SEMG method. We hypothesized that compared with healthy subjects, PD patients would exhibit (1) higher overall amplitude, and (2) smaller multi-channel SEMG amplitude distribution changes with increased contraction level.

2. Materials and Methods

2.1. Subjects
Twenty-five female PD patients (age, 66.8±6.8 years; height, 155.2±2.9 cm; weight, 45.8±4.9 kg) and 25 healthy age-matched female subjects (age, 67.3±5.8 years; height, 154.4±2.4 cm; weight, 47.2±3.3 kg) were enrolled in this study. Our previous research showed that, compared with healthy young males, healthy young females exhibited greater differences in the spatial distribution pattern of sustained isometric contractions (Nishikawa et al., 2017). Therefore, we included only female subjects in the current study. The exclusion criteria were the following: injury to the lower extremities, neuromuscular disease, cardiovascular disease, chronic obstructive pulmonary disease, and diabetes mellitus. All procedures were performed in accordance with the Declaration of Helsinki and were approved by the Hiroshima University’s Committee on Ethics in Research (approval number No. E-53). 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 of all participants.

2.2. Experimental design
All subjects performed MVC during isometric knee extension. Isometric knee extension was performed using the Biodex system (Biodex System 3, Biodex Medical Systems, NY, USA). During the contractions, both the hip and knee extension angles were fixed at 90° (Watanabe et al., 2012c). The MVC involved a gradual increase in the knee extension force exerted by the knee extensor muscles from 0 to maximum over 3 s, and the maximum force was held for 2 s. The subjects performed at least two MVC trials with > 120 s rest between the trials. After MVC, subjects were asked to perform a force ramp contraction from 0% to 80% of the MVC force with an increase rate of approximately 10% of the MVC per sec (Watanabe et al., 2012a). The produced and target torques were shown to the subjects on a personal computer monitor. The subjects practiced the MVC and ramp submaximal contraction > 10 min before the session.

2.3. EMG recordings

Multi-channel SEMG signals were detected from the right vastus lateralis (VL) muscle in healthy subjects using a semi-disposable grid of 64 electrodes (ELSCH064RS3, OT Bioelettronica, Torino, Italy), according to previously described methods (Figure 1) (Nishikawa et al., 2017; Watanabe et al., 2012a). The VL muscle of the most affected side
was measured in PD patients. The grid consisted of 13 columns and 5 rows of electrodes (diameter, 1 mm; inter-electrode distance, 8 mm in each direction), with one missing electrode at the upper left corner. The subject’s hair was removed, the skin was cleaned with alcohol, and the grid was attached to the skin with a bi-adhesive sheet (KITAD064, OT Bioelettronica) after pouring conductive paste (Elefix Z-181BE, NIHON KOHDEN, Tokyo, Japan) in correspondence of the electrodes. The center of the electrode grid was attached 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. The site of the missing electrode was placed proximal to the VL muscle. A reference electrode was attached at the anterior superior iliac spine. For all subjects, we measured the thickness of the VL muscle and the subcutaneous tissue at the center of the electrode (longitudinal or axial) from ultrasound images detected using a linear array probe with a frequency range of 7.5 MHz (Noblus, Hitachi Aloka Medical, Tokyo, Japan) (Nishikawa et al., 2017). All subjects underwent ultrasound measurement in the sitting position. All procedures were performed by the same investigator, including the ultrasound measurements and electrode placement.
Monopolar multi-channel SEMG signals were amplified by a factor of 1,000, sampled at 2,048 Hz, and converted to a digital form by a 12-bit analog-to-digital converter (EMG-USB2+, OT Bioelettronica). The recorded monopolar signals were off-line band-pass filtered (10–500 Hz) and transferred to analysis software (MATLAB 2016a, Math Works GK, MA, USA). Bipolar multi-channel SEMG signals (n=59) along the columns were obtained from the 64 electrodes. The EMG signals were divided in epochs of 1 s centered at each 10% increment from 20% to 80% of the MVC ramp contraction to calculate the root mean square (RMS). Since the selected ramp rate was 10% of the MVC force per second, one epoch of the sampled signal was overlapped by 0.5 s between neighboring torque levels. We normalized the RMS estimates to the values obtained for the lowest torque level (20% MVC).

Furthermore, we calculated that coefficient of variation (CoV) of force (SD/mean × 100, CoV force) for the same epochs considered for SEMG variables estimations.

To characterize the heterogeneity in the spatial multi-channel SEMG potential distribution at each epoch, we determined the modified entropy, CoV of spatial RMS estimates, and correlation coefficients. The correlation coefficients were computed between the RMS distribution at 20% MVC and the RMS distribution obtained for each force level (i.e., from 30% to 80% MVC in 10% steps). The modified entropy of the spatial distribution
of the EMG amplitude was calculated for 59 RMS values (in space) of single differential
signals computed over a 1 s epoch taken at 20% to 80% of the MVC during the ramp
contraction. According to methods published by Farina et al. (2008) in a previous study,
modified entropy was defined as the entropy of the signal power as follows:

\[ E = -\sum_{i=1}^{59} p(i)^2 \log_2 p(i)^2, \]

where \( p(i) \) is the square of the RMS value of channel \( i \) divided by the sum of the squares of all
59 RMS values at the given contraction time. Therefore, \( p(i)^2 \) represents the normalized
power of each channel. The value is \( E=0 \) when all the \( p(i) \) are zero except one and is maximal
and equal to \( \log_2 59=5.884 \) when the \( p(i) \) values are identical and equal to \( 1/59 \) (all channels
have the same energy). The CoV was defined as the quotient of the standard deviation of the
59 RMS measurements and the average of 59 RMS measurements at each given torque level.
A decrease in the modified entropy and increase in the CoV indicate increased heterogeneity
in the spatial multi-channel SEMG potential distribution within the electrode grid (Watanabe
et al., 2012a).

Correlation coefficients were calculated from the 59 pairs of RMS values at the
same regions between 20% of the MVC and those of all other torque levels to compare the
spatial EMG potential distribution pattern. A decrease in the correlation coefficient indicates
changes in the spatial multi-channel SEMG potential distribution pattern (Watanabe et al., 2012a).

2.4. Statistical analyses

Statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). The continuous data are presented as the mean±standard deviation or the median (min, max). Before the analysis, the normal distribution of data was confirmed using the Shapiro-Wilk test. Age, height, weight, MVC force, the thickness of the VL muscle, and subcutaneous tissue were compared between groups using unpaired t-tests. The RMS value at 20% MVC was compared between groups using the Mann-Whitney U test. CoV force values were compared between groups at each torque level using unpaired t-tests. The RMS normalized by the values at 20% MVC, the modified entropy, CoV of RMS, and correlation coefficients were analyzed using the Friedman test for each group. Differences between torque levels were analyzed using the Steel-Dwass post hoc test, and the Mann-Whitney U test was used at each torque level to compare the values between PD patients and healthy subjects. We used a significance level of $p<0.05$. 
3. Results

The general characteristics of the subjects are presented in Table 1. There were no significant differences between the groups in terms of the anthropometric parameters. The PD patients had a slightly lower MVC force (68.7±24.7 Nm) than the healthy subjects (72.1±28.7 Nm), although the difference was not statistically significant.

All of the subjects were able to perform the ramp up contraction from 10% to 80% MVC. PD patients exhibited significantly greater amplitude than healthy subjects at 20% MVC (Figure 2, \( p<0.001 \)).

Figure 3 shows a representative multi-channel SEMG amplitude color maps in a PD patient and a healthy subject and CoV force during ramp up contraction in Parkinson’s disease patients and healthy subjects. The RMS values of the multi-channel SEMG from 20% to 80% of MVC were normalized to those obtained for the 20% MVC. Differences in the spatial multi-channel SEMG potential distribution patterns at each torque level were observed between the PD patient and healthy subject in these representative data. Furthermore, as compared to healthy subjects, PD patients showed significantly higher CoV of force at 20%, 30%, 40%, and 50% MVC (\( p<0.05 \)).
The normalized RMS increased significantly with increasing torque level in both PD patients and healthy subjects in the VL muscle. Furthermore, healthy subjects showed significantly higher normalized RMS increases than PD patients at 30% to 80% MVC (Figure 4, $p<0.05$).

The modified entropy, CoV and correlation coefficients for both PD patients and healthy subjects exhibited significant changes with increased exerted torque (Figure 5, 6, and 7, $p<0.05$). The modified entropy of RMS at 30% to 80% MVC in healthy subjects was significantly lower than that in PD patients (Figure 5, $p<0.05$). In contrast, the CoV of RMS at 30% to 80% MVC in healthy subjects was significantly higher than that in PD patients (Figure 6, $p<0.05$). At 30% to 80% MVC, the correlation coefficients of healthy subjects were significantly lower than those of PD patients (Figure 7, $p<0.05$).

4. Discussion

The present study compared the spatial multi-channel SEMG distribution pattern between PD patients and healthy subjects. The primary results of the present study are the following: PD patients exhibited (1) higher amplitude at 20% MVC, and (2) smaller changes of normalized RMS, modified entropy, CoV, and correlation coefficients with increasing
torque level. These findings support our hypothesis that PD patients showed lower
distribution changes than healthy subjects during ramp up contraction.

In the present study, PD patients had a slightly lower MVC force than healthy
subjects, although the difference was not statistically significant. Stevens-Lapsley et al., 2012
reported that low PD motor sign (UPDRS motor score<31.7) had a slight reduction in
maximum isometric torque production compared with that of healthy controls, which was not
statistically significant. Moreover, the low PD motor signs group produced greater torque
than the high PD motor signs group (UPDRS motor score>31.7). This previous finding is in
accordance with the results of the present study, which showed that low motor sign PD
patients (UPDRS motor score=7.4±3.1) exhibit similar isometric force production to healthy
controls.

All subjects were able to perform the ramp up contraction task. PD patients
exhibited more force fluctuation in the ramp up contraction task than healthy subjects at 20%,
30%, 40%, and 50% MVC (Figure 3). In present study showed that PD patients exhibited a
significantly less activation of VL muscle compared with healthy subjects, which might
influence the accuracy of PD patients to match the required force level.
In the present study, relatively high absolute values in SEMG amplitude were found in PD patients compared with those in healthy subjects at 20% MVC (Figure 2). A previous study reported that PD patients exhibited more activation of action potentials and inconsistent discharge rates of MUs than did healthy subjects in the 20% MVC task (Glendinning and Enoka, 1994). This previous finding is in accordance with the current results, suggesting that PD patients have different activation patterns from those of healthy subjects during muscle contraction. Therefore, we normalized the RMS estimates to those obtained for the lowest torque level (20% MVC).

We found that PD patients exhibited significant differences in modified entropy, and CoV of RMS during ramp up contraction (Figure 5 and 6). Modified entropy and CoV indicate heterogeneity in the spatial multi-channel SEMG potential distribution within the electrode grid (Watanabe et al., 2012a). Heterogeneity in the spatial EMG potential distribution can be explained by spatial inhomogeneity in the location of the different types of muscle fibers, and a clustering of muscle fibers innervated by one MU in a limited territory.

In general, MUs are newly recruited as the force increases in accordance with the size principle (Henneman et al., 1965). The current results showed that compared with healthy subjects, PD patients exhibit different activation patterns during the ramp up contraction task.
The analysis of correlation coefficients can be used to evaluate changes in spatial SEMG potential distribution patterns. We found that both groups exhibited significant changes with increased exerted torque (Figure 7). Recent studies have quantified the spatial distribution pattern of SEMG to estimate MU recruitment patterns using multi-channel SEMG (Holtermann et al., 2008; Watanabe et al., 2015). The correlation coefficient analysis is used to assess changes in the spatial EMG potential distribution (Farina et al., 2008). Previous studies have reported that the correlation coefficient of multi-channel SEMG decreased with increased performed force during ramp isometric contractions (Holtermann et al., 2005; Watanabe et al., 2012a). These previous findings are in accordance with the results of this study showing a decrease in the correlation coefficient of multi-channel SEMG. Furthermore, we showed that the EMG potential distribution pattern is limited during ramp contraction tasks in PD patients compared with that in healthy subjects.

We found that PD patients showed significantly differences in normalized RMS, modified entropy, CoV, and correlation coefficients of RMS during ramp up contraction. Considering the finding of a spatially complex distribution with increased exerted torque, it is supposed that spatial inhomogeneity in the location of different types of MUs or the number of newly recruited MUs is lower in PD patients. The possible pathology-related changes in
SEMG distribution might be associated with central adaptation (e.g., recruitment strategies) and/or peripheral changes (e.g., changes in the size and location of MU territories or in the distribution of MU types). We speculate that changes in central adaptation might be caused by abnormalities in the descending commands sent to motor neurons in PD patients. These abnormalities might originate in spinal cord neurons receiving input from the basal ganglia. A previous study reported that the reticularis gigantocellularis nucleus, which is receiving input from the substantia nigra pars compacta and is degenerated in PD, plays a role in altering spinal cord neurons (Chronister et al., 1988). Another study showed that reticulospinal pathways originating in the reticularis gigantocellularis nucleus were disinhibited in PD, resulting in abnormal descending influences on spinal cord interneurons (Delwaide et al., 1991). Unbalanced influences on interneurons can change the gain of circuitry that mediates reciprocal activation or alter the tonic state of motor neurons, and thus the ability to maintain constant discharge (Glendinning and Enoka, 1994). Furthermore, a previous study reported that fast-twitch muscle fibers appear to atrophy selectively in PD patients (Edstrom, 1970). Lexell et al., (1988) also reported that healthy elderly people exhibit more type 2 fibers atrophy than type 1 fibers. According to the size principle, MUs are recruited in a fixed order that proceeds from small to large MUs (Henneman et al., 1965). In general, MUs that exert
smaller forces are recruited when a muscle contracts at low forces, whereas larger MUs are recruited as the force increases. Watanabe et al., (2012) reported that compared with healthy young subjects, elderly subjects exhibit smaller multi-channel SEMG amplitude distribution changes with ramp up contraction task. Therefore, force production is considered an important factor to not only the central nervous system but also the peripheral nervous system in PD patients. However, our findings may reflect only a portion of the disease-specific physiological changes in PD. Furthermore, the present study recruited only mild PD patients; therefore, the findings of present study may be useful for the early detection and diagnosis of PD in the future.

The present study has several limitations. First, the present study examined only SEMG. SEMG amplitude estimates are a combination of both peripheral and central MU properties, and they provide only a crude estimate of MU recruitment (Farina et al., 2004). Therefore, we were unable to evaluate MU recruitment properties in detail. A recent study predicted MU recruitment from multi-channel SEMG using convolution kernel compensation (Murphy et al., 2015). Further studies using additional analysis methods are needed to elucidate the detailed mechanisms underlying different activation patterns between PD patients and healthy subjects. Second, our results may be influenced by cross-talk from
adjacent muscles. A previous study reported a moderate-to-large degree of cross-talk from the quadriceps femoris muscle in surface EMG signals (Beck et al., 2010). Thus, surface EMG signals from the quadriceps femoris muscle should be interpreted carefully.

5. Conclusions

We compared spatial multi-channel SEMG potential distribution pattern between PD patients and healthy subjects. The results showed that the heterogeneity and the changes in the activation pattern are smaller in the PD patients than in healthy subjects.

Acknowledgments

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Conflict of Interest
The authors declare no conflict of interest and that no companies or manufacturers will benefit from the results of this study.
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Biography

Yuichi Nishikawa received M.S. degree from Saitama prefectural University in 2012. Since 2012, he is working in Department of Clinical Practice and Support at Hiroshima University Hospital as a physical therapist. Since 2014, he is PhD student in the Graduate School of Biomedical and Health Sciences at Hiroshima University. His current research interests include neurophysiology, pathophysiology, and electromyography in the patients with neuromuscular disorder.

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Table 1. Characteristics of the healthy subjects and PD patients.

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects (n=25)</th>
<th>PD patients (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.3±5.8</td>
<td>66.8±6.8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>154.4±2.4</td>
<td>155.2±2.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>47.2±3.3</td>
<td>45.8±4.9</td>
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<tr>
<td>UPDRS, motor</td>
<td>N/A</td>
<td>7.4±3.1</td>
</tr>
<tr>
<td>Disease duration, year</td>
<td>N/A</td>
<td>7.2±4.1</td>
</tr>
<tr>
<td>Thickness of subcutaneous</td>
<td>5.5±2.5</td>
<td>6.3±2.1</td>
</tr>
<tr>
<td>tissue, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickness of VL muscle, mm</td>
<td>15.2±3.1</td>
<td>14.7±2.4</td>
</tr>
<tr>
<td>MVC, Nm</td>
<td>72.1±28.7</td>
<td>68.7±24.7</td>
</tr>
</tbody>
</table>

The data are presented as the mean±standard deviation.

Abbreviations: PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale; VL, vastus lateralis; MVC, maximum voluntary contraction.
Figure legends

Figure 1. A: The multi-channel electromyography electrode grid was placed on the vastus lateralis (VL) muscle. The center of the electrode grid was attached at the center of the line between the superior lateral edge of the patella and the greater trochanter protuberance. A reference electrode was attached at the anterior superior iliac spine.

B: A representative spatial distribution pattern of the surface electromyography amplitude values shown as a color map. The grid consisted of 13 rows and 5 columns of electrodes (diameter, 1 mm; inter-electrode distance, 8 mm in each direction), with one missing electrode in the upper left corner. The site of the missing electrode was proximal to the VL muscle.

Figure 2. Root mean square of the amplitude of multi-channel surface electromyography at 20% maximum voluntary contraction in Parkinson’s disease patients and healthy subjects. *p<0.05.

Figure 3. Illustration of a color map of the representative multi-channel surface electromyography (SEMG) (upper panel) at each torque level in a Parkinson’s disease patient.
(age 61 years, UPDRS motor score 4) and a healthy subject (age 65 years), and Coefficient of variation (CoV) force during ramp up contraction in Parkinson’s disease patients and healthy subjects (lower panel). The root mean square (RMS) values of multi-channel SEMG estimates were normalized by the values at 20% maximum voluntary contraction (MVC). * $p<0.05$, compared with healthy subjects.

Figure 4. Root mean square normalized by the values at 20% MVC in the amplitude of multi-channel surface electromyography during ramp contractions in Parkinson’s disease patients and healthy subjects. * $p<0.05$.

Figure 5. Modified entropy in the amplitude of multi-channel surface electromyography during ramp contractions in Parkinson’s disease patients and healthy subjects. * $p<0.05$.

Figure 6. Coefficient of variation in the amplitude of multi-channel surface electromyography during ramp contractions in Parkinson’s disease patients and healthy subjects. * $p<0.05$. 
Figure 7. Correlation coefficients of the amplitude of multi-channel surface electromyography during ramp contractions in Parkinson’s disease patients and healthy subjects. * $p<0.05$. 
Figure 1. Nishikawa Y.
Figure 3

Author: Nishikawa Y

Torque level

Modified entropy

PD patients
Healthy subjects

20% 30% 40% 50% 60% 70% 80%
Figure 4

- **Healthy subjects**
- **PD patients**

Correlation coefficient (vs. 20%)

Torque level: 20% to 80%
Modified entropy

Torque level (%MVC)

30% 40% 50% 60% 70% 80%

5.50 5.60 5.70 5.80 5.90

PD patients
Healthy subjects

Figure 5. Nishikawa Y.
Coefficient of variation

Torque level (%MVC)

PD patients
Healthy subjects

30% 40% 50% 60% 70% 80%

0 5 10 15 20 25 30 35

Figure 6. Nishikawa Y.
Correlation coefficient

Torque level (%MVC)

PD patients
Healthy subjects

30% 40% 50% 60% 70% 80%

0.40
0.50
0.60
0.70
0.80
0.90
1.00

* * * * * * *

Figure 7. Nishikawa Y.