TKA Patients with unsatisfying Knee Function Show Changes in Neuromotor Synergy Pattern but not Joint Biomechanics

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This work has been done at RUSH university Medical Center

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Abstract

Nearly 20% of patients who have undergone total knee arthroplasty (TKA) report persistent poor knee function. This study explores the idea that, despite similar knee joint biomechanics, the neuro-motor synergies may be different between high-functional and low-functional TKA patients. We hypothesized that (1) high-functional TKA recruit a more complex neuro-motor synergy pattern compared to low-functional TKA and (2) high-functional TKA patients demonstrate more stride-to-stride variability (flexibility) in their synergies.

Gait and electromyography (EMG) data were collected during level walking for three groups of participants: (i) high-functional TKA patients (n=13); (ii) low-functional TKA patients (n=13) and (iii) non-operative controls (n=18). Synergies were extracted from EMG data using non-negative matrix factorization. Analysis of variance and Spearman correlation analyses were used to investigate between-group differences in gait and neuro-motor synergies.

Results showed that synergy patterns were different among the three groups. Control subjects used 5-6 independent neural commands to execute a gait cycle. High functional TKA patients used 4-5 independent neural commands while low-functional TKA patients relied on only 2-3 independent neural commands to execute a gait cycle. Furthermore, stride-to-stride variability of muscles' response to the neural commands was reduced up to 15% in low-functional TKAs compared to the other two groups.

Keywords: Total knee arthroplasty, Electromyography, Neuro-motor synergy, Gait analysis, Knee function

1. Introduction

Nearly one in five patients who has undergone total knee arthroplasty (TKA) is not satisfied with the outcome [Bourne et al , 2009; Dunbaret al, 2013] due to the persistent poor knee function following surgery [Van Onsem et al, 2016; Noble et al, 2006; Baker et al, 2013]. As the annual volume of primary TKAs performed in the United States is anticipated to exceed 3 million by the year 2030, with hospital costs exceeding 2 billion dollars [Kurtz et al, 2007; Lavernia et al, 2006], the number of dissatisfied patients will rise accordingly. These trends combined with an increase in life expectancy, as well as the desire to maintain a more active lifestyle in patients who are now undergoing TKA at a younger age [Goh et al, 2016; McCalden et al, 2013], warrants further research to identify the underlying reasons of sub-optimal knee function postoperatively.

Currently, the etiology of sub-optimal knee function is largely unknown but since total knee arthroplasty relies on the surrounding soft tissue for mechanical stability, lax ligaments [Aunan et al, 2015; Nakano et al, 2016; Kuster et al, 2004] and/or weak muscles [Stevens-Lapsley et al. 2010; Mizner et al., 2005; LaStayo et al, 2009], have been suggested as possible etiologies. During surgery, ligaments such as the anterior-cruciate ligament (ACL) or posterior-cruciate ligament (PCL) are resected while the medial and lateral collateral ligaments (MCL and LCL) are manipulated to balance the knee joint. Muscle integrity is disturbed due to surgical cuts and the utilization of instruments such as a tourniquet which leads to acute peri-articular muscle weakness. While the joint's mechanical environment is clearly disturbed after TKA, this may not be the only reason for sub-optimal knee function, and even patients with appropriate ligament balance and muscle strength can present with poor knee function. Oftentimes, the function deficit

still persists after adequate rehabilitation and muscle strengthening programs [Bily et al., 2016; Moffet et al., 2004].

One idea that has been scarcely explored is that of neuro-motor deficits, since neuro-mechanical receptors are sacrificed (due to the loss of the ACL and sometimes PCL). This loss and injury to the joint capsule cause a disruption of typical neural pathways between the central nervous system (CNS) and lower extremity muscles. Absence of sub-task specific afferent pathways likely increases the reliance of the CNS on the remaining non-specific pathways leading to changes in the neuro-motor synergies; i.e., the neural commands of the CNS to recruit muscles and the muscle responses to these neural commands. The new neuro-motor synergy may lead to undesirable co-contraction of antagonistic muscles, and poor kinematic control of the joint. Such impaired motor control patterns may not immediately manifest themselves as abnormal biomechanics due to muscle redundancy, but will change the knee joint's ability to react to perturbations during activities of daily living.

We hypothesized that (1) high-functional TKA patients recruit a more complex neuro-motor synergy pattern compared to low-functional TKA and (2) high-functional TKA patients demonstrate more stride-to-stride variability (flexibility) in their synergies.

2. Subjects and Methods

2.1. Subjects

Patients with a history of primary, unilateral TKA who participated in a previous motion analysis study [Ngai et al, 2009] and agreed to be included in the Institutional Review Board (IRB)-approved data repository of the Rush Motion Analysis laboratory were reviewed. Only patients with available gait data, electromyography (EMG) measurements and knee functional

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questionnaires were considered for inclusion in the study. Inclusion criteria were restricted to TKA patients implanted with a cruciate retaining design (MG II and NexGen, Zimmer Inc., Warsaw, IN), and patients who performed the gait test at a minimum twelve months after their TKA. In addition, the following exclusion criteria were listed: (1) any other lower extremity joint replacements, (2) pain at the day of the test, (3) insufficient range of motion as defined by a maximum knee flexion angle < 110 deg. and/or a flexion contracture > 10 deg., (4) a significant valgus-varus or anterior-posterior laxity as determined during physical examination, (5) an incomplete questionnaire, and (6) incomplete or corrupted EMG data.

Thirty TKA patients in the database fulfilled the inclusion criteria. Four patients were excluded (two subjects due to incomplete questionnaires and two due to a missing EMG channel) leaving 26 for analysis. For every TKA patient a total knee joint functional questionnaire (originally designed by Weiss et al. (2002) which is now part of the Knee Society Score [Noble et al, 2012]) was available. This included the clinical symptoms and function of the knee joint. The knee functional score (KFS), which ranges from 0 to 10, was calculated for each patient. TKA patients were then split in half forming two groups with a higher and a lower KFS score: Thirteen patients had KFS > 5.5 and were classified as the high-functional TKA group (8F/5M; age: 62.0 ± 5.1(year); BMI: 30.9 ± 8.7 (kg/m^2), weight: 89.4 ± 15.2 (kg)). The remaining 13 TKA subjects with KFS < 5.5 were classified as the low-functional TKA group (8F/5M; age: 61.1 ± 8.4 (year); BMI: 29.8 ± 5.4 (kg/m^2), weight: 88.8 ± 16.5 (kg)). KFS equal to 5.5 was chosen as the midpoint of KFS scale (0 to 10) and also based on our previous study demonstrating that 90% of patients with KFS >5.5 have stable knees which is an important factor in knee joint functionality [Ardestani et al, 2017]. To form a control group, we selected gait and EMG data from a database of unimpaired subjects who had no habitual pain and no history of fracture or surgery in the

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lower limbs, and whose age was within two standard deviations of the mean age of the TKA group. The control group consisted of 18 unimpaired subjects (10F/8M; age: 54.6±6.3 (year), BMI=25.8±7.6 (kg/m^2), weight: 70.1±17.3 (kg)), with a comparable distribution of males and females.

2.2. Gait and EMG Analysis

Details of the gait data collection and gait analyses can be found in the study by Ngai et al (2009). In brief, participants were gait tested with reflective markers mounted on their thigh and shank using the point cluster technique (PCT) [Andriacchi et al, 1998]. Marker trajectories were tracked using a four-camera optoelectronic system at the rate of 120 frames/sec (Qualisys, Gothenburg, Sweden). Ground reaction forces (GRFs) were also recorded using a multi-component force plate (Bertec, Columbus, OH). Three successful trials, in which the operated limb of TKA patients (and the dominant limb of healthy controls) was properly placed on the force plate, were collected at the participant's self-selected normal speed. 3D external moments and intersegmental forces were calculated from 3D GRF data and marker trajectories using inverse dynamics (CFTC, Chicago, USA) [Andriacchi et al, 1985]. Simultaneous to marker trajectory and GRF data collection, surface electromyography (sEMG) signals were collected at a sampling rate of 1200 Hz, using a TeleMyo transmitter and receiver (Noraxon USA Inc, Scottsdale, AZ). EMG signals were collected from six lower limb muscles including vastus medialis (VM), rectus femoris (RF), vastus lateralis (VL), biceps femoris (BF), semimembranosus/semitendinosus (SS) and medial gastrocnemius (MG). Details of EMG data collection have been presented in [Lundberg et al, 2016]. After data collection, sEMG signals were further processed in the Noraxon software as follows: the vertical ground reaction force component with a threshold of 20 (N) and the vertical heel marker trajectory waveforms were

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used to detect consecutive heel strikes on EMG recordings. EMG recordings were marked and segmented per the corresponding vertical heel marker trajectory of the subject such that at least five full gait cycles were extracted from the EMG recordings of each participant. The sEMG signals were then band-pass filtered with a finite impulse response filter (Lancosh type 79-point window filtering, band-pass range from 20 to 450 Hz), rectified, and smoothed using root mean square calculations over a 50-ms window. Knowledge of EMG waveform characteristics was used to visually inspect all the extracted gait cycles. Movement artifacts, low signal-to-noise ratio or a missing EMG channel led to rejection of some of these extracted gait cycles for some of the participants. Subsequently, EMG data corresponding to five gait cycles were considered for each participant. Muscle activities were amplitude-normalized to the corresponding average of their peak values across all the five gait cycles. All gait data and EMG signals were temporally normalized to 100 samples per gait cycle (from heel strike (0%) to the following heel strike of the same leg (100%)) using spline technique (MATLAB R2012a, The Mathworks, Inc, Natick, MA). The magnitudes of joint moments were further normalized to body weight and height (%BW×HT).

2.3. Muscle Synergy Analysis

Using Non-negative Matrix factorization (NNMF), a mathematical algorithm in multivariate analysis, muscle synergies were extracted from normalized EMG envelops [Ting et al, 2010]. All the recorded EMG signals were organized in a matrix and imported into the NNMF algorithm to be factorized in two matrices, namely the underlying neural command (C) and the response of muscles to the neural commands (W). The quality of this factorization was then evaluated if the product of neural commands and muscle responses (W×C) would reconstruct the experimental EMG signals such that $EMG_{(experimental)} \approx W \times C$. For each gait cycle, the NNMF

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factorization was repeated six times, each time with a different number of neural commands ranging from one (i.e., assuming that all muscles were activated simultaneously through a single neural command) to six, the maximum number of muscles available for study. Once the number of neural commands was assumed for each factorization process, the corresponding muscle response (W) was calculated in an optimization routine such that the error between the reconstructed EMG signals (W×C) and the experimentally measured EMG data was minimized. Since five gait cycles were extracted per subject and NNMF was iterated six times for each gait cycle, a total of 30 separate pairs of W and C were generated for each participant. The Intra-class Correlation Coefficient (ICC) amongst the W matrices was calculated for each participant and the average of those W matrices with ICC>0.7 was chosen to represent the participant's most representative neuromuscular strategy during level walking [Chvatal et al, 2012].

Neuro-motor strategies (W and C) were then compared between the high and low functional patient groups as well as the control group: (1) Complexity of neuro-motor strategies was defined as the smallest number of independently-timed neural commands (C) necessary to reconstruct the experimental EMG signals with at least 90% accuracy; (2) The extent to which muscles were activated in response to a neural command was obtained from the magnitude of matrix W; (3) stride-to-stride variability of the neuro-motor strategies was obtained by studying stride-to-stride differences in muscle responses as obtained from matrix W.

2.4. Statistical analysis

Statistical analyses included one-way analysis of variance (ANOVA) and Spearman correlation analysis. ANOVA and Spearman correlation analyses were performed using Statistical Package for the Social Sciences (SPSS), version 22 (IBM, Chicago, IL). One-way ANOVA was used to compare age, weight, BMI, KFS, the number of neural commands, the

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extent of muscles' response to the neural commands and the level of stride-to-stride variability among the groups. Spearman correlation analysis was used to determine whether the neural commands, associated with various sub-phases of gait cycle, were interdependent. Normality of the data was checked with the Shapiro-Wilk test. Homogeneity of variances was verified using Levene's test. The significance level was chosen as $p = 0.05$.

3. Results:

Comparing the high-functional TKA group versus the low-functional TKA group, there were no age (p=1.00, CI=[-6.45 to 7.50]), weight (p=1.00, CI=[-21.14 to 22.02]) or BMI (p=1.00, CI=[-6.79 to 8.94]) differences between these two groups (Table 1). Comparing the low-functional TKA group versus control group, they tended to be older (p=0.06 CI=[-13.03 to 0.14]), and heavier (p=0.08, CI=[-39.15 to 1.62]). This trend became significant for the high-functional TKA patients regarding age (p=0.02, CI=[0.70 to13.24]) and weight (p=0.05, CI=[-0.20 to 38.62]). BMI was not different between high- and low-functional TKA groups (p= 1.00, CI=[-6.79 to 8.94]), between control and high-functional TKA group (p=0.25, CI=[-2.05 to 12.15]) or between control and low-functional TKA group (p=0.54, CI=[-11.27 to 3.31] . Per design, the high-functional TKA group had higher KFS scores ranging from 5.7 to 8.4 compared with the low-functional counterpart, which ranged from 3.4 to 5.2. All three groups (2 TKA and control) were comparable in terms of knee biomechanics. More specifically, there were no significant differences in the sagittal knee joint kinematics and three-dimensional knee joint moments between low- and high-functional TKA patients. Since knee joint biomechanics is not the main focus of this study, detailed comparisons and descriptions are presented in the Appendix.

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3.1. Number of neural commands

Low-functional TKA group used fewer numbers of neural commands to execute a gait cycle compared with the other two groups. Decoupling the EMG signals resulted in 5-6 neural commands for the control group, 4-5 neural commands for the high-functional TKA group, and only 2-3 neural commands for the low-functional TKA group (Figure 1). To facilitate between-group comparison, EMG signals were decoupled to 4 neural commands for all individuals. The resultant 4 neural commands (C1-C4) were mostly independent in non-operative controls (Table 2) and high functional TKA group, as determined using Spearman's correlation. Most inter-dependencies, however, were found in the low-functional TKA group. Independent neural commands facilitated independent execution of major sub-phases of gait in non-operative controls (Figure 2.a) and high-functional TKA patients (Figure 2.b): Neural command 'C1' activated the extensor muscles (vastus medialis and vastus lateralis) at early stance, 'C2' activated the medial gastrocnemius at mid-stance; 'C3' activated the rectus femoris at terminal stance; and 'C4' activated the hamstrings from terminal swing through early stance. Interestingly, in low functional TKA patients, early and terminal stance phase neural commands (C1 and C2) were inter-dependent causing simultaneous activation of the vastus medialis, vastus lateralis and rectus femoris (Figure 2.c). Furthermore, mid-stance and early swing neural commands (C3 and C4) were inter-dependent in the low-functional TKA cohort causing simultaneous activation of the medial gastrocnemius and rectus femoris.

3.2. Muscle response to the neural commands

The levels of muscle response to the neural commands were slightly different among the groups. Two distinct patterns of muscle response were observed in high- and low-functional

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TKA patients (Figure 3) in response to the neural command 'C1' (Table 3), command 'C2' (Table 4), command 'C3' (Table 5) and command 'C4' (Table 6): In high-functional TKA patients, semimembranosus/semitendinosus muscles' response to 'C1', hamstring and quadriceps muscles' response to 'C2', biceps femoris and medial gastrocnemius muscle response to 'C3', and quadriceps muscle response to 'C4' were reduced compared with control subjects. Contrary, vastus lateralis muscle response to 'C1', medial gastrocnemius muscle response to 'C2' and rectus femoris muscle response to 'C3' was increased. Low functional TKA patients demonstrated a different pattern of muscle response to the neural commands. In low-functional TKA patients, the biceps femoris and semimembranosus/semitendinosus muscles' response to 'C1', biceps femoris muscle response to 'C2', and vastus lateralis muscle response to 'C4' were reduced compared with control subjects.

3.3. Stride-to-stride variability in muscle response

Except for the medialis gastrocnemius, the largest stride-to-stride variability was found in high-functional TKA patients when compared with the low functional TKA and normal control groups (Figure 4). Compared to the low-functional TKA group, in high-functional TKA group, the stride-to-stride variability of vastus medialis, vastus lateralis, biceps femoris and semimembranosus/semitendinosus responses to the corresponding neural commands were increased by up to 30%, 40%, 20% and 25% respectively. However these differences did not reach statistical significance. In high-functional TKA group, the stride-to-stride variability of medial gastrocnemius response to the neural commands was decreased by up to 50% compared to the control group (p=0.00, CI=[-0.24 to -0.05]) and by up to 45% compared to the low-functional TKA group (p=0.02, CI=[-0.21 to -0.01]) (Table 7) .

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4. Discussion

Twenty percent of TKA patients complain about persistent poor knee function following surgery. The etiology is largely unknown. Although lax ligaments and/or weak muscles, have been suggested as possible reasons but recent studies demonstrated that patients with appropriate ligament balance and sufficient muscle strength may also experience sub-optimal knee function. Therefore, we investigated whether the neuro-motor synergies (i.e., the number of neural commands and the muscles' response to the neural commands) were different between low-and high-functional TKA patients and compared to the non-operative controls. The investigation brought the following to light: (1) despite similar knee joint kinematics and kinetics, low-functional subjects rely on fewer independent (task-specific) neural commands to execute gait; (2) the extent to which muscles responded to the neural commands was different between high and low-functional TKA; (3) high-functional TKA patients demonstrate more variability in their muscle response to the neural commands compared with the low functional TKA and normal control groups.

In knee joint arthroplasty, the sacrifice of ligaments (and thus neuro-mechanical receptors), likely reduces the number of sub-task specific pathways between the central nervous system and muscles leaving fewer possible neural commands to activate various groups of muscles independently. Increased reliance on inter-dependent neural commands, observed in low-functional TKA, may cause interference between weight acceptance of the index leg and weight transition to the contralateral limb and/or between weight transition at terminal stance and toe clearance at early swing which may explain the higher prevalence of instability complaints in low functional TKA patients compared to the high-functional TKA group.

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In addition, the sacrifice of ligaments not only reduces the task-specific pathways but may also affect the combination of the rhythmic, voluntary and reactive neural commands. Human gait is executed as a result of parallel neural commands from different sources. The basic rhythm of walking is driven by the neural commands from the spinal cord [Rossignol et al, 2008]. Voluntary changes in the gait are driven by the neural commands from the cortical pathway [Drew et al, 2008] while reactive response to unexpected perturbation is driven by the neural command from the brainstem [Macpherson et al, 1999]. Highly constrained neuro-motor synergies, observed in low-functional TKA group, may imply absence or lack of reactive neural commands to adjust for subtle unexpected perturbations which typically arise during walking (e.g., change in the ground stiffness, height or etc). Less stride-to-stride variability equates to less variation in the distribution of load within the joint. This could lead to areas which are consistently under- and over-loaded. Highly constrained neuro-motor synergies may explain the higher prevalence of implant failure reported in low functional TKAs.

The traditional belief is that EMG signals are the main agent where abnormalities or deficiencies are reflected and therefore previous studies typically focused on muscle activation or co-activation between agonistic and antagonistic muscles [Wilquin et al, 2015; Davidson et al, 2013]. However, EMG signals are the product of neural commands administrated by the CNS. Considering that our body has a redundant number of muscles to execute a movement [Aoi et al, 2016; Valero-Cuevas et al, 2015], and muscles are apt to compensate for each other, thus masking abnormal activities in other muscles [Ardestani et al, 2016; Thompson et al, 2013; Goldberg et al, 2007], we believe that impaired neuro-motor synergies, caused by either surgery or osteoarthritis disease, may not immediately manifest themselves as abnormal EMG patterns. Hence, studying the structure of neural commands generated by the CNS and sets of muscles that

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are activated synchronously in response to these neural commands are necessary to reveal factors contributing to sub-optimal knee joint function. If impaired neural strategies of the CNS are proven to play a role in sub-optimal knee function, rehabilitation processes may attempt to re-educate the afferent pathways between the CNS and muscles.

This study had several limitations. First, this was a retrospective study conducted based on a previously-collected EMG data at a single time point. This study cannot provide answers whether abnormal neuro-motor synergies are formed preoperatively (i.e. during the course of osteoarthritic disease) or as a consequence of the surgical intervention. As it is known that the vibratory perception threshold at the metatarsophalangeal joint is associated the Kellgren/Lawrence severity of osteoarthritis disease at the knee joint [Shakoor et al, 2012], it is very likely that the osteoarthritis disease process harm pathways that could transmit neural commands.

Second, our study population was fairly small (13 TKA patients in each group) and all TKA patients wore cruciate-retaining implants from a single manufacturer. Future studies should enroll a larger population of TKA patients, and compare the neuro-motor synergies among TKA patients with different knee designs. Third, the study was limited to six available muscles with EMG data. The number and the choice of muscles impact the results of non-negative matrix factorization, although the number of calculated independent command signals for the healthy control population was similar to what has been reported in the literature [Clark et al, 2012]. Nevertheless, future EMG studies should include additional lower extremity muscles (e.g. gluteus maximus, gluteus medius, and tibialis anterior muscles) to obtain a more complete picture.

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Conclusion:

In summary, neuro-motor synergy may play an important role in knee function and rehabilitation after TKA. In particular, the number of neural commands and the stride-to-stride variability of muscles' responses to these neural commands seemed to be reduced in low-functional patients. Future clinical studies may look into possibilities whether this course can be reversed through appropriate training programs.

Conflict of interest

None to be declared

<u>Appendix</u>

Spatial parameter mapping (SPM), was conducted using SPM software package (MATLAB 2012b) SPM test, a recently-developed statistical test facilitating waveform comparisons [Pataky et al, 2013]. Low-functional TKA group tend to had lower maximum knee flexion during stance and swing phases accompanied with a lower magnitude of knee flexion moment, knee adduction moment and lower knee internal rotation moment at early stance (Figure A.1). Despite, none of these subtle differences reached the statistical significance as t continuum remains below the significance threshold (Figure A.2). High-functional TKA group demonstrated more similarity to

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the control group except a trend of higher knee adduction moment and higher knee external rotation moment during mid-stance. Nevertheless these differences did not reach the statistical significance (Figure A.2).

A   B

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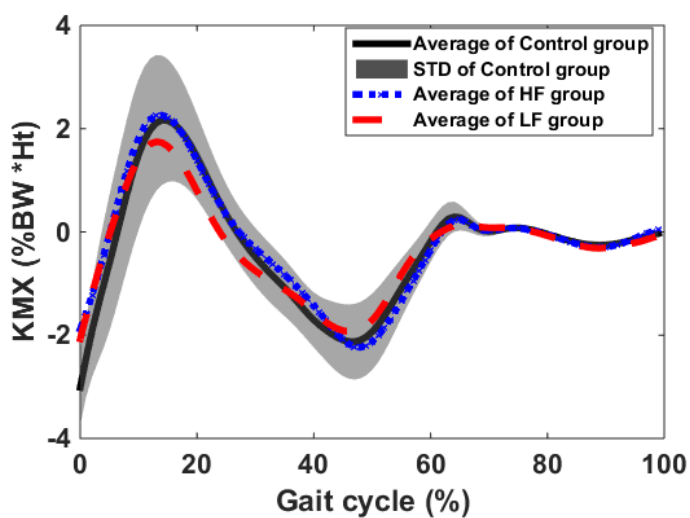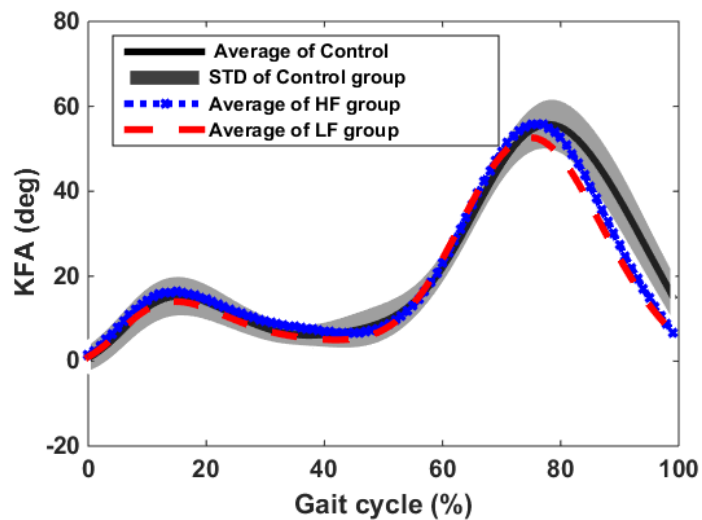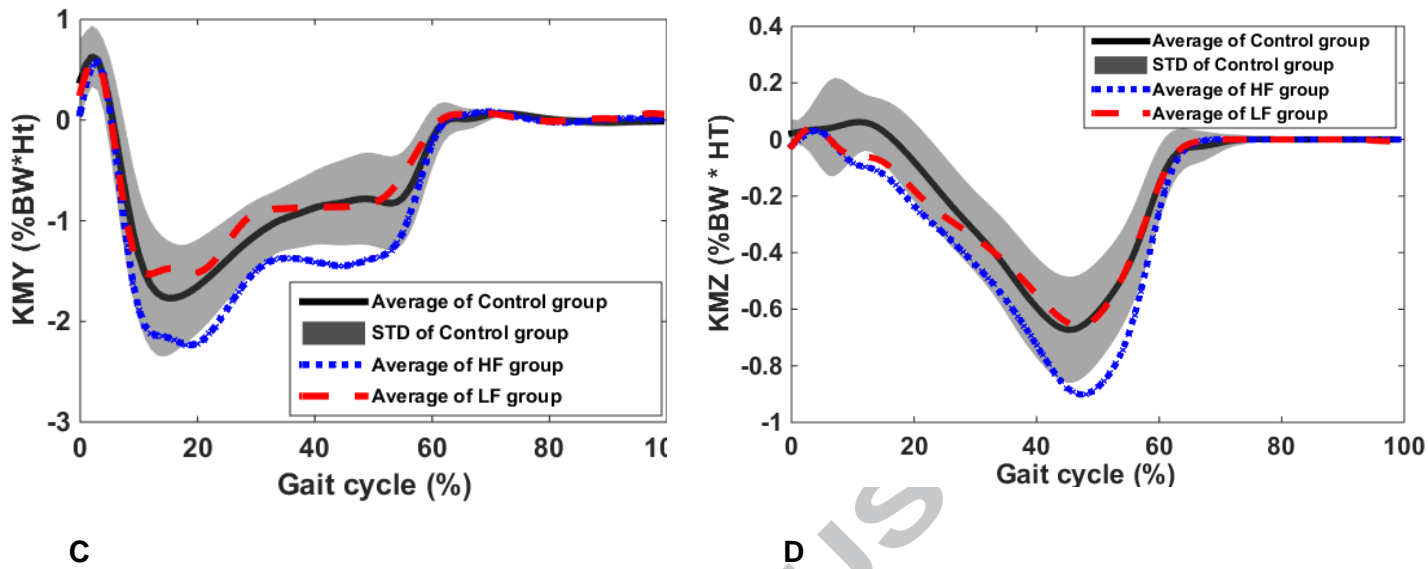
Figure A.1 Comparison of knee joint biomechanics including (A) knee flexion angle (KFA), (B) knee flexion/extension moment (KMX), (C) knee abduction/adduction moment (KMY), and (D) knee internal/external rotation moment(KMZ)

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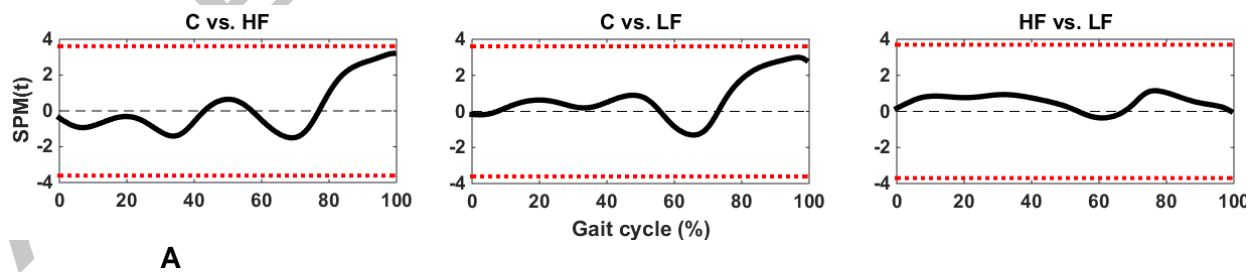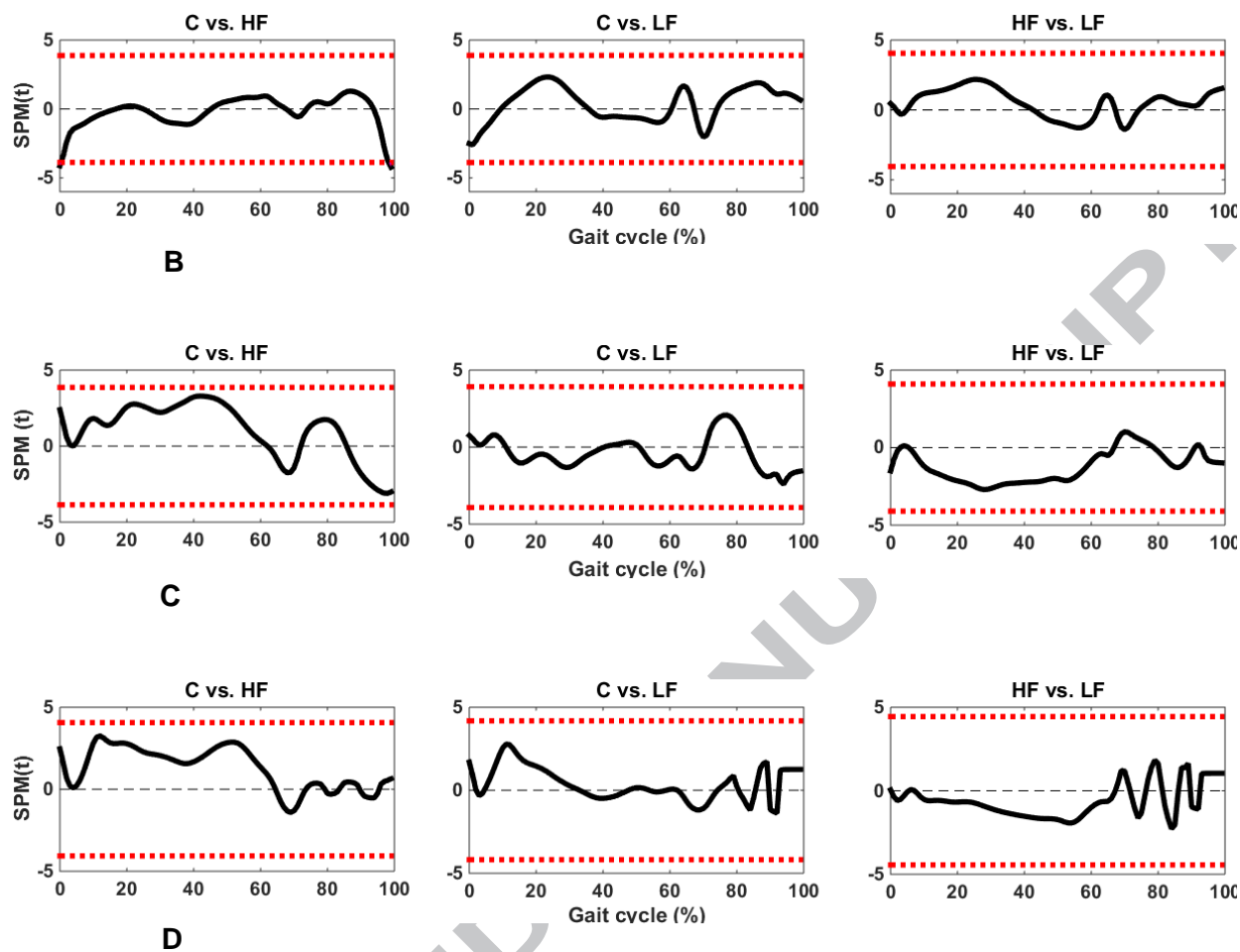
Figure A.2. SPM (t), i.e. t-statistic values over the entire gait cycle. Dashed red lines represent the critical t-statistic value. No significant differences were found in terms of (A) knee flexion/extension angle; (B) knee flexion/extension moment ; (C) knee abduction/adduction moment and (D) knee internal/external; rotation moment. HF= high-functional TKA subjects; LF = low-functional TKA subjects, C= healthy control subjects

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Figure Legends

Figure 1 Percentage of variance of EMG signals, explained by neural commands (i.e., the accuracy of the reconstructed EMG), was increased with the number of neural commands. Note that more neural commands were required to reconstruct the EMG signals of high-functional TKA and control subjects compared to low-functional TKA group. One neural command could explain approximately 70% of the variance of EMG signals in low-functional TKA group whilst one neural command could explain only 20-40% of the variance of EMG signals in high-functional TKA and control groups.

Figure 2. Four neural commands (C1 to C4) calculated from the EMG signals for a representative subject of (A) control, (B) high-functional TKA and (C) low-functional TKA. The X axis represents the percentage of gait cycle (0% for heel strike and 100% for the following heel strike of the same leg). The Y axis represent the amplitude of the neural command. Please note that neural commands were calculated based on EMG signals with the normalized magnitude between 0 to 1.

Figure 3 Muscle responses to (A) the neural command C1 at early stance, (B) the neural command C2 at mid-stance, (C) the neural command C3 at early swing, and (D) the neural command C4 at terminal stance. The black bars represent the average of muscle activations in each group. The narrow stems represent subject-by-subject muscle activations.

Figure 4 Stride-to-stride variability for high-functional TKA (HF group) and low-functional TKA (LF group) versus nonoperative controls.

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A

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High-functional TKA

B

Low-Functional TKA

C

Control   High functional TKA   Low functional TKA

A

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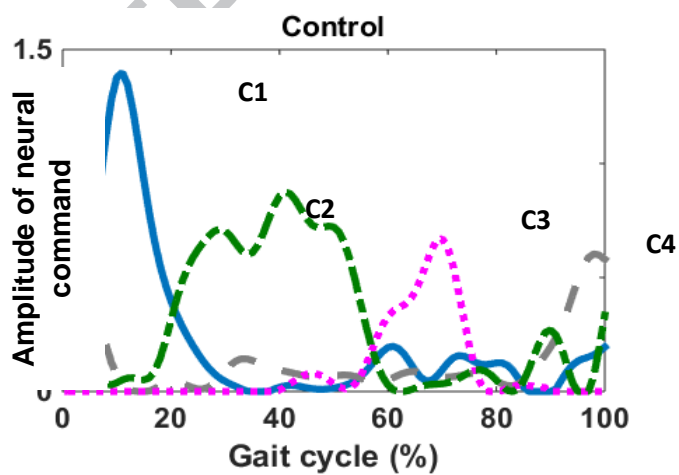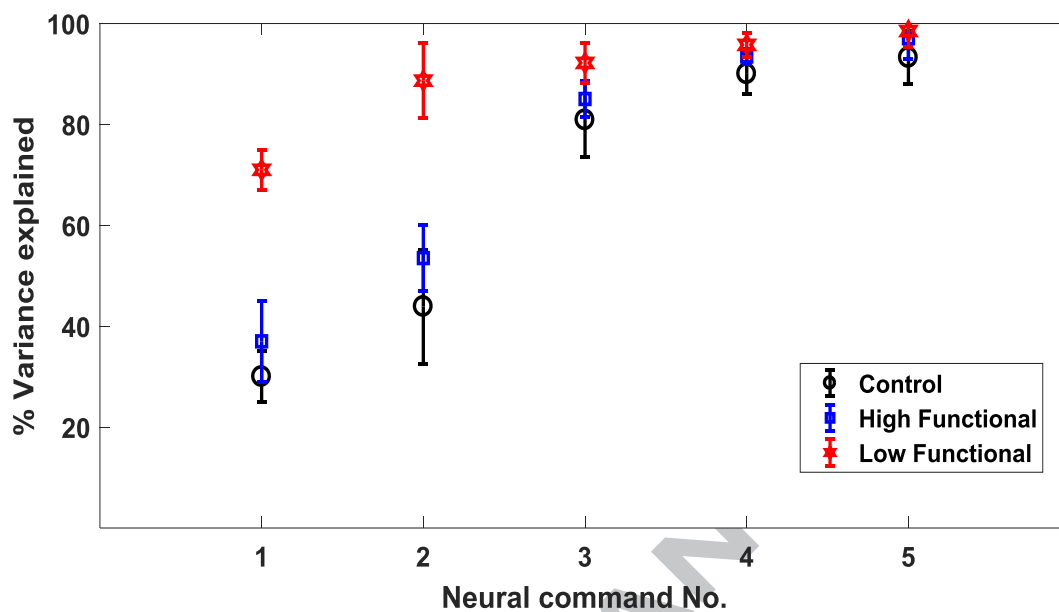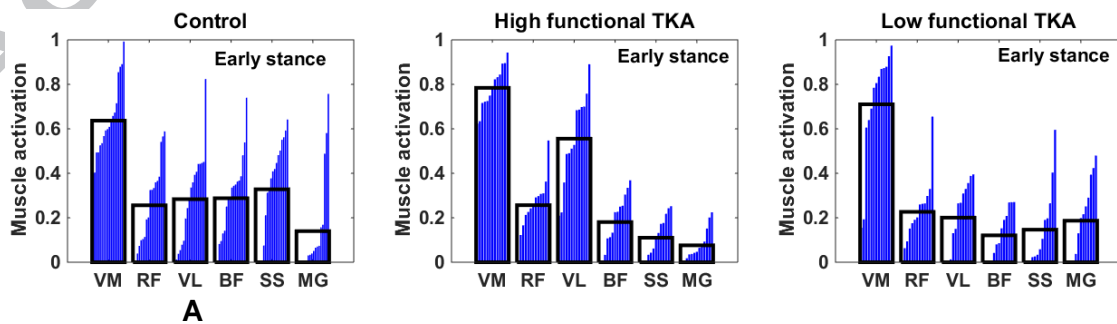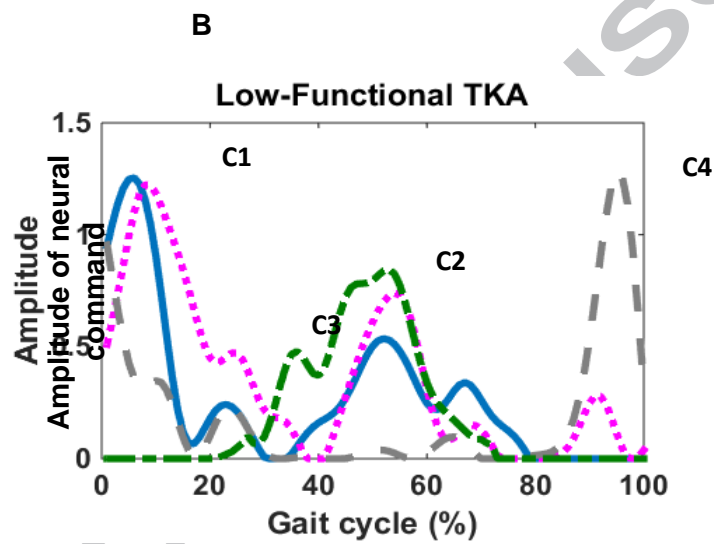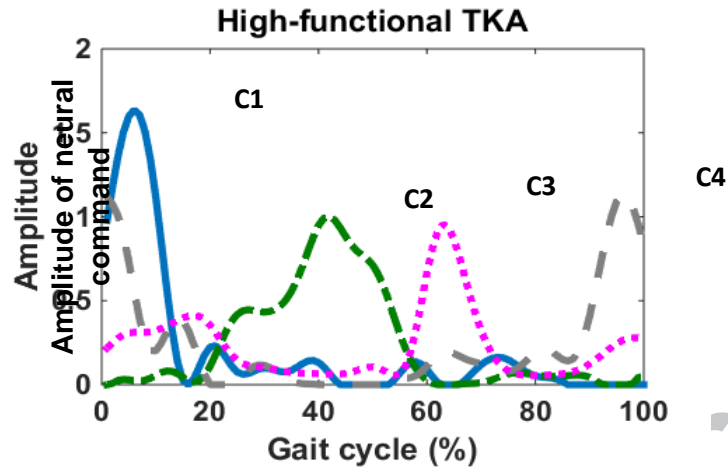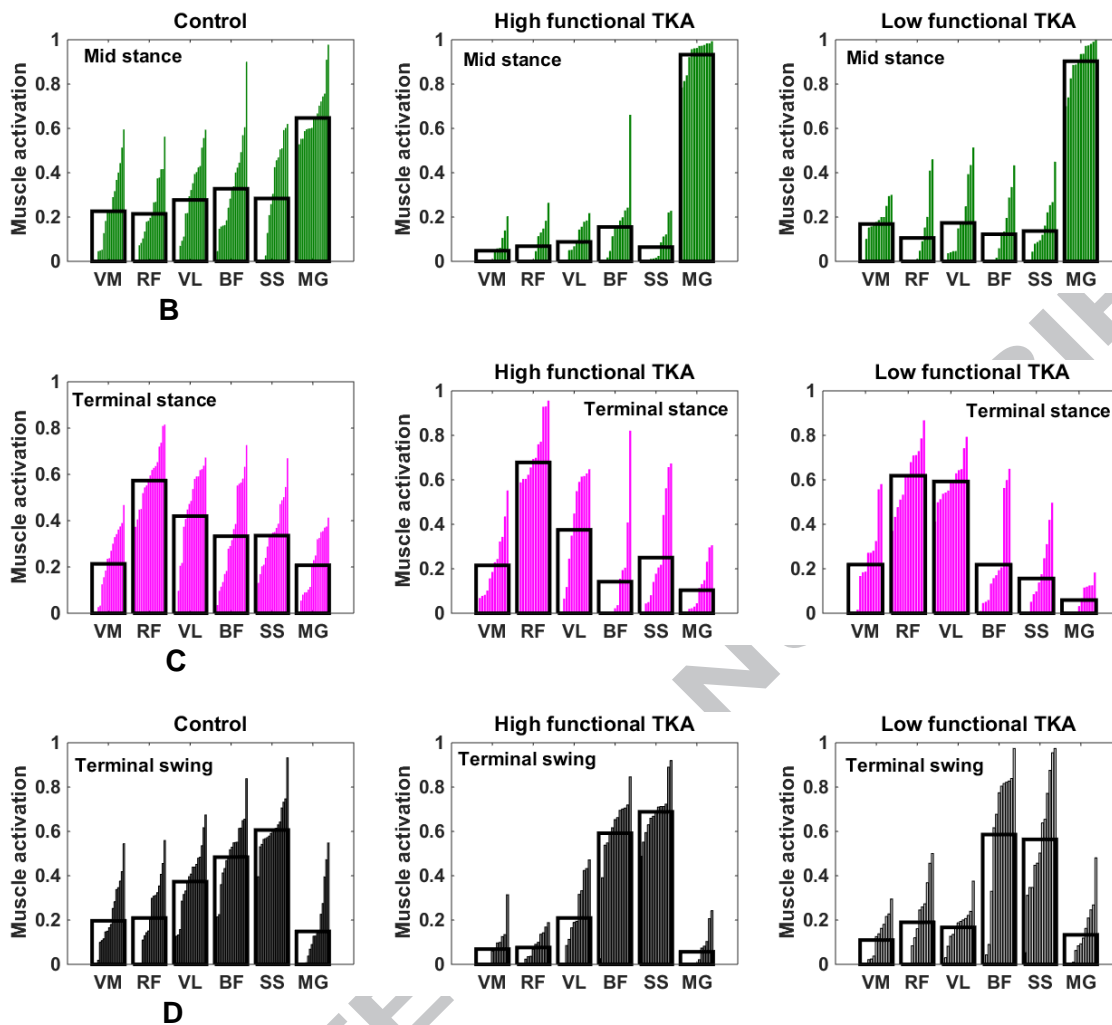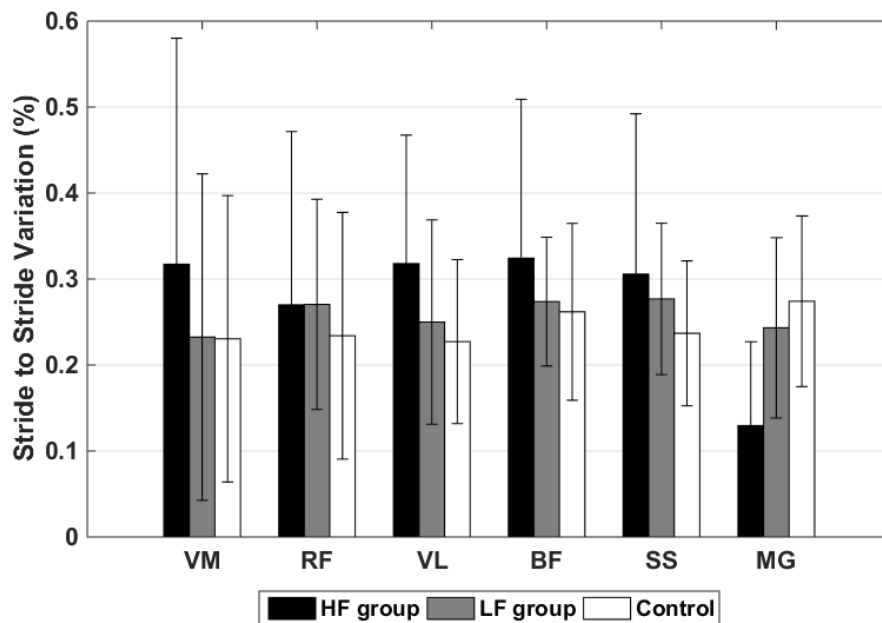
Table 1- Demographic data and time in situ for the groups of subjects in this study.

	Dependent Variable		Mean Difference (I-J)	Std. Error	p	95% Confidence Interval	
						Lower Bound	Upper Bound
Age (year)	High functional TKA	Low functional TKA	0.52	2.78	1.00	-6.45	7.50
	High functional TKA	Control	6.96	2.50	0.02	0.70	13.24
	Control	Low functional TKA	-6.44	2.63	0.06	-13.03	0.14
Weight (kg)	High functional TKA	Low functional TKA	0.44	8.62	1.00	-21.14	22.02
	High functional TKA	Control	19.21	7.75	0.05	-0.20	38.62
	Control	Low functional TKA	-18.76	8.14	0.08	-39.15	1.62
BMI (kg/m^2)	High functional TKA	Low functional TKA	1.07	3.14	1.00	-6.79	8.94
	High functional TKA	Control	5.05	2.83	0.25	-2.05	12.15
	Control	Low functional TKA	-3.98	2.91	0.54	-11.27	3.31

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Group

Table 3 Between-group comparison of muscle response (W) at early stance phase of gait corresponding to the neural command C1

Muscle	Group I	Group j	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
	HF*	LF**	.07	.07	.96	-.11	.25
Vastus Medialis	HF	C***	.14	.06	.11	-.02	.31
	LF	C	.07	.06	.87	-.09	.24
	HF	LF	.02	.06	1.0	-.13	.19
Rectus Femoris	HF	C	.00	.06	1.0	-.15	.15
	LF	C	-.02	.06	1.0	-.18	.12
	HF	LF	.35	.07	.00	.16	.54
Vastus Lateralis	HF	C	.27	.07	.00	.09	.45
	LF	C	-.08	.07	.75	-.26	.09
	HF	LF	.05	.05	.97	-.09	.20
Biceps Femoris	HF	C	-.10	.05	.18	-.24	.03

Low-functional TKA					
	C1	1.00(0.00)			
	C2	0.11 (0.35)	1.0(0.00)		
	C3	-.44(0.00)	-.39(0.00)	1.0(0.00)	
	C4	-.27(0.03)	-.28(0.01)	.10 (0.51)	1.0(0.00)

Table 2. Inter-dependency among neural commands for control group, high functional TKA and low-functional TKA groups. Highlighted data demonstrate significant interdependency between the two neural commands. Please note that the Spearman's rho values in this table are the average of the corresponding Spearman rho values of all the subjects in each group.

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Muscle							
	LF	C	-.16	.05	.01	-.30	-.02
semimembranosus/semitendinosus	HF	LF	-.03	.07	1.0	-.21	.14
	HF	C	-.21	.06	.00	-.38	-.05
	LF	C	-.18	.06	.02	-.34	-.01
Medial Gastrocnemius	HF	LF	-.11	.06	.36	-.28	.06
	HF	C	-.06	.06	.99	-.22	.09
	LF	C	.04	.06	1.0	-.11	.20

*HF: High-functional TKA group

**LF: Low-functional TKA group

***C: Nonoperative control group

Table 4 Between-group comparison of muscle response (W) at midstance phase of gait corresponding to the neural command C2

Muscle	Group I	Group J	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
Vastus Medialis	HF	LF	-.12	.05	.084	-.25	.011
	HF	C	-.17	.04	.002	-.30	-.055
	LF	C	-.05	.04	.739	-.18	.064
Rectus Femoris	HF	LF	-.03	.05	1.000	-.17	.104
	HF	C	-.14	.05	.026	-.27	-.014
	LF	C	-.10	.05	.138	-.24	.023
Vastus Lateralis	HF	LF	-.08	.06	.569	-.24	.07
	HF	C	-.18	.05	.008	-.33	-.040
	LF	C	-.10	.05	.268	-.25	.04
Biceps Femoris	HF	LF	.032	.07	1.000	-.15	.21
	HF	C	-.17	.069	.051	-.34	.00
	LF	C	-.20	.069	.015	-.378	-.0319
Semimembranosus /semitendinosus	HF	LF	-.072	.069	.905	-.24	.100
	HF	C	-.219	.064	.004	-.38	-.058
	LF	C	-.14	.06	.084	-.307	.013
Medial Gastrocnemius	HF	LF	.029	.0466	1.000	-.086	.145
	HF	C	.285	.0433	.000	.177	.393
	LF	C	.256	.043	.000	.147	.364

*HF: High-functional TKA group

**LF: Low-functional TKA group

***C: Nonoperative control group

Table 5 Between-group comparison of muscle response (W) at terminal stance-early swing phase of gait corresponding to the neural command C3

Muscle	(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
Vastus Medialis	HF	LF	-.00	.066	1.0	-.168	.161

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Muscle	(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.	Lower Bound	Upper Bound
	HF	C	.00	.061	1.0	-.151	.155
	LF	C	.00	.061	1.0	-.147	.158
Rectus Femoris	HF	LF	.059	.071	1.0	-.118	.237
	HF	C	.104	.066	.36	-.060	.270
	LF	C	.045	.066	1.0	-.119	.210
Vastus Lateralis	HF	LF	-.217	.081	.03	-.420	-.0142
	HF	C	-.044	.075	1.0	-.233	.143
	LF	C	.172	.075	.08	-.0159	.361
Biceps Femoris	HF	LF	-.076	.090	1.0	-.302	.149
	HF	C	-.190	.083	.08	-.400	.018
	LF	C	-.114	.083	.54	-.323	.095
Semimembranosus /semitendinosus	HF	LF	.093	.075	.66	-.0949	.282
	HF	C	-.085	.070	.69	-.260	.090
	LF	C	-.179	.070	.044	-.354	-.003
Medial Gastrocnemius	HF	LF	.044	.045	1.0	-.0685	.156
	HF	C	-.10	.041	.05	-.208	.000
	LF	C	-.14	.041	.003	-.2524	-.0433

*HF: High-functional TKA group

**LF: Low-functional TKA group

***C: Nonoperative control group

Table 6 Between-group comparison of muscle response (W) at terminal swing of gait corresponding to the neural command C4

Muscle	(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
Vastus Medialis	HF	LF	-.040	.0495	1.000	-.164	.0827
	HF	C	-.127	.04599	.025	-.242	-.0130
	LF	C	-.086	.0459	.198	-.201	.027
Rectus Femoris	HF	LF	-.113	.0597	.191	-.263	.035
	HF	C	-.133	.055	.062	-.271	.005
	LF	C	-.019	.0554	1.000	-.157	.119
Vastus Lateralis	HF	LF	.0422	.05958	1.000	-.1062	.191
	HF	C	-.163	.05529	.015	-.30172	-.025
	LF	C	-.2062*	.0552	.002	-.3442	-.068
Biceps Femoris	HF	LF	.0062	.09672	1.000	-.23514	.247
	HF	C	.1080	.0897	.707	-.1160	.332
	LF	C	.1017	.089753	.791	-.1222	.325
Semimembranosus /semitendinosus	HF	LF	.1243	.0716	.270	-.054398	.303
	HF	C	.0820	.066	.671	-.08377	.247
	LF	C	-.0422	.06644	1.000	-.2081	.123
Medial Gastrocnemius	HF	LF	-.0765	.055	.523	-.21486	.0617
	HF	C	-.0916	.05141	.246	-.2199	.0367
	LF	C	-.0150	.0514	1.000	-.14338	.1132

*HF: High-functional TKA group

**LF: Low-functional TKA group

***C: Nonoperative control group

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Table 7 Between-group comparison of stride-to-stride variability in muscle response to the neural commands

Muscle	group I	group J	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval Lower Bound	Upper Bound
Vastus Medialis	HF*	LF**	0.08	0.08	0.97	-0.13	0.30
	HF	C***	0.08	0.08	1.00	-0.13	0.28
	C	LF	0.01	0.08	1.00	-0.19	0.21
Rectus Femoris	HF	LF	0.00	0.06	1.00	-0.15	0.15
	HF	C	0.03	0.06	1.00	-0.12	0.17
	C	LF	-0.03	0.06	1.00	-0.17	0.12
Vastus Lateralis	HF	LF	0.06	0.05	0.68	-0.06	0.18
	HF	C	0.09	0.04	0.15	-0.02	0.20
	C	LF	-0.03	0.04	1.00	-0.14	0.08
Biceps Femoris	HF	LF	0.05	0.05	0.94	-0.07	0.17
	HF	C	0.06	0.05	0.73	-0.06	0.17
	C	LF	0.00	0.05	1.00	-0.12	0.11
Semimembranosus /semitendinosus	HF	LF	0.03	0.05	1.00	-0.09	0.15
	HF	C	0.06	0.05	0.53	-0.05	0.18
	C	LF	-0.03	0.05	1.00	-0.15	0.08
Medial Gastrocnemius	HF	LF	-.111	0.04	0.02	-0.21	-0.01
	HF	C	-.141	0.04	0.00	-0.24	-0.05
	C	LF	0.03	0.04	1.00	-0.07	0.12

*HF: High-functional TKA group
**LF: Low-functional TKA group
***C: Nonoperative control group

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