Title

Complexity of Knee Neuromuscular Control in Uninjured Physically Active Adults: Right/Left and Dominant/Nondominant Asymmetry Analyses

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ABSTRACT

Context: Motor pathways include upper motor-neurons from the cerebrum and brainstem and lower motor-neurons from the spinal cord. Together, these physiological components are effectors of knee neuromuscular control. Because multiple components are involved, each with an output that is asynchronous to the others, ‘whole-system’ output is characterized by irregular temporal behavior and signal fluctuations. The irregular temporal behavior of physiological signals is analyzed using ‘complexity’. Complexity-based measures reflect the ability to adapt motor output rapidly and accurately in response to external perturbations and provide physiological information missed by magnitude-based (variability) measures.

Objective: To characterize side-to-side symmetry of knee neuromuscular control (sub-maximal isometric knee extension constant-force task) using variability (coefficient of variation [CV%]) and complexity (approximate entropy [ApEn], detrended fluctuation analysis [DFA α]) measures.

Design: Cross-sectional.

Setting: Laboratory.

Patients or Other Participants: Sixteen (male/female n=11/5; age 24.0 ± 5.3 yr; height 1.74 ± 0.08 m; body-mass 68.3 ± 11.1 kg).

Main Outcome Measure(s): Right/left and dominant/nondominant group-level (t-test) and individual-level (absolute-asymmetry [%]) comparisons. A limb-symmetry-index was calculated for each variable and clinically-significant absolute-asymmetry defined ($>15\%$). Clinically-significant absolute-asymmetry prevalence (%) was computed for each variable.

Results: The only significant side-to-side difference was for right/left DFA α ($P=.000$). Maximum absolute-asymmetries were (right/left, dominant/nondominant): CV 18.2%, 18.0%; ApEn 34.5%, 32.3%; DFA α 4.9%, 5.0%. Clinically-significant absolute-asymmetry prevalence was (right/left, dominant/nondominant): CV 43.8%, 43.8%; ApEn 62.5%, 50.0%; DFA α 0.0%, 0.0%.

Conclusions: Different side-to-side comparison methods yield different findings. Large proportions of participants demonstrated wide ranges of side-to-side absolute-asymmetries. The finding of a significant

difference for the right/left DFA α comparison but not for the right/left ApEn comparison suggests that different complexity variables assess different aspects of complexity. Consideration for how side-to-side comparisons are performed (right/left, dominant/nondominant) is required. Approximate entropy and DFA α assess different aspects of complexity and both should be used alongside other traditional magnitude-based measures when studying knee neuromuscular control.

Key Words: Knee, neuromuscular control, complexity, limb symmetry index, asymmetry

INTRODUCTION

The knee accounts for up to 46.8% of musculoskeletal injuries.¹ Knee ligament injuries are common and meniscus injuries frequent.² The consequences of knee injury include physical disability,³ substantial healthcare costs,⁴ and post-trauma osteoarthritis.⁵ Knowledge of factors contributing to knee health is, therefore, necessary for responsibly informing knee injury prevention and rehabilitation interventions that enable athletes' lifelong physical activity and sports participation. Functional joint stability (FJS) refers to joint stability during functional tasks, resulting from interactions between non-contractile tissues (e.g. ligaments) and sensorimotor control of the dynamic restraints (i.e. skeletal muscles).⁶ Optimal sensorimotor control of FJS results from proprioception, central nervous system operations, and neuromuscular control.⁶ In joint injury prevention and rehabilitation, neuromuscular control refers specifically to activation of the dynamic restraints in preparation for and response to joint loading and motion to maintain or restore FJS.⁶ Neuromuscular control includes both neural activation and force generation components in order for the skeletal muscles to facilitate knee FJS.⁶ The activation component is studied using electromyography (EMG) whilst the force generation component is examined using dynamometry (e.g. isokinetics).⁷ For both, the process involves a physiological characteristic being detected by a sensing device, quantified using a pre-determined scale, and recorded by another device *for one moment-in-time* as a single data-point.⁸ When measurements continue *for a period-of-time*, thousands

of data-points are recorded and a biological ‘signal’ is generated.⁸ Biological signals represent the interaction of multiple physiological components and asynchronous feedback loops operating over a range of temporal and spatial scales and are characterized by constant *fluctuations* of the system’s output even under resting/basal conditions.⁹ In neuromuscular control, neuroanatomical and physiological components include the descending tracts formed by upper motor-neurons originating in the cerebrum and brainstem and lower motor-neurons originating in the spinal cord; all contribute to a motor pathway that ultimately stimulates skeletal muscle.⁶ The quantification of *signal fluctuations* is necessary to better analyze athletes’ knee neuromuscular control characteristics.

Historically, signal fluctuations were viewed as unwanted ‘noise’ relative to the perspective that healthy physiological processes (e.g. heart-rate) operate to reduce variability and maintain constancy of function.^{9,10} Subsequently, it has been common practice to undertake noise reduction using forms of mathematical filters.⁸ One method for analyzing behavior of physiological signals is using ‘variability’ which refers to fluctuations in the magnitude-domain⁹ (Figure 1, y-axis). Variability traditionally assesses aspects of magnitude using the signal’s standard deviation (SD) and coefficient of variation (CV),¹¹ providing information about absolute variability and variability normalized to the mean value, respectively.¹¹ Recently, irregular (random, chaotic) behavior of physiological signals has been consistently observed in healthy people, for example: heart-rate, respiratory-rhythm, and brain activity.¹² Given that irregular signal fluctuations are apparent in the outputs of healthy people, magnitude-based analyses of signal characteristics miss “hidden information” regarding signal fluctuations.¹³ The irregular behavior of physiological signals is analyzed using ‘complexity’ which refers to fluctuations in the time-domain^{9,13} (Figure 1, x-axis). Complexity assesses the moment-to-moment relationship between successive data-points^{11,13} and how signal structure evolves over time. Therefore, use of both magnitude-based and complexity-based measures are necessary for the thorough evaluation of signal fluctuations.¹³

Figure 1. Illustration of how variability-based (magnitude-domain, y-axis) and complexity-based (time-domain, x-axis) variables relate to the graphical plot of an isometric knee extension signal. Nm = Newton-meters; s = seconds; SD = standard deviation; CV = coefficient of variation; ApEn = approximate entropy; DFA α = detrended fluctuation analysis α .

It has been repeatedly demonstrated that regular (non-random, periodic) behavior of physiological signals characterizes ageing,⁹ disease,¹⁴ injury,¹⁵ and fatigue.¹¹ Signal fluctuations in the time-domain (*sic*, ‘complex fluctuations’), subsequently, are not random noise *per se*; rather, they include normal complex fluctuations in physiological processes.^{9,10} Complex fluctuations in physiological processes are recognized increasingly as representing the range across which biological systems function and their ability to respond and adapt to unpredictable environments containing rapidly altering constraints.^{9,10,13} Complex fluctuations in neuromuscular control, particularly, reflect an ability to adapt motor output rapidly and accurately in response to task demands.¹⁶ Consequently, excessive signal filtering may remove valuable information about a physiological system’s status and capacity.^{9,10} Knowledge of alternative signal analysis methods is, therefore, useful to better understand how neuromuscular control contributes to knee FJS. Complexity-based analyses draw from nonlinear dynamics and include those

drawn from information theory (e.g. entropy statistics) and fractal geometry.^{9,17} Entropy statistics, such as approximate entropy (ApEn),¹⁸ measure the apparent regularity or randomness of a signal.^{9,17} The term ‘entropy’ is not used in the thermodynamics sense⁹; rather, it relates to the rate at which information is produced or the amount of information derived from a signal.¹⁸ Fractals traditionally measure irregular geometric shapes with underlying structural patterns of units, sub-units, sub-sub-units, etc. (e.g. neuronal dendrites).⁹ For physiological systems, outputs are fractal if, as a function of time, they undergo similar changes regardless of the time interval over which data-points are collected.¹² An example of a fractal metric is detrended fluctuation analysis (DFA).¹² Because entropy and fractal metrics represent different physiological characteristics, both should be used to profile signal complexity.⁹

When considering aspects of knee health and factors contributing to neuromuscular control of knee FJS, reference data is required from uninjured individuals. Such data creates a benchmark against which data from injured athletes can be interpreted, thereby supporting clinical decision-making processes in knee injury prevention screening, diagnosis, and rehabilitation.¹⁹ For the knee, reference data is required for both right and left sides for thorough within-athlete (individual-level) and between-group (group-level) analyses.¹⁹ In knee neuromuscular control, some researchers have used variability-based measures including the CV,²⁰ others have used complexity-based measures including entropy and fractal metrics,¹¹ but few have used both variability-based and complexity-based measures.¹¹ No published work reports examining knee neuromuscular control using both variability-based and complexity-based analyses for right and left sides, or dominant and nondominant sides, in uninjured athletes.

There were two purposes for this study. First, to establish if there were statistically significant side-to-side differences (right/left, dominant/nondominant) for variability (CV) and complexity (ApEn, DFA) during an isometric knee extension 50% maximum-voluntary-effort (MVE) constant-force task. It was hypothesized there would be no statistically significant side-to-side differences for either comparison for any variable. Fifty percent MVE was deemed appropriate because sub-maximal MVEs are sufficient to

enhance knee joint stability.²¹ Since calculation of 50% MVE requires a 100% MVE measurement, findings for isometric knee extension 100% MVE moment are also reported along with findings for vastus lateralis (VL) rectified surface-EMG during the 50% MVE constant-force task. Second, to determine the mean side-to-side (right/left, dominant/nondominant) absolute-asymmetry for the variability and complexity variables using the limb-symmetry-index (LSI). It was hypothesized the mean absolute-asymmetry would be $\leq 15\%$ for both comparisons for all variables. An absolute-asymmetry threshold of 15% was chosen because mean LSIs of approximately 85% are reported for isometric knee extension MVEs in uninjured athletes.²² Prevalence of absolute-asymmetries $>15\%$ are also reported. This study is practically significant because it advances the science of sports medicine by providing new reference data that will support interpretations of future complexity-based analyses of knee neuromuscular control and clinical decision-making for athletes with knee injuries.

METHODS

Ethical Approval, Informed Consent, Participants

University ethics approval was obtained. Participants were a sample of convenience recruited by flyers posted on university campuses and group emails sent to student cohorts. Informed consent and a physical activity readiness questionnaire were completed by all participants. Inclusion criteria were physically-active males/females aged 18-40 years. Exclusion criteria were current lower-limb pain and any lower-limb injury in the previous three months. Sixteen uninjured participants volunteered (11 male, 5 female; mean $\pm$ SD: age 24.0 ± 5.3 years; height 1.74 ± 0.08 m; body mass 68.3 ± 11.1 kg).

Experimental Design.

Participants attended the laboratory on three occasions with ≥ 48 hours between sessions (Figure 2). Participants were instructed to avoid any fatiguing exercise/sports for 48 hours before sessions. During the first session (Figure 2), participants were familiarized with instrumentation and procedures, their individual dynamometer settings were recorded, and their limb dominance was established by asking

which leg is preferred to kick a football. For the next two sessions (Figure 2), isometric knee extension efforts were performed and data collected for all variables. Limb order was randomized, with one limb assessed in session 2 and the opposite limb assessed in session 3.

Figure 2. Sequence of study sessions and procedures. EMG = electromyography; MVE = maximum-voluntary-effort

Dynamometry

Isometric knee extension efforts were sampled with a CSMi isokinetic dynamometer (HUMAC Norm, Massachusetts, USA), initialized and calibrated according to manufacturers' instructions. For all dynamometry, participants sat with their hips and knees flexed 85° and 90°, respectively, and the lateral epicondyle of the knee aligned with the axis-of-rotation of the dynamometer lever-arm. The trunk, pelvis, and thigh were secured using the device's straps. The lever-arm's attachment was adjusted so the lower edge of the shin-pad was just above the malleoli. Participants crossed their arms and held the dynamometer chest-straps for all trials. Sampling frequency was 1000Hz.

Surface Electromyography

The EMG of the VL was sampled using 32mm x 32 mm Ag/AgCl electrodes (Nessler Medizintechnik, Innsbruck, Austria) with an interelectrode distance of 35mm. Prior to attachment of the electrodes, the skin was shaved, abraded, and cleaned with an alcohol swab in order to reduce impedance. Participants were seated on the dynamometer in 90° knee flexion and performed manually resisted isometric knee extension to outline the length and belly of the VL. The electrodes were placed 10cm superior to the margin of the patellar base, in a direction parallel to the alignment of the muscle fibers. A reference electrode was placed on prepared skin medial to the tibial tuberosity. Raw EMG signals were sampled at 1000Hz, amplified (gain 1000; Biopac MP150, Biopac Systems Inc., California, USA) and band-pass filtered (10-500Hz; Biopac MP150).

Isometric Knee Extension Efforts

Prior to the 100% MVE task, participants were encouraged to warm-up using a self-selected number of trials at a self-selected intensity for each trial, building up to a perceived 100% maximal effort.

Participants were instructed to report when they felt ready to undertake the measured trials, after which they were given a countdown and strong verbal encouragement to facilitate a maximal effort. Three trials were performed, each lasting three seconds and separated by 60 seconds rest.¹¹

For the 50% MVE constant-force task, a chart containing the instantaneous knee extension moment was projected onto a screen placed ~1m in front of the participant. A scale consisting of a 1mm thick line was superimposed on the chart and acted as a target so that participants were able to match their instantaneous moment to the 50% MVE target moment during each trial. Participants were instructed to match their instantaneous moment with a target bar superimposed on the display for as much of each trial as possible. Five trials were performed, each lasting six seconds and separated by four seconds rest.¹¹

Data Acquisition and Reduction

All devices were connected by BNC cables (Digitimer, Welwyn Garden City, UK) to the Biopac MP150 unit and a CED Micro 1401-3 interface unit (Cambridge Electronic Design, Cambridge, UK) interfaced with a personal computer. Data were collected in Spike2 software (Version 7, Cambridge Electronic Design, Cambridge, UK). Raw data were processed using customized code in MATLAB R2017a (Mathworks, Massachusetts, USA).

For the three 100% MVE trials, the peak knee extension moment was identified and used to calculate the 50% MVE target value for the constant-force trials. The EMG output from the VL was full-wave rectified for each 50% MVE trial.¹¹ The average rectified EMG (arEMG) was calculated and normalized for each trial by expressing the arEMG as a fraction of the peak 100% MVE arEMG.¹¹

For all variability and complexity analyses, the steadiest five seconds of each 50% MVE trial was identified as the five-second epoch with the lowest SD.¹¹ Variability was measured using the CV¹¹ and complexity measured using ApEn^{11,18} and the DFA α scaling exponent.¹¹ The equations for calculating ApEn [1] and DFA α [2] are:

$$ApEn(m, r, N) = \frac{1}{N - m} \sum_{i=1}^{N-m} \log \frac{A_i}{B_i} \quad [1]$$

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2} \quad [2]$$

Detailed explanations for each equation are provided by previous work¹¹ and in the Appendix. In brief, ApEn was calculated with the template length, m , set at two and the tolerance, r , set at 10% of the SD of

knee extension moment output, and DFA was calculated across time-scales (57 boxes ranging from 1250 to four data points.¹¹ Because ApEn and DFA α are both statistics, they are unitless numbers: ApEn returns values close to zero if the signal is smooth and/or periodic (e.g. a sine wave) and values near two if the signal is highly irregular;^{11,18} DFA α typically ranges from ~0.5 to ~1.5 and acts as an indicator of the ‘roughness’ of the time-series, the larger the value of α the smoother (more regular) the time-series.¹²

Statistical Analyses

The mean CV, ApEn, DFA α , and arEMG from the five 50% MVE constant-force trials, and the peak knee extension moment from the three 100% MVE trials, were used for analyses. Summary statistics were calculated, including the absolute side-to-side differences (right – left, dominant – nondominant). The $\pm$ sign was removed from the difference. There were no missing data.

For statistical analyses (group-level), normality of data was assessed with histogram inspection and Shapiro-Wilk tests. Alpha was set *a priori* at 0.05. Paired *t*-tests were used for right/left and dominant/nondominant side-to-side comparisons across all variables. Bonferroni-corrected alpha was set *a priori* at 0.005. Ninety-five percent confidence intervals (CI) were estimated for all variables and within-group Cohen’s *d* was calculated for all side-to-side comparisons; an effect-size of 0.20, 0.50, and 0.80 considered small, medium, and large, respectively.²³

For clinical analyses (individual-level), two LSIs were calculated: right/left LSI (R/L-LSI)¹⁹ and dominant/nondominant LSI (D/ND-LSI). The R/L-LSI (%) was calculated: $(\text{right} \div \text{left}) \times 100$.¹⁹ A R/L-LSI of 100% represented side-to-side symmetry, <100% lower right-side/higher left-side values, >100% lower left-side/higher right-side values. The D/ND-LSI (%) was calculated as: $(\text{dominant} \div \text{nondominant}) \times 100$. A D/ND-LSI of 100% represented side-to-side symmetry, <100% lower dominant-side/higher nondominant-side values, >100% lower nondominant-side/higher dominant-side values. Therefore, for the R/L-LSI and D/ND-LSI, each indicated both the magnitude (size) and direction (side) of asymmetry.¹⁹

Because the size of an absolute-asymmetry is frequently the principal matter of clinical interest,¹⁹ the absolute-asymmetry for both the R/L-LSI and D/ND-LSI was calculated as: $100\% - \text{participant's LSI}$.¹⁹ The $\pm$ sign was removed from the difference.¹⁹ Counts were made of participants with absolute-asymmetries $>15\%$ and overall-prevalence (%) computed for each variable for both LSIs: (number of participants with an absolute-asymmetry $>15\% \div$ total number of participants) $\times 100$.¹⁹

RESULTS

No participant experienced pain or adverse event during data collection. Summary statistics are presented in Tables 1 and 2. Data were normally distributed. Example findings from the 50% MVE constant-force task for two different participants are illustrated in Figure 3 and 4. The only significant side-to-side differences were for the right/left DFA α ($P=.001$; Table 1) and the dominant/nondominant knee extension moment ($P=.000$; Table 2).

Table 1. Summary statistics and effect sizes for variability and complexity variables (n=16)

	CV (%)			CV (%)			ApEn			ApEn			DFA α			DFA α		
	R	L	R-L Absolute Difference	D	ND	D-ND Absolute Difference	R	L	R-L Absolute Difference	D	ND	D-ND Absolute Difference	R	L	R-L Absolute Difference	D	ND	D-ND Absolute Difference
Min	2.01	2.28	0.02	2.22	2.01	0.02	0.25	0.14	0.01	0.25	0.14	0.01	1.17	1.26	0.00	1.26	1.17	0.00
Max	3.51	6.20	3.64	3.51	6.20	3.64	0.65	0.54	0.29	0.65	0.62	0.29	1.52	1.62	0.21	1.56	1.62	0.21
95% CI	2.53, 2.96	2.67, 3.82	0.20, 1.22	2.54, 2.93	2.68, 3.83	0.20, 1.22	0.37, 0.50	0.31, 0.42	0.06, 0.14	0.34, 0.46	0.33, 0.46	0.06, 0.14	1.33, 1.47	1.40, 1.50	0.04, 0.99	1.36, 1.45	1.38, 1.49	0.41, 0.99
Mean	2.75	3.24	0.71	2.74	3.25	0.71	0.43	0.36	0.10	0.40	0.39	0.10	1.38 ^a	1.45	0.07	1.40	1.43	0.07
SD	0.40	1.07	0.96	0.37	1.08	0.96	0.12	0.10	0.07	0.11	0.13	0.07	0.10	0.09	0.06	0.09	0.11	0.06
ES	0.45			0.47			0.73			0.08			1.12			0.34		

CV = coefficient of variation; ApEn = approximate entropy; DFA α = detrended fluctuation analysis α

R = right; L = left; R-L Absolute Difference = right – left (+/- sign removed)

D = dominant; ND = nondominant; D-ND Absolute Difference = dominant – nondominant (+/- sign removed)

Min = minimum; Max = maximum; 95% CI = 95% confidence interval (lower bound, upper bound); SD = standard deviation; ES = effect size

^aSignificant side-to-side difference, $P=.001$

Table 2. Summary statistics and effect sizes for isometric knee extension moment and surface electromyography (n=16)

	Knee Extension Moment (Nm)			Knee Extension Moment (Nm)			arEMG (% MVE)			arEMG (% MVE)		
	R	L	R-L Absolute Difference	D	ND	D-ND Absolute Difference	R	L	R-L Absolute Difference	D	ND	D-ND Absolute Difference
Min	136.6	145.7	2.1	155.4	136.6	2.1	40.9	35.0	0.5	35.0	43.1	0.5
Max	407.9	378.9	56.2	407.9	378.9	56.2	67.8	82.6	26.6	67.8	82.6	26.6
95% CI	200.2, 277.4	186.7, 264.1	13.2, 31.7	206.5, 281.1	184.1, 259.7	13.2, 31.7	49.9, 57.2	53.1, 67.2	7.0, 17.0	48.0, 57.4	54.9, 67.1	7.0, 17.0
Mean	238.8	226.9	22.5	243.8 ^a	221.9	22.5	53.6	60.1	12.0	52.7	61.0	12.0
SD	72.4	69.9	17.3	70.1	71.0	17.3	6.9	13.2	9.4	8.8	11.4	9.4
ES	0.68			0.83			0.46			0.63		

Nm = Newton-meters; arEMG = average rectified electromyogram; % MVE = percentage of maximum-voluntary-effort

R = right; L = left; R-L Absolute Difference = right – left (+/- sign removed)

D = dominant; ND = nondominant; D-ND Absolute Difference = dominant – nondominant (+/- sign removed)

Min = minimum; Max = maximum; 95% CI = 95% confidence interval (lower bound, upper bound); SD = standard deviation; ES = effect size

^aSignificant side-to-side difference, $P=.000$

Figure 3. Raw output from a trial for a participant with similar complexity and variability values in the right (a) and left (b) sides. Nm = Newton-meters; s = seconds; ApEn = approximate entropy; DFA α = detrended fluctuation analysis α ; CV = coefficient of variation. ApEn right/left limb-symmetry-index = 102.9%; ApEn right/left absolute-asymmetry = 2.9%. DFA α right/left limb-symmetry-index = 94.4%; DFA α right/left absolute-asymmetry = 5.6%. CV right/left limb-symmetry-index = 103.5%; CV right/left absolute-asymmetry = 3.5%.

Figure 4. Raw output from a trial for a participant with different complexity and variability values in the right (a) and left (b) sides. Nm = Newton-meters; s = seconds; ApEn = approximate entropy; DFA α = detrended fluctuation analysis α ; CV = coefficient of variation. ApEn right/left limb-symmetry-index = 131.6%; ApEn right/left absolute-asymmetry = 31.6%. DFA α right/left limb-symmetry-index = 86.8%; DFA α right/left absolute-asymmetry = 13.2%. CV right/left limb-symmetry-index = 63.1%; CV right/left absolute-asymmetry = 36.9%.

For effect-sizes, a little under large effect was evident for right/left ApEn (Table 1), a very large effect was evident for right/left DFA α (Table 1), a little over medium effect was evident for the right/left knee

extension moment (Table 2) and dominant/nondominant arEMG (Table 2), and a large effect was evident for the dominant/nondominant knee extension moment (Table 2).

Summary statistics for R/L-LSIs, D/ND-LSIs, and absolute-asymmetries are presented in Tables 3 and 4. The mean absolute-asymmetry values for both side-to-side comparison methods were >15% for CV and ApEn (Table 3), and arEMG (Table 4). Inspection of the maximum absolute-asymmetry values for both side-to-side comparison methods demonstrates some participants had very large absolute-asymmetries for the CV and ApEn (Table 3), and the knee extension moment and arEMG (Table 4). The overall-prevalence of absolute-asymmetry >15% indicated that for either side-to-side comparison method, substantial proportions of participants had absolute-asymmetries beyond the set threshold for CV and ApEn (Table 3), and the knee extension moment and arEMG (Table 4).

Table 3. Summary statistics for variability and complexity variables' limb symmetry indices and absolute-asymmetries (n=16)

	CV		CV		ApEn		ApEn		DFA α		DFA α	
	R/L Limb Symmetry Index (%)	R/L Absolute Asymmetry (%)	D/ND Limb Symmetry Index (%)	D/ND Absolute Asymmetry (%)	R/L Limb Symmetry Index (%)	R/L Absolute Asymmetry (%)	D/ND Limb Symmetry Index (%)	D/ND Absolute Asymmetry (%)	R/L Limb Symmetry Index (%)	R/L Absolute Asymmetry (%)	D/ND Limb Symmetry Index (%)	D/ND Absolute Asymmetry (%)
Min	41.2	0.7	41.2	0.7	58.3	2.4	58.3	2.4	86.8	0.3	86.8	0.3
Max	131.2	58.8	120.7	58.8	309.6	209.6	309.6	209.6	101.7	13.2	108.1	13.2
95% CI	78.3, 102.3	9.7, 26.7	78.2, 101.7	9.7, 26.4	99.6, 156.1	8.5, 60.4	83.2, 144.2	6.4, 58.2	93.2, 97.7	3.0, 6.9	94.9, 101.4	3.0, 7.0
Mean	90.3	18.2	90.0	18.0	127.9	34.5	113.7	32.3	95.5	4.9	98.2	5.0
SD	22.6	16.0	22.0	15.7	53.0	48.6	57.2	48.6	4.2	3.7	6.1	3.7
O-Prevalence (%)	43.8		43.8		62.5		50.0		0.0		0.0	

CV = coefficient of variation; ApEn = approximate entropy; DFA α = detrended fluctuation analysis α ; R/L = right/left; D/ND = dominant/nondominant
Limb Symmetry Index, see text for equation and explanation; Absolute Asymmetry, see text for equation and explanation
Min = minimum; Max = maximum; 95% CI = 95% confidence interval (lower bound, upper bound); SD = standard deviation
O-Prevalence = overall-prevalence for an absolute-asymmetry >15%, see text for equation and explanation

Table 4. Summary statistics for isometric knee extension and surface electromyography limb symmetry indices and absolute-asymmetries (n=16)

	Knee Extension Moment		Knee Extension Moment		arEMG		arEMG	
	R/L Limb Symmetry Index (%)	R/L Absolute Asymmetry (%)	D/ND Limb Symmetry Index (%)	D/ND Absolute Asymmetry (%)	R/L Limb Symmetry Index (%)	R/L Absolute Asymmetry (%)	D/ND Limb Symmetry Index (%)	D/ND Absolute Asymmetry (%)
Min	83.0	0.7	98.9	0.7	62.5	1.0	61.8	1.0
Max	138.4	38.4	138.4	38.4	161.7	61.7	122.7	38.2
95% CI	98.7, 113.8	5.6, 16.7	105.55, 117.1	5.9, 17.2	79.9, 106.9	11.2, 28.6	78.1, 99.4	11.6, 25.4
Mean	106.3	11.2	111.3	11.5	93.4	19.9	88.8	18.5
SD	14.1	10.4	10.8	10.6	25.3	16.3	20.0	13.0
O-Prevalence (%)	31.3		37.5		50.0		50.0	

arEMG = average rectified electromyogram; R/L = right/left; D/ND = dominant/nondominant
Limb Symmetry Index, see text for equation and explanation; Absolute Asymmetry, see text for equation and explanation
Min = minimum; Max = maximum; 95% CI = 95% confidence interval (lower bound, upper bound); SD = standard deviation
O-Prevalence = overall-prevalence for an absolute-asymmetry >15%, see text for equation and explanation

DISCUSSION

The first purpose of this study was to test the hypothesis that there would be no statistically significant side-to-side differences (right/left, dominant/nondominant) for variability and complexity during an isometric knee extension 50% MVE constant-force task. It was demonstrated that the only significant difference for either comparison was for right/left DFA α (Table 1). Further analyses demonstrated a significant difference existed for dominant/nondominant isometric knee extension peak moment (Table 2). The second purpose of this study was to test the hypothesis that mean side-to-side (right/left, dominant/nondominant) absolute-asymmetry for the variability and complexity variables, assessed using the LSI, would be $\leq 15\%$ for both comparison for all variables. It was demonstrated that the mean absolute-asymmetry was $>15\%$ for both comparisons for CV and ApEn, but not for either comparison for DFA α (Table 3). Prevalence analyses indicated substantial proportions of participants had absolute-asymmetries beyond the set threshold for variability and complexity variables (Table 3), and for knee extension moment and arEMG (Table 4).

In knee injury prevention screening, diagnosis, and rehabilitation, side-to-side comparisons are made to inform clinical reasoning and support clinical decision-making.^{19,24} At group-level, symmetry analyses examine whether statistically significant side-to-side differences exist for measures of central tendency.¹⁹ In this study, the only significant side-to-side group-level differences were for right/left DFA α (Table 1) and dominant/nondominant knee extension moment (Table 2). This is the first study to analyze, and demonstrate, side-to-side differences in complexity variables. Interestingly, one significant finding is for a right/left comparison, the other is for a dominant/nondominant comparison. Therefore, careful consideration should underpin the clinical reasoning for which comparison method is employed because different statistical findings can be evident for one method versus another. Such consideration is supported by the finding that side-to-side effect-sizes were substantially different between comparison methods for most variables (Tables 1 and 2).

At individual-level, symmetry analyses examine whether clinically-significant side-to-side differences exist for an individual's mean or maximum values.¹⁹ An absolute-asymmetry threshold of 15% was chosen because mean LSIs of approximately 85% are reported for isometric knee extension MVEs in uninjured athletes.²² The mean absolute-asymmetries for right/left and dominant/nondominant comparisons of CV and ApEn were >15% (Table 3), whereas the mean absolute-asymmetry for both comparisons for DFA α were $\leq$ 5%. The mean absolute-asymmetries for right/left and dominant/nondominant knee extension moment and arEMG were similar (Table 4). Interestingly, across all variables, the magnitude of the mean absolute-asymmetry was consistent regardless of whether a right/left or dominant/nondominant comparison was performed. No other published work has reported similar analyses with the same variables. Because the mean absolute-asymmetry ranged from 4.9-34.5% across all variables and side-to-side comparison methods (Tables 3 and 4), further work is needed to determine whether the isometric knee extension strength mean LSIs of approximately 85%,²² and corresponding absolute-asymmetries of 15%, apply to complexity measures. Such consideration is supported given that, relative to the side-to-side comparison method, the overall-prevalence of an absolute-asymmetry >15% was approximately one-third to two-thirds for the majority of variables (Tables 3 and 4).

Variability assesses aspects of signal magnitude using the SD and CV whereas complexity assesses the signal irregularity using ApEn and DFA α .^{11,13} Use of both variability and complexity variables, therefore, is necessary for thorough evaluations of signal fluctuations.¹³ There were no significant differences for either side-to-side comparison method for CV (Table 1). There was, however, a significant difference for the right/left comparison of DFA α (Table 1). This supports the notion that complexity-based metrics may be more sensitive to subtle side-to-side differences than variability-based metrics.¹⁴ Subsequently, the finding that there was a significant difference for the right/left DFA α comparison but not the right/left ApEn comparison also supports the notion that different complexity variables do, indeed, assess subtly different aspects of complexity.¹² Such a notion is supported further given that, relative to the side-to-side

comparison method, 50.0-62.5% of participants demonstrated an absolute-asymmetry >15% for ApEn whereas for DFA α zero participants demonstrated such an absolute-asymmetry (Table 3). Because ApEn measures the *regularity/randomness* of a time-series across *one time-scale*,¹⁸ and DFA α measures *fractal scaling* across *multiple time-scales*,¹² agreement between the two metrics is not guaranteed. Insensitivity of one metric does not imply that other metrics will not yield meaningful information about a physiological system's functionality.²⁵ Moreover, the observation that side-to-side effect-size findings for right/left ApEn and DFA α are not similar (Table 1), supports the notion that each variable provides unique information about knee extensor neuromuscular control complexity. Researchers should, therefore, use both ApEn and DFA α to assess knee neuromuscular control complexity, regardless of whether a right/left or dominant/nondominant side-to-side comparisons are made.

Complex fluctuations in physiological signals represent the functional range across which biological systems operate and their resultant ability to respond and adapt to unpredictable environments.^{9,10,13,17} For both comparison methods, there was no significant side-to-side difference for ApEn (Table 1), suggesting that potential adaptability in knee extensor neuromuscular control is similar between sides. However, the medium-to-large effect size for the right/left ApEn comparison (Table 1) may indicate potential side-to-side adaptability does actually differ. The significant side-to-side difference and very large effect-size for the right/left DFA α (Table 1) supports the perspective that side-to-side adaptability in knee extensor neuromuscular control is different in the present sample of uninjured individuals. Potential differences in the complexity of knee extensor neuromuscular control are reflective of differences in co-ordination, and could have implications for the risk of injury, particularly knee injury.^{26,27} Indeed, low complexity has been speculated to reflect a narrowing of system responsiveness and lower adaptability, which could increase the risk of failing a motor task.²⁸

Complex fluctuations result from multiple physiological components operating together to generate a whole-system output.^{9,12} In neuromuscular control, motor pathways combine multiple neuroanatomical

and physiological components including the descending tracts formed by upper motor-neurons originating in the cerebrum and brainstem and lower motor-neurons originating in the spinal cord.⁶ If adaptability in knee extensor neuromuscular control differs between sides, the difference could originate from structural and/or physiological side-to-side differences in any component of a motor pathway on either side of the body. For example, it has been argued that changes in complexity are a consequence of variations in common synaptic input to the motor unit pool,^{25,28} which are themselves the main determinant of the magnitude of force fluctuations.²⁹ Increased common synaptic input, and motor unit synchronization (a necessary consequence of common synaptic input²⁹), have been speculated to be associated with lower complexity.²⁸ Indeed, differences in motor unit synchronization have been observed between the muscles of the dominant/nondominant arms.³⁰

The present study had several potential limitations. First, limb dominance was defined by the preferred kicking limb rather than the strongest limb. This was because we were interested in sub-maximal knee extensor efforts which are effective for increasing knee joint stability and resisting external perturbations.²¹ Future research should compare different methods of defining limb dominance and how they affect variability and complexity side-to-side absolute-asymmetries. Second, the constant-force task used only one sub-maximal level of effort. Given that complexity varies with the level of isometric efforts,¹³ a variety of sub-maximal levels may be useful for revealing differences in knee extensor moment complexity. Accordingly, future research should use different levels of isometric knee extension MVE constant-force tasks. Third, an absolute-asymmetry threshold of >15% was used to define a clinically-significant side-to-side asymmetry. As this is the first study investigating side-to-side differences in complexity, it is unknown if a single percentage threshold, or range of percentages, is clinically meaningful when considering absolute-asymmetries in knee neuromuscular control. Future research should continue to investigate aspects of absolute-asymmetry in knee neuromuscular control complexity (and variability).

CONCLUSIONS

This is the first study to report side-to-side comparisons of complexity-based and variability-based analyses of knee neuromuscular control in uninjured individuals. Statistically significant side-to-side differences in knee neuromuscular control variability and complexity manifested according to the comparison method used (right/left, dominant/nondominant) and the variable employed. Specifically, a significant side-to-side difference and very large effect-size existed for the right/left DFA α and supports the perspective that side-to-side adaptability of knee extensor neuromuscular control in uninjured individuals is different. Side-to-side differences in the adaptability of knee extensor neuromuscular control may have clinical implications for the risk of future knee injury. Large proportions of participants demonstrated a wide range of side-to-side absolute-asymmetries in knee neuromuscular control variability and complexity also according to the comparison method used and the variable employed. Researchers should carefully consider which method is used for side-to-side comparisons and the threshold or range employed to define a clinically-significant absolute-asymmetry for each variable. Approximate entropy and DFA α assess subtly different aspects of complexity and both should be used alongside other traditional magnitude-based variables when studying knee neuromuscular control.

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APPENDIX

ApEn and DFA α were calculated as in Pethick et al.,¹ with these calculations detailed below.

ApEn quantifies the negative natural logarithm of the conditional probability that a template of length m (set at 2) is repeated during a time-series. Matching templates that remain similar (i.e. within the tolerance, r , set at 0.1 SD)² are counted, with the number of matches to the i^{th} template of length m designated B_i . The number of these matches that remain similar for the $m+1^{\text{th}}$ point is counted, with this number for the i^{th} template designated A_i . The conditional probability that the template including the $m+1^{\text{th}}$ data point matches given the template of length m is then calculated for each template match. The negative logarithm of the conditional probability is calculated for all templates and the results averaged. Equation for calculating approximate entropy:

$$ApEn(m, r, N) = \frac{1}{N - m} \sum_{i=1}^{N-m} \log \frac{A_i}{B_i}$$

N is the number of data points in the time series, m is the length of the template, A_i is the number of matches of the i^{th} template of length $m+1$ data points, and B_i is the number of matches of the i^{th} template of length m data points.

If the data are highly ordered then templates similar for m points are likely to be similar for $m+1$ points. The conditional probability will be close to 1, and the negative logarithm, and therefore the entropy, will be close to zero. This reflects low complexity and high predictability.

In the DFA algorithm,³ the time-series is first integrated and the vertical characteristics of this integrated time-series measured. The integrated time-series is then divided into boxes of equal length, n , and a least squares line fitted, representing the trend in each box. The y co-ordinate of the straight-line segment of length n in the k^{th} box is denoted by $y_n(k)$, and the integrated time-series is detrended by subtracting the local trend in each box. For a given box size, n , the characteristic size of fluctuation for the integrated and detrended time series is given. This computation is repeated over all box sizes to provide a relationship between box size and $F(n)$. As in Pethick et al.,¹ DFA was calculated using 57 boxes, ranging from 1250 to 4 data points.

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2}$$

The slope of the log-log plot of n and $F(n)$ determines the scaling parameter α . When $\alpha = 0.5$, each value in a time-series is completely random and independent from previous values (i.e. white noise). When $\alpha \neq 0.5$, each observation is not completely independent and is correlated, to some extent, with previous values. An α exponent of 1.0 is consistent with long-range correlations and $1/f$ (pink) noise, while an α exponent of 1.5 is indicative of Brownian noise.⁴

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