

1   **Title page**

2   **Title:**

3   Understanding muscle coordination during gait based on muscle synergy and its association with symptoms in patients  
4   with knee osteoarthritis

5

6   **The names of the authors:** \* These authors contributed equally.

7   Masashi Taniguchi <sup>1\*</sup>, RPT, PhD (ORCID: 0000-0003-0548-0210), Jun Umehara <sup>1, 2\*</sup>, RPT, PhD (0000-0002-1258-  
8   0714), Momoko Yamagata <sup>1, 2</sup>, RPT, PhD (0000-0001-8192-5651), Masahide Yagi <sup>1</sup>, RPT, PhD (0000-0002-1825-  
9   3570), Yoshiki Motomura <sup>1, 3</sup>, RPT, MSc (0000-0002-6544-0678), Sayaka Okada <sup>1</sup>, RPT, MSc (0000-0002-6743-9021),  
10   Shogo Okada <sup>1</sup>, RPT, MSc (0000-0002-7956-5017), Kaede Nakazato <sup>1</sup>, RPT (0000-0002-9126-9843), Yoshihiro  
11   Fukumoto <sup>1, 2</sup>, RPT, PhD (0000-0003-0516-770X), Masashi Kobayashi <sup>3</sup>, MD, PhD (0000-0001-5401-9581), Kyoseki  
12   Kanemitsu <sup>4</sup>, MD, PhD, Noriaki Ichihashi <sup>1</sup>, RPT, PhD (ORCID: 0000-0003-2508-2172)

13

14   **Affiliations:**

15   <sup>1</sup> Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan

16   <sup>2</sup> Faculty of Rehabilitation, Kansai Medical University, Osaka, Japan

17   <sup>3</sup> Kobayashi Orthopaedic Clinic, Kyoto, Japan

18   <sup>4</sup> Kanemitsu Clinic, Kyoto, Japan

19

20    **Corresponding Author**

21    Masashi Taniguchi, RPT, PhD, ORCID Number: 0000-0003-0548-0210,

22    Human Health Sciences, Graduate School of Medicine, Kyoto University

23    53-Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

24    Email: [taniguchi.masashi.7a@kyoto-u.ac.jp](mailto:taniguchi.masashi.7a@kyoto-u.ac.jp)

25    Tel.: +81-75-751-3964      Fax: +81-75-751-3964

26

## Abstract

**Objective:** We aimed to investigate the muscle coordination differences between a control group and patients with mild and severe knee osteoarthritis (KOA) using muscle synergy analysis and determine whether muscle coordination was associated with symptoms of KOA.

**Method:** Fifty-three women with medial KOA and 19 control patients participated in the study. The gait analyses and muscle activity measurements of seven lower limb muscles were assessed using a motion capture system and electromyography. Gait speed and knee adduction moment impulse were calculated. The spatiotemporal components of muscle synergy were extracted using non-negative matrix factorization, and the dynamic motor control index during walking (walk-DMC) was computed. The number of muscle synergy and their spatiotemporal components were compared among the mild KOA, severe KOA, and control groups. Moreover, the association between KOA symptoms with walk-DMC and other gait parameters was evaluated using multi-linear regression analysis.

**Results:** The number of muscle synergies were lower in mild and severe KOA compared with those in the control group. In synergy 1, the weightings of biceps femoris and gluteus medius in severe KOA were higher than that in the control group. In synergy 3, the weightings of higher tibial anterior and lower gastrocnemius lateralis were confirmed in the mild KOA group. Regression analysis showed that the walk-DMC was independently associated with knee-related symptoms of KOA after adjusting for the covariates.

**Conclusions:** Muscle coordination was altered in patients with KOA. The correlation between muscle coordination and KOA may be attributed to the knee-related symptoms.

45

46 **Key Points**

- 47 ● Patients with knee osteoarthritis (OA) experienced a deterioration in muscle coordination when walking.
- 48 ● Loss of muscle coordination was associated with severe knee-related symptoms in knee OA.
- 49 ● Considering muscle coordination as a knee OA symptom-related factor may provide improved treatment.

50

51 **Keywords:** gait analysis, electromyography, muscle activity, non-negative matrix factorization, dynamic motor

52 control index

53

54

## Introduction

Gait characteristics in knee osteoarthritis (OA) include decreased gait speed, stride length asymmetry, decreased double knee action, and increased external knee adduction moment (KAM) [1, 2]. Increased KAM is a risk factor for knee OA progression and functional decline [3-5]. In medial knee OA, it is associated with knee joint instability, causing greater muscle co-contraction [6], which has been observed between agonist and antagonist muscles in multiple lower extremity joints [7, 8]. Therefore, assessing KAM and multi-joint muscle activity dynamics is important when evaluating the gait characteristics in knee OA.

For individuals with knee OA, increased co-contraction during walking is associated with cartilage loss and severe OA [9, 10]. Co-contraction is quantified as the difference in electromyography (EMG) amplitude between agonist and antagonist muscles and accounts for muscle activation patterns [11]. The co-contraction index is used to evaluate the muscle activation pattern in a pair of agonist and antagonist muscles, but only between two muscles. A dimensionality reduction technique can be used to quantify muscle activity patterns among numerous muscles based on the covariant component of muscle activations, providing a few blocks of muscle coordination called muscle synergy [12-14]. Because muscle synergy represents several muscle activation patterns in an integrated fashion, a decrease in muscle synergy number represents a lack of muscle coordination and an abnormal muscle co-contraction among numerous muscles [15, 16]. Moreover, since muscle synergy analysis does not require normalization by the EMG amplitude during maximum isometric voluntary contraction, it can be used for patients with painful knee OA [17]. Related studies are scarce, only Kubota et al., [18] have evaluated the muscle synergy number during walking in

patients with knee OA. They observed fewer muscle synergies in patients with knee OA than in healthy young individuals, whereas no difference in number was observed when compared with healthy older individuals. However, whether there are differences in the muscle activation patterns associated with worsening radiographic knee OA remains unknown.

Coordination of muscle activity is altered in patients with musculoskeletal pain, such as femoroacetabular impingement [19]. Previous studies [20, 21] have suggested that a higher co-contraction was related to severe knee-related symptoms. Since knee OA-related pain interacts with alterations of the central nervous system [22, 23], the coordination of muscle activity patterns during walking may deteriorate in patients with knee OA due to pain. However, to our knowledge, no studies have clarified the association between knee-related symptoms and muscle activity patterns during walking using muscle synergy analysis in patients with knee OA.

This study aimed to determine 1) the difference in muscle activation patterns during walking between healthy control and mild-to-severe knee OA groups, assessed using muscle synergy analysis, and 2) the association of muscle activation patterns with knee-related symptoms in patients with knee OA. We hypothesized that the number of muscle synergies decreased with severe knee OA and that loss of muscle coordination during walking was associated with severe knee-related symptoms.

## **Material and methods**

## *Study participants*

This study employed a case-controlled design. Fifty-three women with symptomatic medial knee OA were recruited from two community orthopedic clinics. All patients had knee OA symptoms and were assessed radiographically using the Kellgren-Lawrence (KL) grading system for both knees. The inclusion criteria for the knee OA group included symptomatic knee OA with KL grade  $\geq 2$  and ability to live independently and walk without assistive devices. For bilateral knee OA, data on the more severe side were taken. If both knees had equal radiographic severity, the more painful side was selected. Then, patients with knee OA were classified based on the KL grade of the targeted knee side: mild OA group having a KL grade of 2 and severe OA group with KL grade of 3 or 4. Nineteen healthy controls were also recruited from local communities in Kyoto city and included those with a KL  $< 2$ , no history of knee pain, and ability to live independently and walk without assistive devices. The exclusion criteria for both groups were rheumatoid arthritis, surgical and fracture history for both limbs or the back, and neurological disorders. For the healthy control participants, the collected data related to the knee of their dominant leg. The dominant leg was defined as the leg of the foot they used to kick the ball, and the right leg was found to be dominant in all the healthy control participants.

As physical characteristics, height and body weight measurements were recorded. Participants were instructed to remove their shoes and stand against a stadiometer while their height was recorded to the nearest 0.1 cm. Furthermore, they were instructed to wear light workout clothes and then stand on a scale while their weight was recorded to the nearest 0.1 kg.

The sample size was determined based on similar previous studies [17, 18]. Furthermore, due to the inclusion of five independent variables in the multiple regression analysis, 50 patients with knee OA (at least 10 observations per variable) were required to clarify the association between muscle coordination and knee OA symptoms.

All study procedures were approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (R3014). Participants were informed of the purpose and procedures of this study and provided written informed consent.

#### *Gait analysis*

Participants were instructed to walk a 6-m walkway; data for gait analysis were obtained three times after sufficient practice. Kinetics data during comfortable gait were acquired using a motion capture system (Vicon; Oxford, UK) with force plate (9286A; Kistler, Switzerland). The 35 reflective markers were affixed to specific landmarks on the participant's body according to the VICON Plug-in-gait full-body model set. Data from the reflective markers were acquired using eight infrared cameras with sampling at 200 Hz, and low-pass filtered at 6 Hz with 4<sup>th</sup> order, zero-lag Butterworth filter. The ground reaction force for calculating kinetics parameters was obtained from force plates embedded in the pathway, sampling at 1000 Hz, with low-pass filtered at 20 Hz at 4<sup>th</sup> order, zero-lag Butterworth filter [24]. We calculated the external KAMs using standard inverse dynamics to represent knee OA-related abnormal gait parameters. The time integral values of the KAMs during stance phase were calculated as KAM impulse (Nm S). The

127 KAM impulse on target knee side was extracted and normalized by body weight (kg) by converting the value to Nm  
128 S/kg, and finding the average of the three trials.

129

### 130 *EMG analysis*

131 Surface EMG data were recorded synchronously with motion capture system. EMG signals were acquired from seven  
132 muscles including the gluteus medius (Gmed), vastus lateralis (VL), rectus femoris, vastus medialis, long head of  
133 biceps femoris (BF), tibialis anterior (TA), and gastrocnemius lateralis (GL), with sampling at 1000 Hz using wireless  
134 telemetry EMS system (Telemyo DTS; Noraxon, USA). After cleaning skin with alcohol, disposable electrodes (Blue  
135 Sensor; Medicotest, Denmark) were attached to each muscle on target side of lower extremity according to SENIAM  
136 guidelines (Supplemental file 1). The EMG signals were processed, and then the EMG envelopes were created (Figure  
137 1).

138

### 139 *Muscle synergy extraction*

140 The muscle synergies were extracted from the EMG signal matrix (7 muscles  $\times$  300 temporal samples) using non-  
141 negative matrix factorization (NMF) [25]. NMF assumes that the muscle activation patterns (E) comprised a linear  
142 combination of the muscle weightings (W) and activation coefficients (C) of a muscle synergy:

$$143 \quad E = W \times C + e \quad (W \geq 0, C \geq 0) \quad (1)$$

144 Where  $E$  is  $p \times n$  matrix, with  $p$  and  $n$  indicating the number of muscles and temporal gait points, respectively;  $W$  is  $p$

$\times k$  matrix of the muscle weighting, representing the spatial component; and  $C$  is  $k \times n$  matrix of the activation coefficient, representing the temporal component,  $k$  is the number of muscle synergies, while  $e$  is the residual. This technique was repeated 20 times; the average data was used for further analysis because of dependency on the initial value. NMF was performed using a custom programming software (Matlab R2019b; MathWorks, USA). The EMG signal of each muscle was scaled before unit variance to avoid bias of the weighting on the muscle with high variance and inversely scaled after NMF.

We extracted the muscle synergies by varying the number from one to seven. A variance accounted for (VAF) was calculated between the measured and reconstructed EMG data to evaluate decomposition accuracy of NMF:

$$VAF = \left( 1 - \frac{\sum_{i=1}^p \sum_{j=1}^n (e_{i,j})^2}{\sum_{i=1}^p \sum_{j=1}^n (E_{i,j})^2} \right) \quad (2)$$

We defined the number of muscle synergy as that reaching over 90% of the VAF. To calculate the group-wise average of muscle synergy for the knee OA groups, a functional sorting was performed by grouping the muscle weighting of synergy based on the cosine similarity between an arbitrary subject and the remaining subjects, where the muscle weightings with highest cosine similarity were classified into the same category. Then, we averaged the sorted muscle weighting and activation coefficient to calculate the group-wise averages for the knee OA groups.

The dynamic motor control index during walking (walk-DMC) was computed as a summary metric of synergy complexity. The walk-DMC is a z-score based on VAF of one synergy ( $VAF_1$ ), the average ( $VAF_{AVE}$ ), and the standard deviation ( $VAF_{SD}$ ) of  $VAF_1$  for control group:

163 
$$walk - DMC = 100 + 10 \left( \frac{VAF_{AVE} - VAF_1}{VAF_{SD}} \right) (3)$$

164 Thus, the average walk-DMC score of the control group was 100; each 10 deviations represent one standard deviation  
 165 from the control group. We used this summary metric for further analysis because the walk-DMC is strongly associated  
 166 with clinical assessment and treatment of motor control [26, 27].

167

#### 168 *Self-reported knee-related symptoms*

169 The Knee Society's Knee Scoring System (KSS) 2011 was used to assess knee-related symptoms. The KSS 2011  
 170 Japanese edition is a patient-reported outcome tool for knee conditions [28]. The symptom category in KSS comprises  
 171 the degree of knee pain during walking and climbing stairs and knee stiffness. KSS symptom scores range from 0 to  
 172 25 points, with lower scores representing worse symptoms.

173

#### 174 *Statistical analysis*

175 All values were expressed as means (standard deviations; SDs). All statistical analyses were conducted with statistical  
 176 software (SPSS 25.0; SPSS Japan, Japan). The level of statistical significance was set at  $p < 0.05$ .

177 A one-way analysis of variance (ANOVA) was applied to test differences between the control and knee OA  
 178 subgroups in terms of participant characteristics, number of synergies, walk-DMC, KAM impulse, and gait speed;  
 179 post-hoc comparisons were performed. Levene's test was used to confirm equality of variances; depending on the  
 180 result, whereas the Tukey or Games-Howell test was used for post-hoc comparison. Using the statistical parametric

mapping (SPM; SPM1d version 4) [29], one-way ANOVAs were conducted to assess the statistical differences between the mild knee OA, severe knee OA, and control groups in the temporal component in synergy 1-3. Then, post-hoc two-sample SPM{t} tests were conducted to compare the waveform of synergy 1-3 between the groups. Significant group differences indicate regions where SPM{t} values exceeded the critical threshold. Furthermore, for spatial component in synergy 1-3, one-way ANOVAs and post-hoc tests were conducted to test differences between the three groups in each muscle.

To determine the relationship between knee-related symptoms and muscle coordination in knee OA, we conducted a multiple linear regression analysis with KSS symptom scores as the dependent variable. The regression analyses included the walk-DMC and KAM impulse as independent variables, with adjustment variables for gait speed, age, and KL grade.

## Results

Table 1 presents the participant and gait characteristics in the healthy control and knee OA subgroups. The mild and severe knee OA groups had a higher body weight than the control group (control vs mild,  $p=0.010$ ; 95% confidence interval [CI], 1.56-13.76; vs severe,  $p=0.038$ ; 95%CI, 0.27-12.00); no difference was observed in age between groups ( $p=0.275$  to  $0.863$ ). The KSS symptom scores were also lower in mild and severe knee OA groups than in the control group (control vs mild,  $p<0.001$ ; 95%CI, -10.21 to -3.74; vs severe,  $p=0.038$ ; 95%CI, -12.00 to -0.27), but no

199 difference was observed between mild and severe knee OA groups ( $p=0.204$ ; 95%CI, -4.99 to 0.82).

200         The mild and severe knee OA groups had fewer synergies than the control group (Table 1). Supplemental  
201 file 2 shows the number of patients in terms of synergies in each group: most healthy controls had three to four  
202 synergies; mild knee OA, three; and severe knee OA, two to three. The walk-DMC was also lower in mild and severe  
203 knee OA groups compared with that of the control group (control vs mild,  $p=0.004$ ; 95%CI, -20.80 to -3.28; vs severe,  
204  $p<0.001$ ; 95%CI, -26.55 to -9.71). Additionally, the KAM impulse was higher in the severe knee OA group compared  
205 with that of both the control and mild knee OA groups (severe vs control,  $p<0.001$ ; 95%CI, 0.05-0.14; vs mild,  
206  $p<0.001$ ; 95%CI, 0.03-0.12). Gait speed did not differ between groups ( $p=0.171$  to 0.969).

207         Figure 1 shows EMG envelopes of individual muscles during gait cycle for the control, mild OA, and severe  
208 OA groups. Figure 2 shows the temporal component in synergy 1-3 in each group. With the one-way ANOVA using  
209 SPM for the temporal component, main effects were confirmed in synergy 1 and 3 (Supplemental file 3). In post-hoc  
210 two-sample SPM{t} tests, the early stance phase (18-21% of gait cycle) in synergy 1 was different between the healthy  
211 control and severe knee OA groups; the early swing phase in synergy 3 (60-75% of gait cycle) was different between  
212 the control and mild knee OA groups. Figure 3 indicates the results of spatial components between the three groups  
213 in synergy 1-3. In synergy 1, the weightings of BF and Gmed in severe knee OA were higher than those in healthy  
214 controls (in BF,  $p=0.002$ ; 95%CI, 0.12-0.57; in Gmed,  $p=0.030$ ; 95%CI, -0.36 to -0.02); the weighting of VL was  
215 lower in severe knee OA than in mild knee OA ( $p=0.009$ ; 95%CI, -0.41 to -0.05). In synergy 3, the weightings of TA  
216 in knee OA groups were higher than those in healthy controls (control vs mild,  $p<0.001$ ; 95%CI, 0.29-0.75; vs severe,

$p=0.003$ ; 95%CI, 0.10-0.54); the weighting of GL was lower in mild knee OA than in healthy controls ( $p=0.019$ ; 95%CI, -0.59 to -0.04).

Multiple linear regression analysis showed that the walk-DMC (Beta [B], 0.13;  $p=0.023$ ; 95%CI, 0.02-0.25) was independently associated with the KSS symptom score in knee OA after adjusting for the covariates, excluding the KAM impulse and gait speed (Table 2).

## Discussion

To our knowledge, this study is the first to clarify the differences in muscle synergy of knee OA severities during walking and the association of muscle coordination with knee-related symptoms. In partial agreement with our hypothesis, the number of synergy and walk-DMC were lower in mild and severe knee OA groups compared with the values in the healthy control group, but did not differ between the knee OA groups. This result suggests that muscle coordination between multiple EMG activities in knee OA deteriorated. Additionally, a lower walk-DMC (the loss of muscle coordination during walking) was associated with severe knee-related symptoms in knee OA, supporting our hypothesis. These findings suggested that the loss of muscle coordination was an abnormal gait characteristic in knee OA, and its decrease was associated with more severe symptoms.

Furthermore, patients with knee OA had fewer muscle synergies during walking compared with that of the healthy controls. Generally, the number of muscle synergies in normal walking is four to five [12, 30]. Most patients

with knee OA had three synergies during gait, which decreased as the severity of knee OA increased. Previous studies [31-33] have shown that muscle synergies decreased in patients with neurological and musculoskeletal disorders [19, 34], including those with painful knee OA. There are currently no studies which have assessed the walk-DMC in patients with knee OA; however, a previous study reported a decline in walk-DMC with increasing severity of neurological impairment in patients with cerebral palsy [27]. Our results agreed that as the severity of a patient's impairment increased the walk-DMC decreased.

The results of the temporal component indicated that differences between groups were in the early stance phase of synergy 1 and early swing phase of synergy 3. Analysis of the spatial component showed higher BF and lower Gmed activities in severe knee OA in the early stance phase of synergy 1 than those in healthy controls. Additionally, in the early swing phase of synergy 3, there were higher TA and lower GL weightings in the knee OA groups compared with that of the healthy controls. Taken together, the lack of muscle coordination during walking in knee OA reflects altered muscle activity patterns during early stance and swing phases resulting from excessive and scanty EMG signals, respectively, in muscles that play a major role in each phase.

Muscle activity of the BF in the early stance is high in knee OA [7, 35, 36]. An increased lateral knee muscle activity is protective against cartilage loss [10], suggesting that higher BF activity is a compensatory adaptation to medial knee joint stress. Meanwhile, decreased Gmed activity in stance phase increases medial knee joint stress [37]. Decreased contribution of the Gmed in stance limb causes pelvic drop in contralateral swing limb and, consequently, increased KAM and worsening symptoms [38, 39]. Therefore, neuromuscular re-adaptation of the Gmed is necessary

for loss of muscle coordination in the early stance in patients with knee OA. Furthermore, knee OA groups had higher TA and lower GL weightings in the early swing phase of synergy 3 compared with that of the healthy controls. As TA muscle activity in the early swing phase plays a role in lifting the forefoot from the ground [40], excessive muscle activity of TA accompanied by relatively reduced GL activity could contribute to toe clearance during the swing phase. This finding suggests that alteration of ankle muscle coordination is also a compensatory adaptation in knee OA.

The important finding of this study was that knee-related symptom severities in patients with knee OA were associated with lower muscle coordination, but not mechanical loading of the knee. This is the first study to demonstrate the relationship between pain and muscle coordination during walking in patients with knee OA. For pain-related muscle activity changes, acute pain induced by hypertonic saline injection did not change muscle coordination [41, 42], whereas patients with femoroacetabular impingement and protracted pain had poor muscle coordination despite no kinematic changes [19]. These findings could help interpret chronic pain in musculoskeletal disorders due to poor muscle coordination. Chronic knee OA pain and changes in morphology and blood flow in the brain are closely related [23, 43], suggesting an interaction between changes in the central nervous system and decreased muscle coordination. In contrast, although the KAM impulse was higher in severe knee OA than in healthy controls, our results ruled out the association between knee-related symptom and KAM impulse. Higher KAM impulse in severe knee OA was associated with worsening knee-related symptoms, whereas no association was found in mild knee OA [44]. Since half the knee OA patients had a mild form of the disease, KAM impulse may not have been associated with knee-related symptoms. As a clinical indication, improving muscle co-contraction by training

intervention may relieve knee-related symptoms [21]. Although training strategies that improve muscle synergy during walking should be developed, it should be emphasized that muscle synergy is a changeable factor.

This study had several limitations. First, the cross-sectional design hindered our ability to clarify whether knee OA caused poor muscle coordination during walking. Thus, future studies should examine the association between knee OA progression and altered muscle coordination, focusing on knee-related symptoms. Second, the measured number of muscles was limited to seven in the symptomatic lower limb. The muscle synergy analysis highly depends on the measured muscle. Therefore, to better understand muscle coordination in knee OA, trunk and contralateral lower limb muscles should be included.

In conclusion, the number of muscle synergies were lower in mild and severe cases of knee OA compared with those in the control group. Altered muscle coordination for specific muscles was prominent in the early stance and swing phases of severe and mild OA, respectively. A lower walk-DMC (the loss of muscle coordination during walking) was independently associated with knee-related symptoms. Therefore, understanding the muscle coordination mechanism behind gait abnormalities could lead to improved therapeutic interventions for patients with knee OA. Future studies should focus on the association between altered muscle coordination and knee OA progression to gain greater insight into their correlation regarding knee-related symptoms.

## **Declarations**

289     **Funding:**

290     This study was supported by the JSPS KAKENHI Grant-in-Aid for Scientific Research (18H03164 and 20K19376).

291

292     **Conflicts of interest:**

293     Authors declare no conflicts of interest.

294

295     **Availability of data and material**

296     Data will be made available on request.

297

298     **Code availability**

299     Not applicable.

300

301     **Authors' contributions**

302     All authors have made substantial contributions to the conception and design of the study, revising it critically for

303     important intellectual content, and final approval of the version to be submitted. The specific contributions of each

304     author are as follows. (1) Analysis and interpretation of data: MT, JU, MoY, and NI. (2) Article drafting: MT, JU, MoY,

305     and NI.

306

**Ethics approval:**

All study procedures were approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (R3014) and were conducted in accordance with the principles of the Declaration of Helsinki.

**Consent to participate and consent for publication:**

Written informed consent for participation and the use of data was obtained from all participants.

**Acknowledgements:**

The authors would like to thank all staff and patients for their participation in this study. We would like to thank Editage ([www.editage.jp](http://www.editage.jp)) for English language editing.

**References**

1. Saxby DJ, Lloyd DG (2017) Osteoarthritis year in review 2016: mechanics. Osteoarthritis Cartilage 25 (2):190-198. <https://doi.org/10.1016/j.joca.2016.09.023>
2. Boeckesteijn RJ, van Gerven J, Geurts ACH, Smulders K (2022) Objective gait assessment in individuals with knee osteoarthritis using inertial sensors: A systematic review and meta-analysis. Gait Posture 98:109-120. <https://doi.org/10.1016/j.gaitpost.2022.09.002>

- 325 3. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S (2002) Dynamic load at baseline can predict  
326 radiographic disease progression in medial compartment knee osteoarthritis. *Ann Rheum Dis* 61 (7):617-622.
- 327 4. Kito N, Shinkoda K, Yamasaki T, Kanemura N, Anan M, Okanishi N, Ozawa J, Moriyama H (2010) Contribution  
328 of knee adduction moment impulse to pain and disability in Japanese women with medial knee osteoarthritis.  
329 *Clin Biomech (Bristol, Avon)* 25 (9):914-919. <https://doi.org/10.1016/j.clinbiomech.2010.06.008>
- 330 5. Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, Zhang Y, Almagor O, Belisle L, Hayes  
331 K, Sharma L (2015) External knee adduction and flexion moments during gait and medial tibiofemoral disease  
332 progression in knee osteoarthritis. *Osteoarthritis Cartilage* 23 (7):1099-1106.  
333 <https://doi.org/10.1016/j.joca.2015.02.005>
- 334 6. Lewek MD, Rudolph KS, Snyder-Mackler L (2004) Control of frontal plane knee laxity during gait in patients  
335 with medial compartment knee osteoarthritis. *Osteoarthritis Cartilage* 12 (9):745-751.  
336 <https://doi.org/10.1016/j.joca.2004.05.005>
- 337 7. Schmitt LC, Rudolph KS (2007) Influences on knee movement strategies during walking in persons with medial  
338 knee osteoarthritis. *Arthritis Rheum* 57 (6):1018-1026. <https://doi.org/10.1002/art.22889>
- 339 8. Zeni JA, Rudolph K, Higginson JS (2010) Alterations in quadriceps and hamstrings coordination in persons with  
340 medial compartment knee osteoarthritis. *J Electromyogr Kinesiol* 20 (1):148-154.  
341 <https://doi.org/10.1016/j.jelekin.2008.12.003>
- 342 9. Hubley-Kozey CL, Hill NA, Rutherford DJ, Dunbar MJ, Stanish WD (2009) Co-activation differences in lower

- limb muscles between asymptomatic controls and those with varying degrees of knee osteoarthritis during walking. Clin Biomech (Bristol, Avon) 24 (5):407-414. <https://doi.org/10.1016/j.clinbiomech.2009.02.005>
10. Hodges PW, van den Hoorn W, Wrigley TV, Hinman RS, Bowles KA, Cicuttini F, Wang Y, Bennell K (2016) Increased duration of co-contraction of medial knee muscles is associated with greater progression of knee osteoarthritis. Man Ther 21:151-158. <https://doi.org/10.1016/j.math.2015.07.004>
11. Heiden TL, Lloyd DG, Ackland TR (2009) Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait. Clin Biomech (Bristol, Avon) 24 (10):833-841. <https://doi.org/10.1016/j.clinbiomech.2009.08.005>
12. Ivanenko YP, Poppele RE, Lacquaniti F (2004) Five basic muscle activation patterns account for muscle activity during human locomotion. J Physiol 556 (Pt 1):267-282. <https://doi.org/10.1113/jphysiol.2003.057174>
13. d'Avella A, Bizzi E (2005) Shared and specific muscle synergies in natural motor behaviors. Proc Natl Acad Sci U S A 102 (8):3076-3081. <https://doi.org/10.1073/pnas.0500199102>
14. Torres-Oviedo G, Ting LH (2007) Muscle synergies characterizing human postural responses. J Neurophysiol 98 (4):2144-2156. <https://doi.org/10.1152/jn.01360.2006>
15. Tang L, Li F, Cao S, Zhang X, Wu D, Chen X (2015) Muscle synergy analysis in children with cerebral palsy. J Neural Eng 12 (4):046017. <https://doi.org/10.1088/1741-2560/12/4/046017>
16. Cheung VC, Turolla A, Agostini M, Silvoni S, Bennis C, Kasi P, Paganoni S, Bonato P, Bizzi E (2012) Muscle synergy patterns as physiological markers of motor cortical damage. Proc Natl Acad Sci U S A 109 (36):14652-

14656. <https://doi.org/10.1073/pnas.1212056109>

17. Kubota K, Yokoyama M, Onitsuka K, Kanemura N (2023) The investigation of an analysis method for co-activation of knee osteoarthritis utilizing normalization of peak dynamic method. *Gait Posture* 101:48-54. <https://doi.org/10.1016/j.gaitpost.2023.01.021>

18. Kubota K, Hanawa H, Yokoyama M, Kita S, Hirata K, Fujino T, Kokubun T, Ishibashi T, Kanemura N (2021) Usefulness of Muscle Synergy Analysis in Individuals With Knee Osteoarthritis During Gait. *IEEE Trans Neural Syst Rehabil Eng* 29:239-248. <https://doi.org/10.1109/TNSRE.2020.3043831>

19. Diamond LE, Van den Hoorn W, Bennell KL, Wrigley TV, Hinman RS, O'Donnell J, Hodges PW (2017) Coordination of deep hip muscle activity is altered in symptomatic femoroacetabular impingement. *J Orthop Res* 35 (7):1494-1504. <https://doi.org/10.1002/jor.23391>

20. Astephen Wilson JL, Deluzio KJ, Dunbar MJ, Caldwell GE, Hubley-Kozey CL (2011) The association between knee joint biomechanics and neuromuscular control and moderate knee osteoarthritis radiographic and pain severity. *Osteoarthritis Cartilage* 19 (2):186-193. <https://doi.org/10.1016/j.joca.2010.10.020>

21. Preece SJ, Jones RK, Brown CA, Cacciatore TW, Jones AK (2016) Reductions in co-contraction following neuromuscular re-education in people with knee osteoarthritis. *BMC Musculoskelet Disord* 17 (1):372. <https://doi.org/10.1186/s12891-016-1209-2>

22. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C (2015) Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 23 (7):1043-1056.

379 <https://doi.org/10.1016/j.joca.2015.02.163>

380 23. Liao X, Mao C, Wang Y, Zhang Q, Cao D, Seminowicz DA, Zhang M, Yang X (2018) Brain gray matter  
381 alterations in Chinese patients with chronic knee osteoarthritis pain based on voxel-based morphometry.  
382 Medicine 97 (12):e0145. <https://doi.org/10.1097/MD.00000000000010145>

383 24. Yamagata M, Taniguchi M, Tateuchi H, Kobayashi M, Ichihashi N (2021) The effects of knee pain on knee  
384 contact force and external knee adduction moment in patients with knee osteoarthritis. J Biomech 123:110538.  
385 <https://doi.org/10.1016/j.jbiomech.2021.110538>

386 25. Lee DD, Seung HS (1999) Learning the parts of objects by non-negative matrix factorization. Nature 401  
387 (6755):788-791. <https://doi.org/10.1038/44565>

388 26. Schwartz MH, Rozumalski A, Steele KM (2016) Dynamic motor control is associated with treatment outcomes  
389 for children with cerebral palsy. Dev Med Child Neurol 58 (11):1139-1145. <https://doi.org/10.1111/dmcn.13126>

390 27. Steele KM, Rozumalski A, Schwartz MH (2015) Muscle synergies and complexity of neuromuscular control  
391 during gait in cerebral palsy. Dev Med Child Neurol 57 (12):1176-1182. <https://doi.org/10.1111/dmcn.12826>

392 28. Taniguchi N, Matsuda S, Kawaguchi T, Tabara Y, Ikezoe T, Tsuboyama T, Ichihashi N, Nakayama T, Matsuda F,  
393 Ito H (2015) The KSS 2011 reflects symptoms, physical activities, and radiographic grades in a Japanese  
394 population. Clin Orthop Relat Res 473 (1):70-75. <https://doi.org/10.1007/s11999-014-3650-6>

395 29. Pataky TC, Robinson MA, Vanrenterghem J (2013) Vector field statistical analysis of kinematic and force  
396 trajectories. J Biomech 46 (14):2394-2401. <https://doi.org/10.1016/j.jbiomech.2013.07.031>

- 397 30. Lacquaniti F, Ivanenko YP, Zago M (2012) Patterned control of human locomotion. *J Physiol* 590 (10):2189-  
398 2199. <https://doi.org/10.1113/jphysiol.2011.215137>
- 399 31. Clark DJ, Ting LH, Zajac FE, Neptune RR, Kautz SA (2010) Merging of healthy motor modules predicts reduced  
400 locomotor performance and muscle coordination complexity post-stroke. *J Neurophysiol* 103 (2):844-857.  
401 <https://doi.org/10.1152/jn.00825.2009>
- 402 32. Falaki A, Huang X, Lewis MM, Latash ML (2017) Motor equivalence and structure of variance: multi-muscle  
403 postural synergies in Parkinson's disease. *Exp Brain Res* 235 (7):2243-2258. [https://doi.org/10.1007/s00221-](https://doi.org/10.1007/s00221-017-4971-y)  
404 [017-4971-y](https://doi.org/10.1007/s00221-017-4971-y)
- 405 33. Hashiguchi Y, Ohata K, Osako S, Kitatani R, Aga Y, Masaki M, Yamada S (2018) Number of Synergies Is  
406 Dependent on Spasticity and Gait Kinetics in Children With Cerebral Palsy. *Pediatric Physical Therapy* 30  
407 (1):34-38. <https://doi.org/10.1097/Pep.0000000000000460>
- 408 34. Allison K, Salomoni SE, Bennell KL, Wrigley TV, Hug F, Vicenzino B, Grimaldi A, Hodges PW (2018) Hip  
409 abductor muscle activity during walking in individuals with gluteal tendinopathy. *Scand J Med Sci Sports* 28  
410 (2):686-695. <https://doi.org/10.1111/sms.12942>
- 411 35. Liikavainio T, Bragge T, Hakkarainen M, Karjalainen PA, Arokoski JP (2010) Gait and muscle activation changes  
412 in men with knee osteoarthritis. *Knee* 17 (1):69-76. <https://doi.org/10.1016/j.knee.2009.05.003>
- 413 36. Rutherford DJ, Hubley-Kozey CL, Stanish WD (2013) Changes in knee joint muscle activation patterns during  
414 walking associated with increased structural severity in knee osteoarthritis. *J Electromyogr Kinesiol* 23 (3):704-

- 415 711. <https://doi.org/10.1016/j.jelekin.2013.01.003>
- 416 37. Yamagata M, Tateuchi H, Asayama A, Ichihashi N (2022) Influence of lower-limb muscle inactivation on medial  
417 and lateral knee contact forces during walking. Med Eng Phys 108:103889.  
418 <https://doi.org/10.1016/j.medengphy.2022.103889>
- 419 38. Mundermann A, Dyrby CO, Andriacchi TP (2005) Secondary gait changes in patients with medial compartment  
420 knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum 52 (9):2835-2844.  
421 <https://doi.org/10.1002/art.21262>
- 422 39. Chang A, Hayes K, Dunlop D, Song J, Hurwitz D, Cahue S, Sharma L (2005) Hip abduction moment and  
423 protection against medial tibiofemoral osteoarthritis progression. Arthritis Rheum 52 (11):3515-3519.  
424 <https://doi.org/10.1002/art.21406>
- 425 40. Sutherland DH (2001) The evolution of clinical gait analysis part I: kinesiological EMG. Gait Posture 14 (1):61-  
426 70. [https://doi.org/10.1016/s0966-6362\(01\)00100-x](https://doi.org/10.1016/s0966-6362(01)00100-x)
- 427 41. van den Hoorn W, Hodges PW, van Dieen JH, Hug F (2015) Effect of acute noxious stimulation to the leg or  
428 back on muscle synergies during walking. J Neurophysiol 113 (1):244-254.  
429 <https://doi.org/10.1152/jn.00557.2014>
- 430 42. Gizzi L, Muceli S, Petzke F, Falla D (2015) Experimental Muscle Pain Impairs the Synergistic Modular Control  
431 of Neck Muscles. PLoS One 10 (9):e0137844. <https://doi.org/10.1371/journal.pone.0137844>
- 432 43. Iwabuchi SJ, Xing Y, Cottam WJ, Drabek MM, Tadjibaev A, Fernandes GS, Petersen KK, Arendt-Nielsen L,

433 Graven-Nielsen T, Valdes AM, Zhang W, Doherty M, Walsh D, Auer DP (2020) Brain perfusion patterns are  
434 altered in chronic knee pain: a spatial covariance analysis of arterial spin labelling MRI. Pain 161 (6):1255-1263.  
435 <https://doi.org/10.1097/j.pain.0000000000001829>

436 44. Hall M, Bennell KL, Wrigley TV, Metcalf BR, Campbell PK, Kasza J, Paterson KL, Hunter DJ, Hinman RS  
437 (2017) The knee adduction moment and knee osteoarthritis symptoms: relationships according to radiographic  
438 disease severity. Osteoarthritis Cartilage 25 (1):34-41. <https://doi.org/10.1016/j.joca.2016.08.014>

439

Table 1. Participant and gait characteristics in the healthy control and knee OA subgroups

|                        | Control      | Mild OA       | Severe OA          |
|------------------------|--------------|---------------|--------------------|
|                        | n = 19       | n = 24        | n = 29             |
| Age, years             | 68.3 (8.6)   | 70.5 (6.4)    | 71.5 (6.6)         |
| Height, cm             | 152.0 (3.8)  | 156.7 (5.7) * | 152.8 (7.6)        |
| Body weight, kg        | 49.0 (5.7)   | 56.7 (10.2) * | 55.2 (8.0) †       |
| KSS symptom score, /25 | 23.7 (1.9)   | 16.7 (4.7) ** | 14.6 (5.2) ††      |
| Number of synergies, n | 3.37 (0.45)  | 3.00 (0.42) * | 2.76 (0.58) ††     |
| Walk-DMC, %            | 100.0 (10.0) | 88.0 (9.5) ** | 81.9 (14.5) ††     |
| KAM impulse, Nm S/kg   | 0.17 (0.05)  | 0.18 (0.07)   | 0.26 (0.07) ††, ‡‡ |
| Gait speed, m/s        | 1.69 (0.31)  | 1.51 (0.29)   | 1.53 (0.35)        |

\*  $p < 0.05$  and \*\*  $p < 0.01$ , significantly difference compared with the healthy group

†  $p < 0.05$  and ††  $p < 0.01$ , significantly difference compared with the healthy group

‡‡  $p < 0.01$ , significantly difference compared with the mild OA group

Abbreviation: OA, osteoarthritis; KSS, knee scoring system; DMC, dynamic motor control; KAM, knee adduction

moment.

448 Table 2. Association of the gait characteristics with knee symptom

|             | B     | $\beta$ | <i>p</i> -value | 95% CI          |
|-------------|-------|---------|-----------------|-----------------|
| Walk-DMC    | 0.13  | 0.34    | 0.023           | [0.02, 0.25]    |
| KAM impulse | -8.74 | -0.13   | 0.393           | [-29.11, 11.63] |
| Gait speed  | 1.80  | 0.11    | 0.420           | [-2.65, 6.25]   |
| Age         | 0.04  | 0.06    | 0.698           | [-0.18, 0.27]   |
| KL grade    | 0.35  | 0.06    | 0.716           | [-1.56, 2.26]   |

449 A multiple linear regression analysis was conducted with KSS symptom scores as the dependent variable, and walk-  
450 DMC, KAM impulse, and gait speed as independent variables, with adjustment variables for age and KL grade.

451  
452 Abbreviation: CI, confidence interval; DMC, dynamic motor control; KAM, knee adduction moment; KL, Kellgren-  
453 Lawrence.

454

## Figure legends

Figure 1. EMG envelopes of individual muscles during gait cycle for the control, mild OA, and severe OA groups

The EMG signal corresponding to one gait cycle was extracted based on the spatiotemporal gait parameters of the heel strike of targeted leg and the following heel strike of same leg. The EMG signals were processed using the band-pass filter (zero-phase-lag 4th-order Butterworth filter from 20 to 450 Hz) and rectified. Then, the rectified EMG signals were low-pass filtered at 10 Hz using zero-phase lag 4th-order Butterworth filter to create EMG envelopes. The EMG envelopes of individual muscles were temporally normalized to 100 samples representing a percent gait cycle (1–100 %) by interpolation and normalized by the maximal value during the gait cycles. The EMG envelopes were concatenated for three gait cycles.

Figure 2. The temporal component in synergy 1-3

The temporal component in synergy 1-3. The waves indicate the activation coefficient calculated from the EMG signals during gait cycle. The temporal component (each solid line) indicates the mean value across all participants in each group.

Figure 3. The spatial component in synergy 1-3

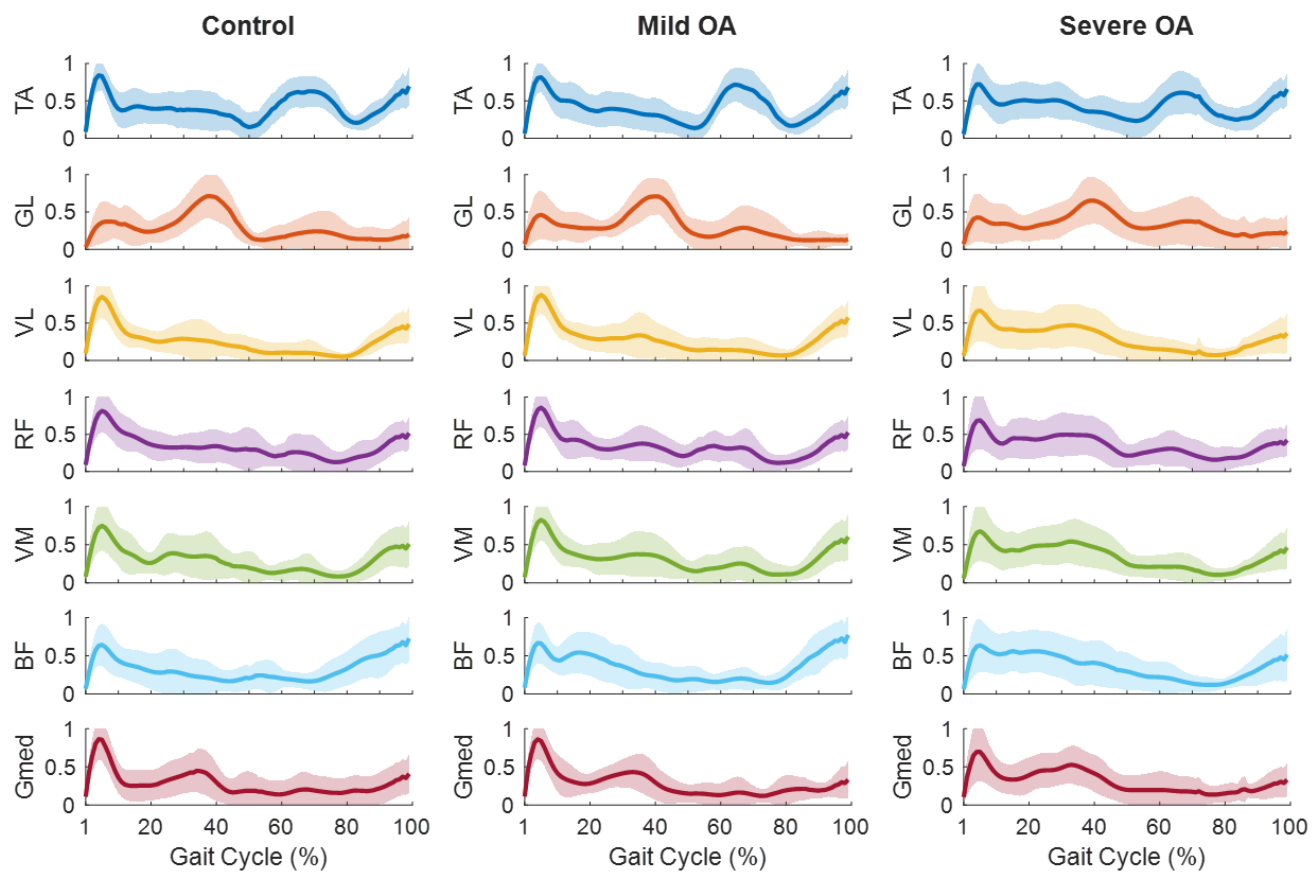
473 The spatial component (each bar) indicates the mean value across all participants in each group.

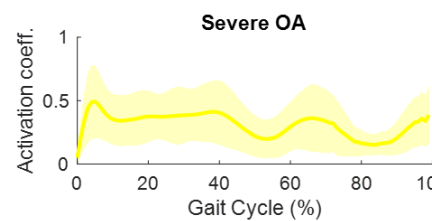
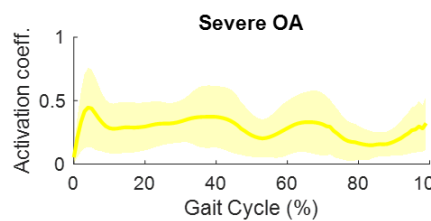
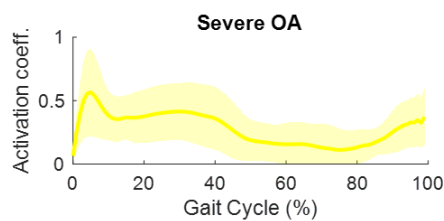
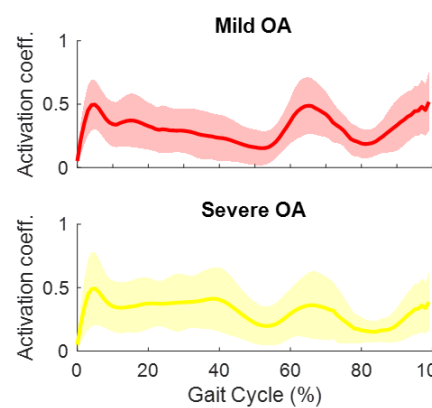
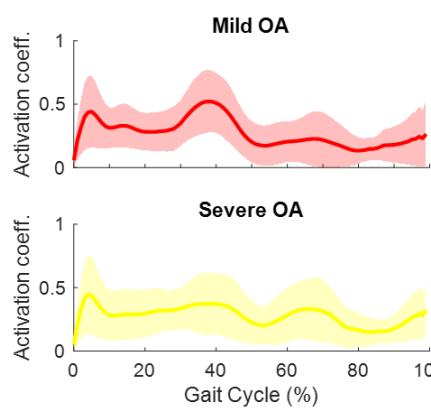
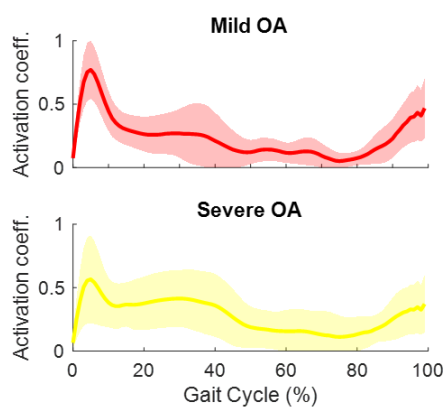
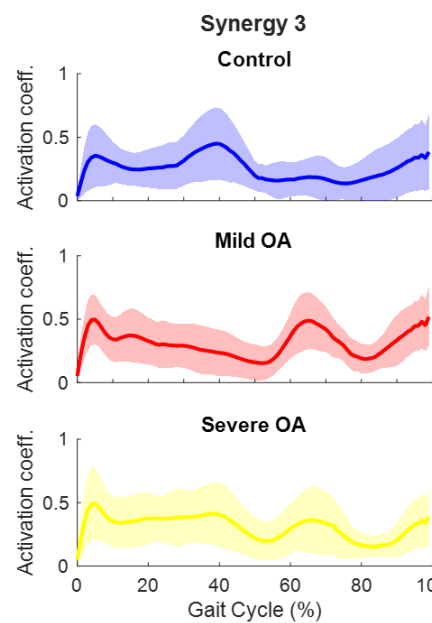
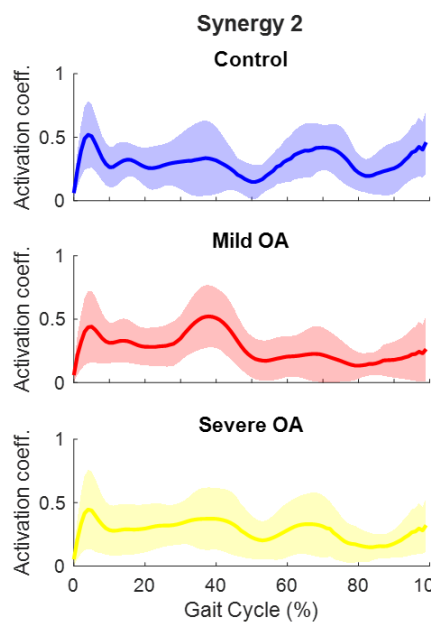
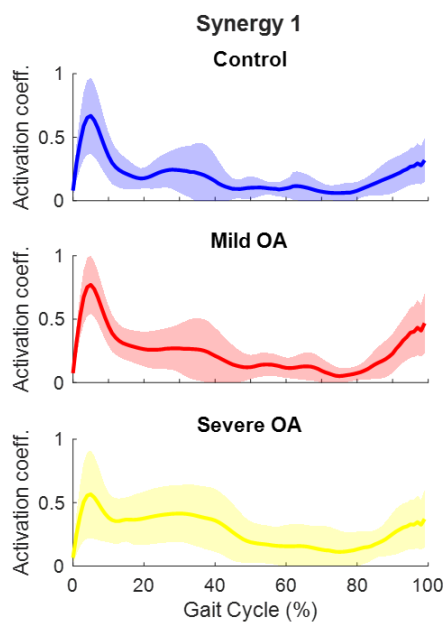
474 \*  $p < 0.05$  and \*\*  $p < 0.01$ , significant difference between the healthy and mild OA groups

475 †  $p < 0.05$  and ††  $p < 0.01$ , significant difference between the healthy and severe OA groups

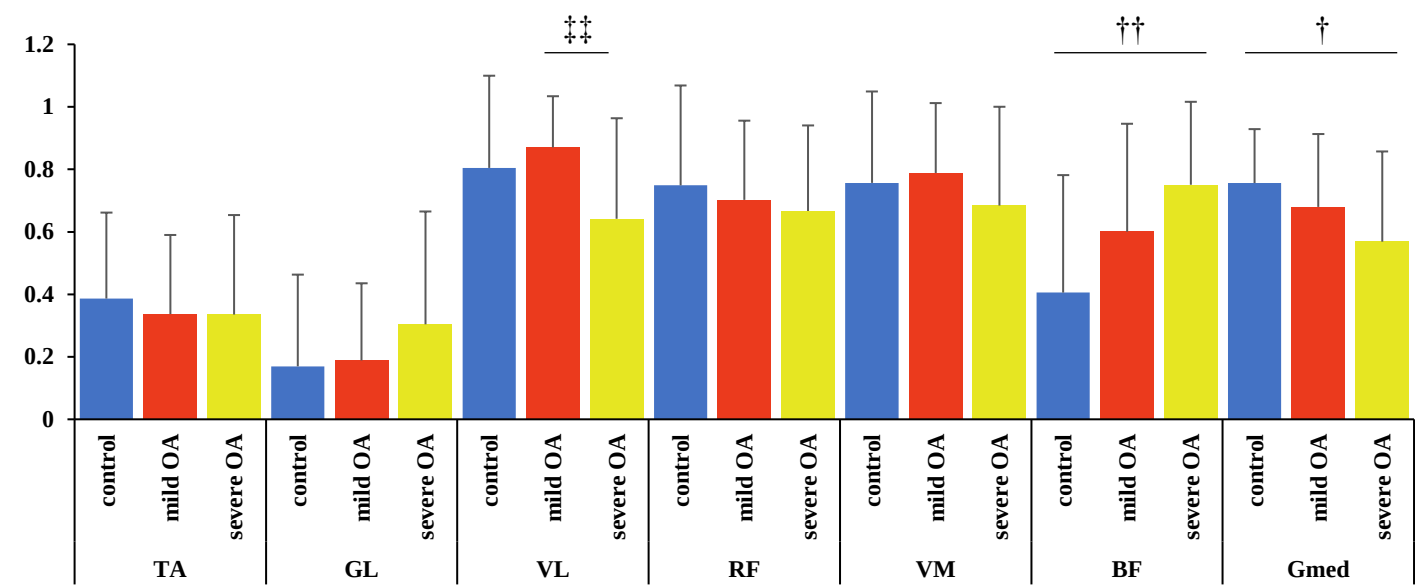
476 ‡  $p < 0.05$  and ‡‡  $p < 0.01$ , significant difference between the mild and severe OA groups

477

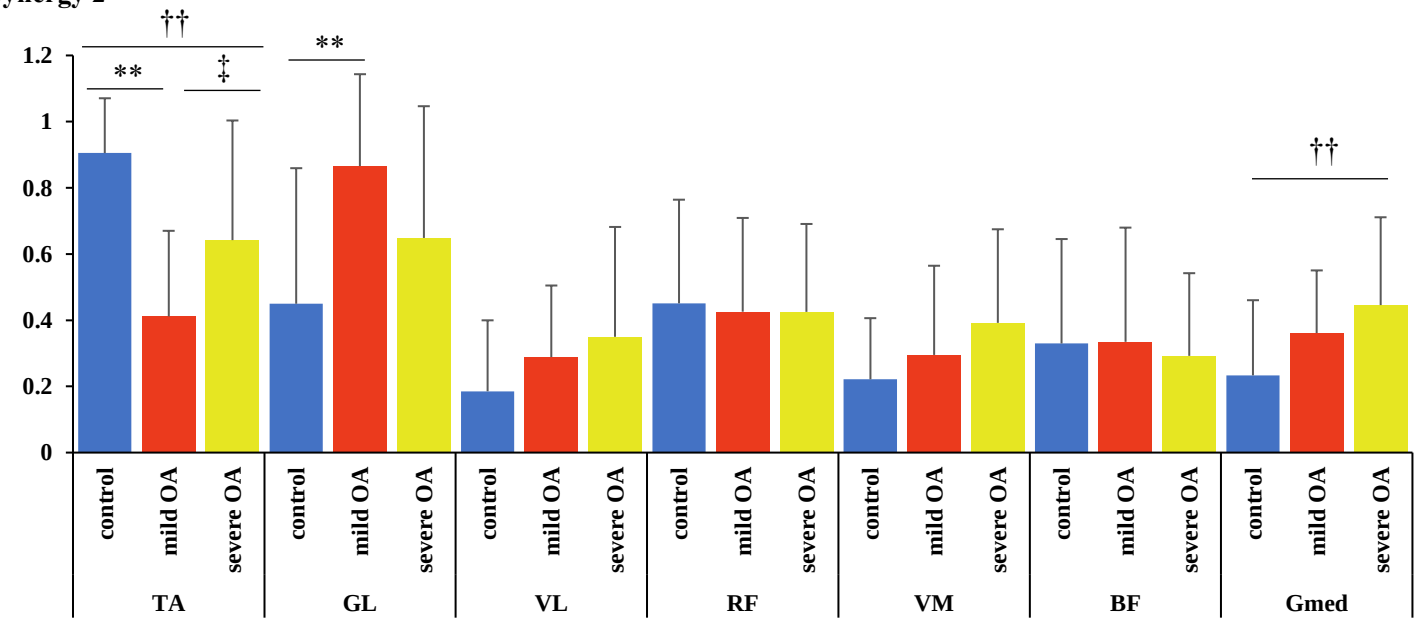




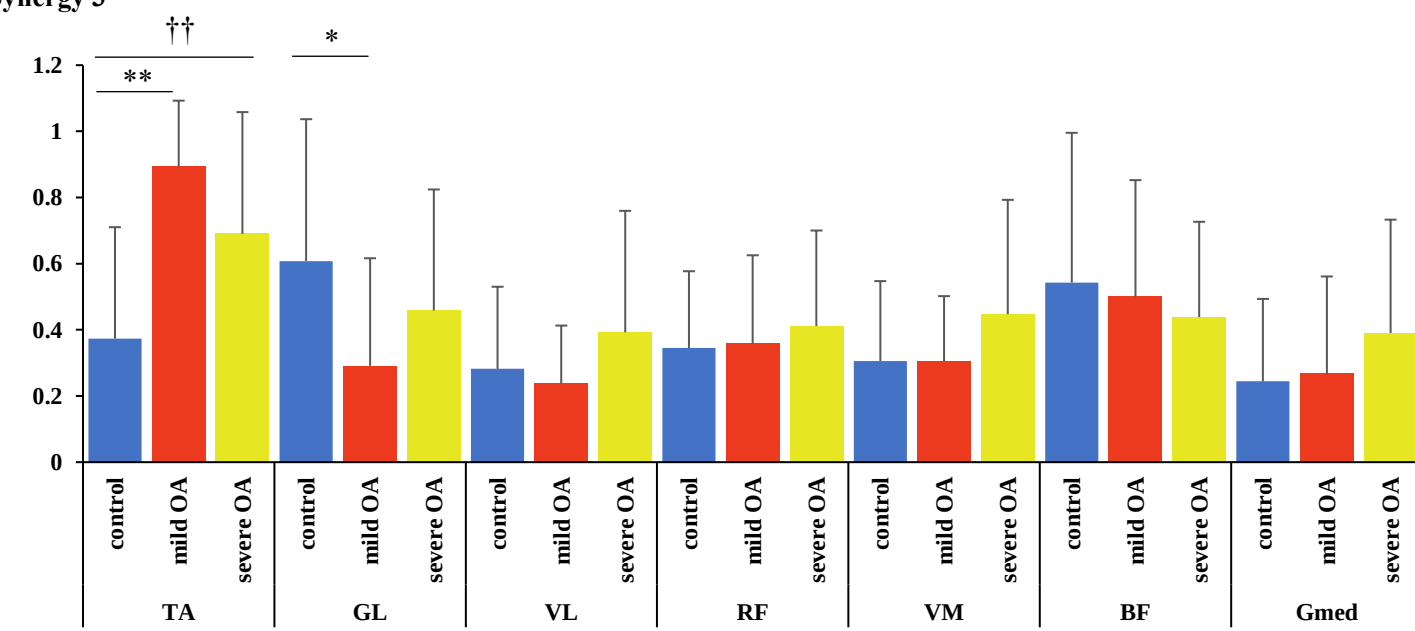
Synergy 1



Synergy 2



Synergy 3

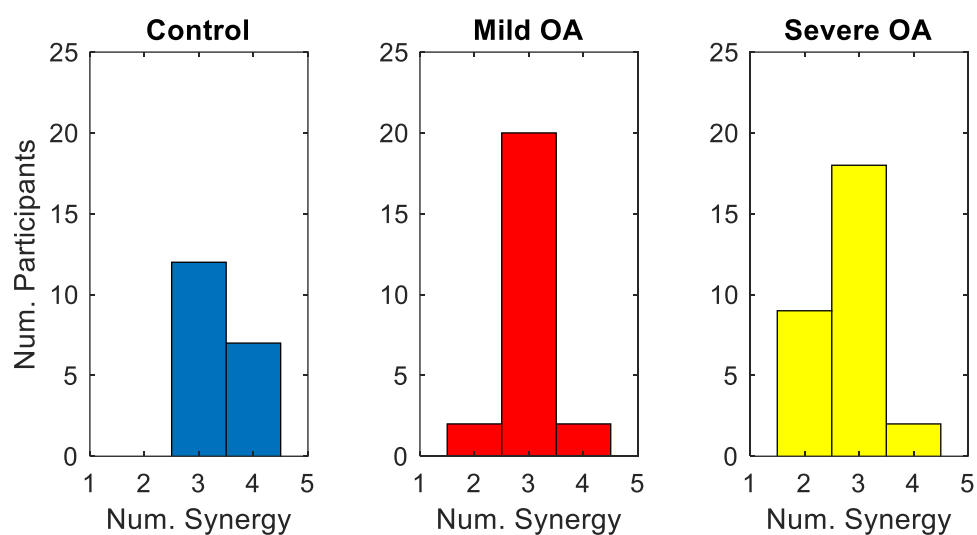


## Supplemental file 1

### Sensor locations for EMG acquisition in each muscle

| Muscle                       | Sensor location                                                                                             |
|------------------------------|-------------------------------------------------------------------------------------------------------------|
| Gluteus medius (Gmed)        | Middle point of the line between the greater trochanter and the crista iliac                                |
| Vastus lateralis (VL)        | Two thirds distal of the line between the anterior spina iliac superior and the lateral side of the patella |
| Rectus femoris (RF)          | Middle point of the line between the anterior spina iliac superior and superior border of the patella       |
| Vastus medialis (VM)         | 80% distal of the line between the anterior spina iliac superior and the medial knee joint space            |
| Biceps femoris (BF)          | Middle point of the line between the ischial tuberosity and the lateral epicondyle of the tibia             |
| Tibialis anterior (TA)       | One thirds proximal of the line between the tip of the fibula and the tip of the medial malleolus           |
| Gastrocnemius lateralis (GL) | One thirds proximal of the line between the head of the fibula and the heel.                                |

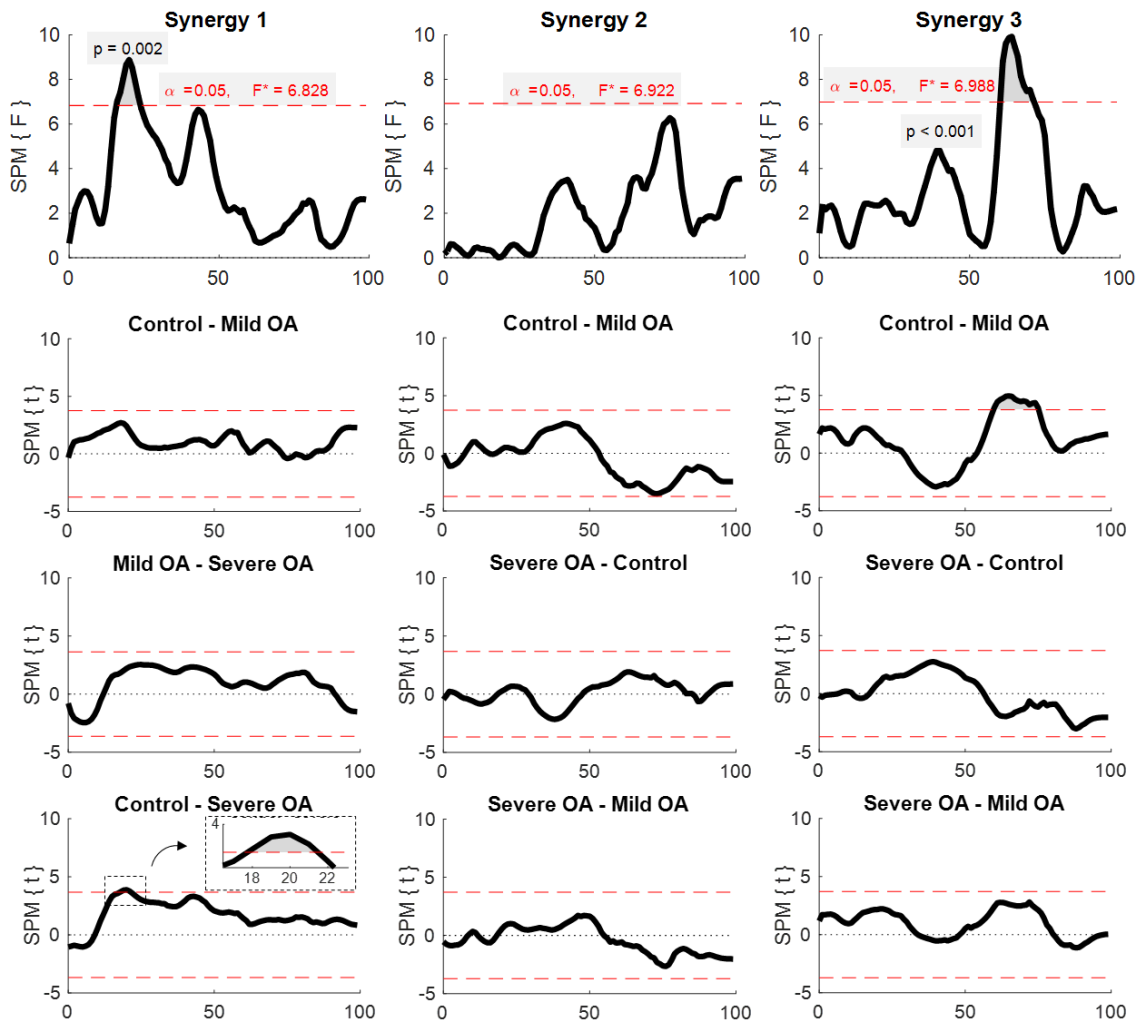
Supplemental file 2



Histogram on number of synergies and participants in each group

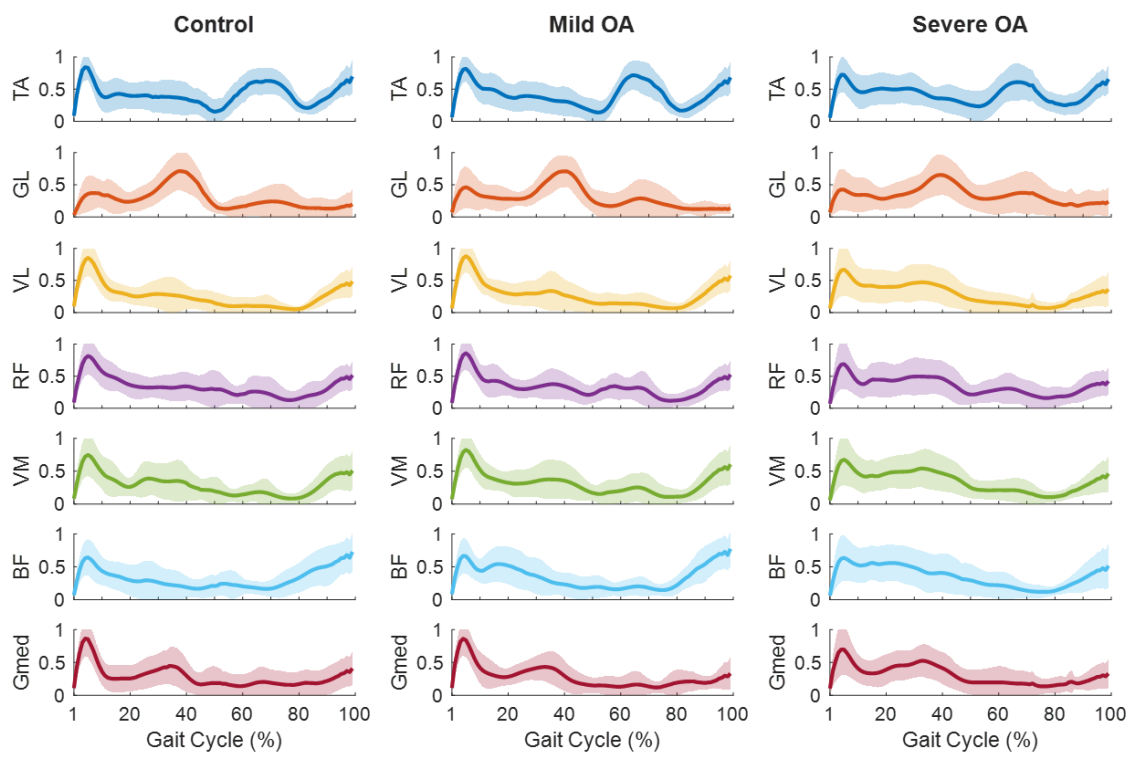
The horizontal axis indicates the number of synergies, and the vertical axis indicates the number of participants. Abbreviation: OA, osteoarthritis.

### Supplemental file 3

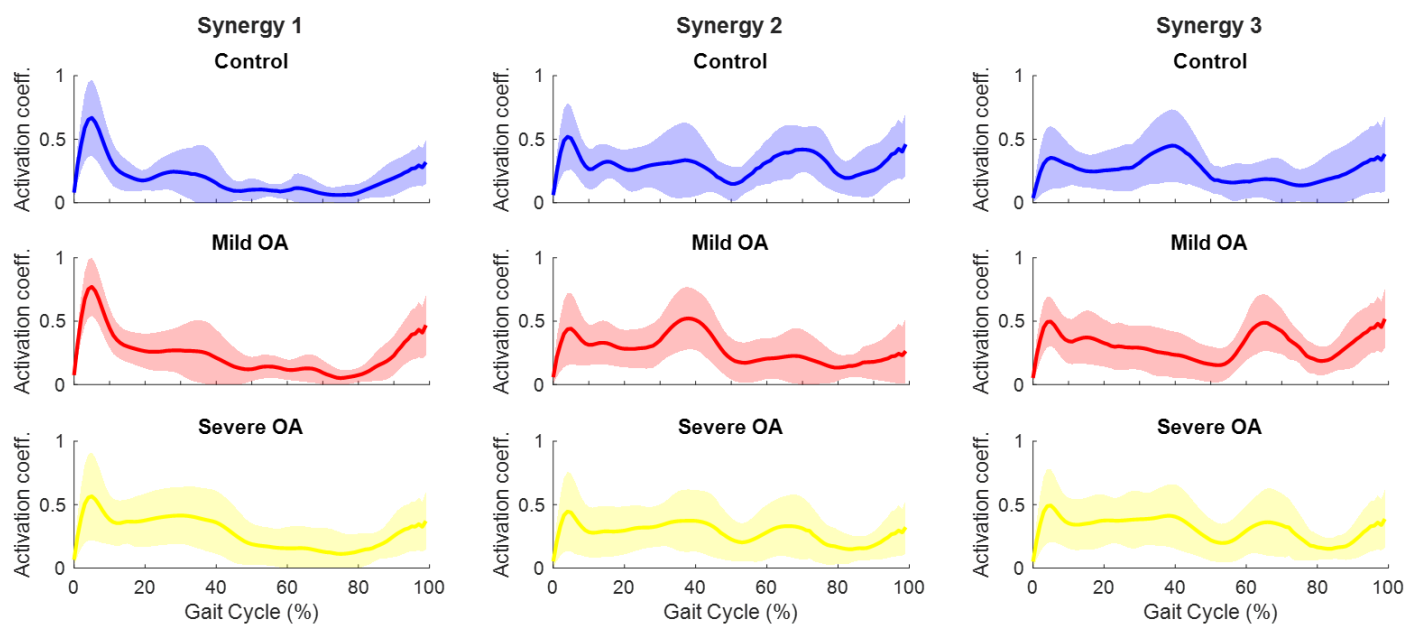


The results of one-way analysis of variances and post hoc tests using the statistical parametric mapping against the temporal component in synergy 1-3

The main effects and significant group differences indicate regions where SPM{F} and SPM{t} values exceeded the critical threshold (dashed line). Abbreviation: OA, osteoarthritis; SPM, statistical parametric mapping.

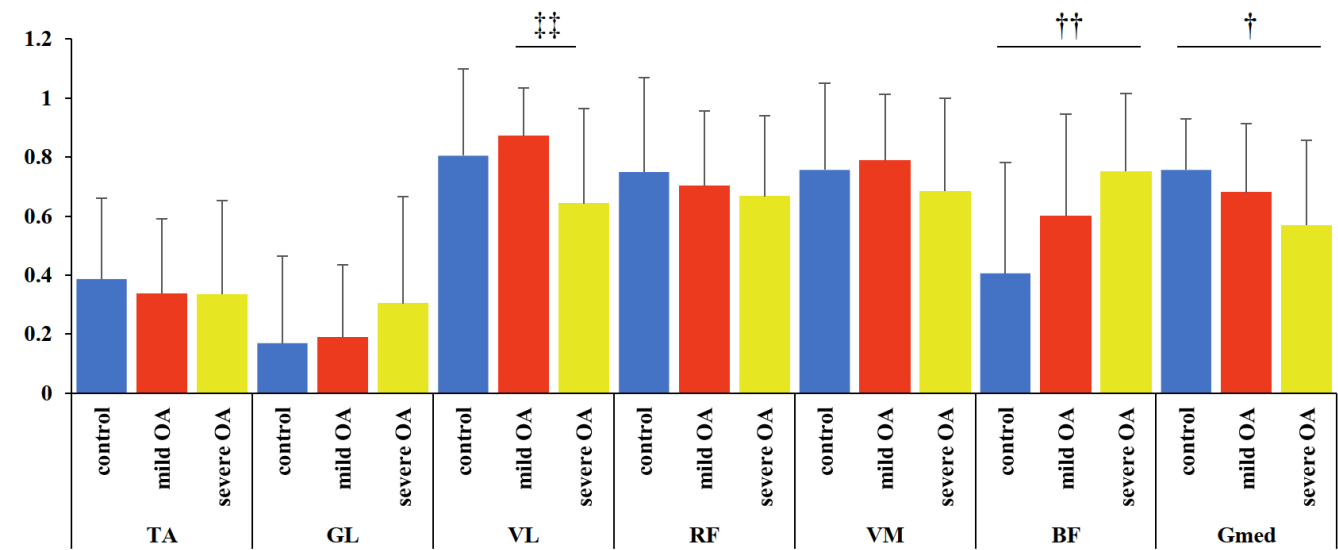


**Figure 1**

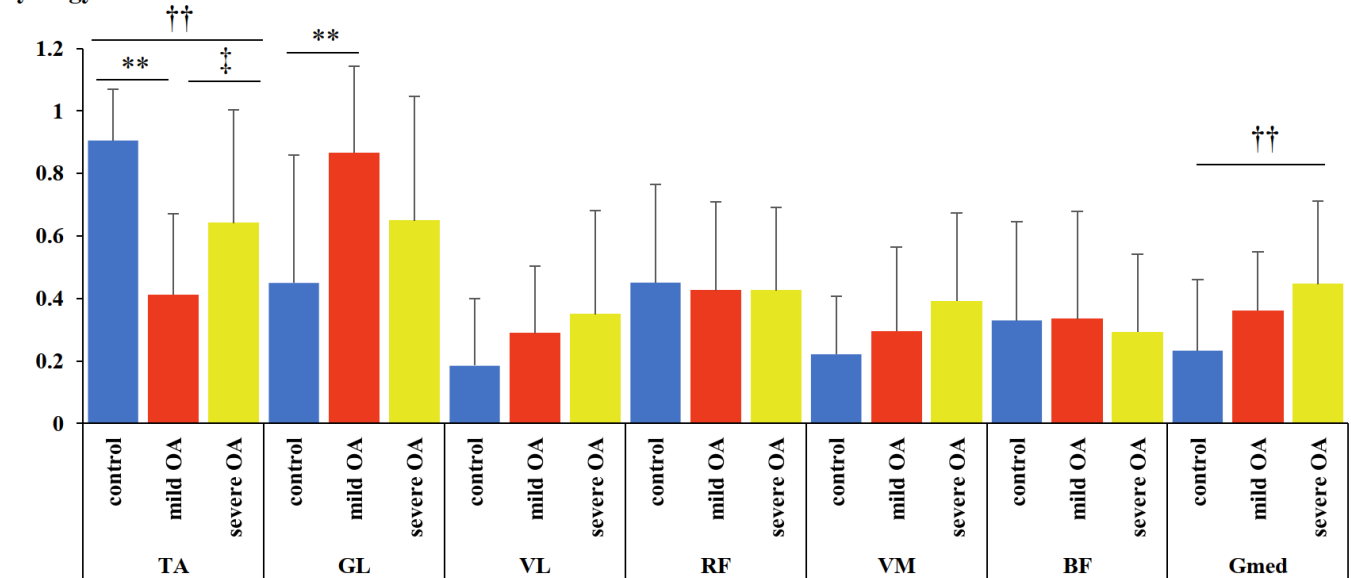


**Figure 2**

Synergy 1



Synergy 2



Synergy 3

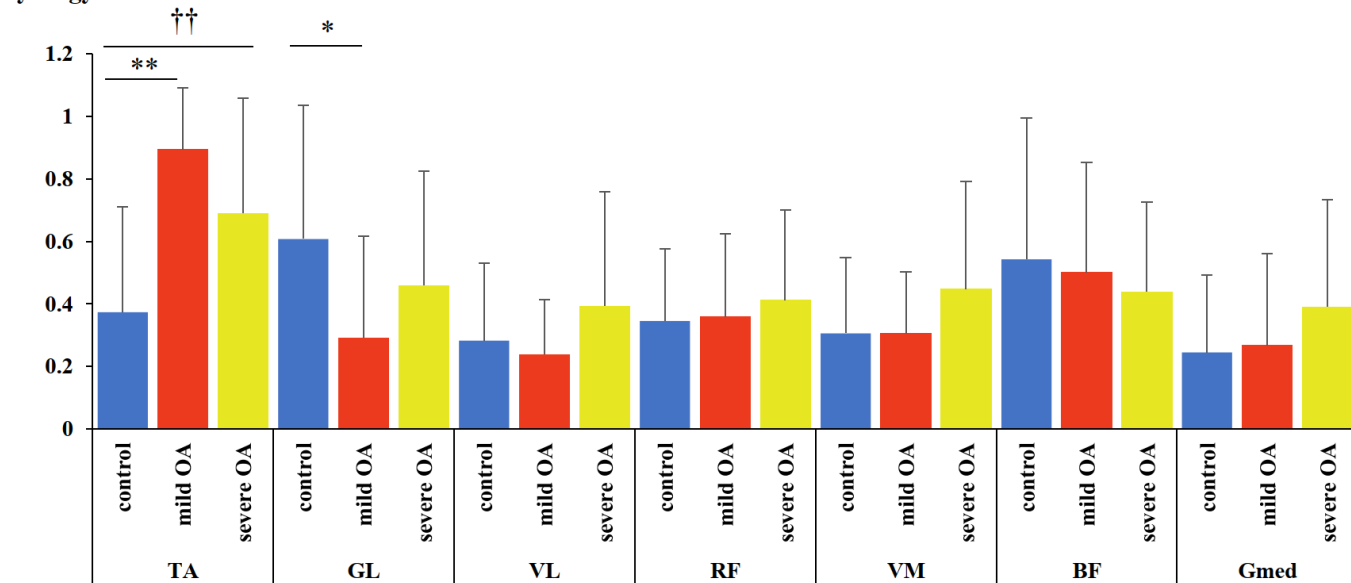


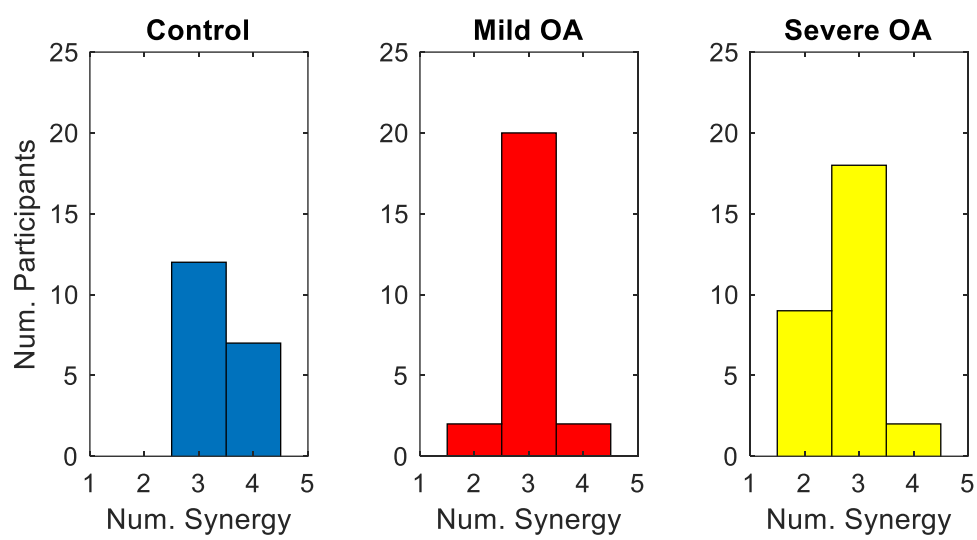
Figure 3

## Supplemental file 1

### Sensor locations for EMG acquisition in each muscle

| Muscle                       | Sensor location                                                                                             |
|------------------------------|-------------------------------------------------------------------------------------------------------------|
| Gluteus medius (Gmed)        | Middle point of the line between the greater trochanter and the crista iliac                                |
| Vastus lateralis (VL)        | Two thirds distal of the line between the anterior spina iliac superior and the lateral side of the patella |
| Rectus femoris (RF)          | Middle point of the line between the anterior spina iliac superior and superior border of the patella       |
| Vastus medialis (VM)         | 80% distal of the line between the anterior spina iliac superior and the medial knee joint space            |
| Biceps femoris (BF)          | Middle point of the line between the ischial tuberosity and the lateral epicondyle of the tibia             |
| Tibialis anterior (TA)       | One thirds proximal of the line between the tip of the fibula and the tip of the medial malleolus           |
| Gastrocnemius lateralis (GL) | One thirds proximal of the line between the head of the fibula and the heel.                                |

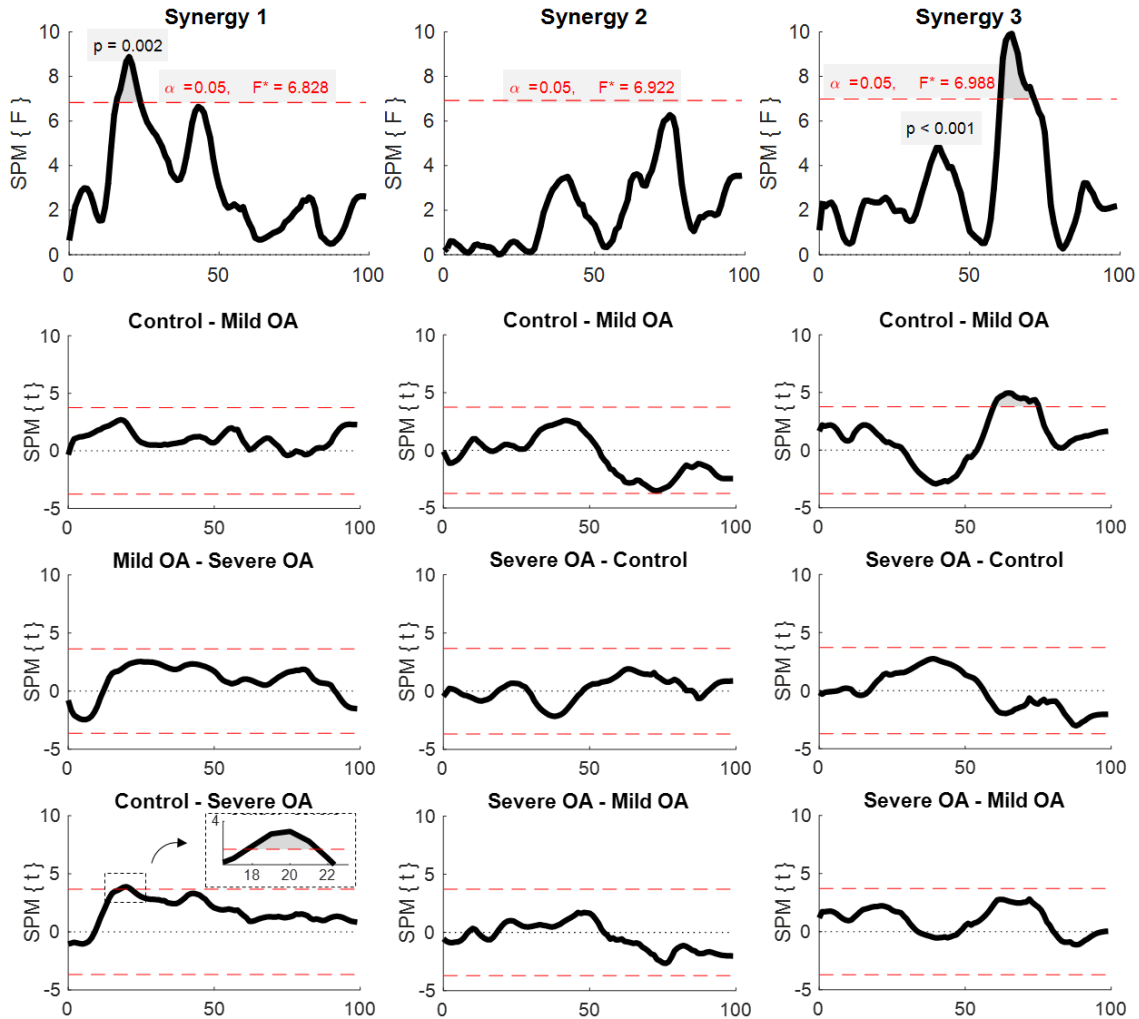
Supplemental file 2



Histogram on number of synergies and participants in each group

The horizontal axis indicates the number of synergies, and the vertical axis indicates the number of participants. Abbreviation: OA, osteoarthritis.

### Supplemental file 3



The results of one-way analysis of variances and post hoc tests using the statistical parametric mapping against the temporal component in synergy 1-3

The main effects and significant group differences indicate regions where SPM{F} and SPM{t} values exceeded the critical threshold (dashed line). Abbreviation: OA, osteoarthritis; SPM, statistical parametric mapping.