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Investigating Aging-Related Changes in the Coordination of Agonist and Antagonist Muscles Using Fuzzy Entropy and Mutual Information

Wenbo Sun [1,2,†], Jingtao Liang [1,2,†], Yuan Yang [1,2], Yuanyu Wu [1,2], Tiebin Yan [3] and Rong Song [1,2,*]

1 Key Laboratory of Sensing Technology and Biomedical Instrument of Guang Dong province, School of Engineering, Sun Yat-sen University, Guangzhou 510275, China; sunwb3@mail2.sysu.edu.cn (W.S.); leungjingtau@icloud.com (J.L.); ykbpy@126.com (Y.Y.); luby47@yeah.net (Y.W.)

2 Guangdong Provincial Engineering and Technology Center of Advanced and Portable Medical Devices, Guangzhou 510275, China

3 Department of Rehabilitation Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510120, China; Dr.Yan@126.com

* Correspondence: songrong@mail.sysu.edu.cn; Tel.: +86-20-3933-2148

† These authors contributed equally to this work.

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Abstract: Aging alters muscular coordination patterns. This study aimed to investigate aging-related changes in the coordination of agonist and antagonist muscles from two aspects, the activities of individual muscles and the inter-muscular coupling. Eighteen young subjects and 10 elderly subjects were recruited to modulate the agonist muscle activity to track a target during voluntary isometric elbow flexion and extension. Normalized muscle activation and fuzzy entropy (FuzzyEn) were applied to depict the activities of biceps and triceps. Mutual information (MI) was utilized to measure the inter-muscular coupling between biceps and triceps. The agonist activation decreased and the antagonist activation increased significantly during elbow flexion and extension with aging. FuzzyEn values of agonist electromyogram (EMG) were similar between the two age groups. FuzzyEn values of antagonist EMG increased significantly with aging during elbow extension. MI decreased significantly with aging during elbow extension. These results indicated increased antagonist co-activation and decreased inter-muscular coupling with aging during elbow extension, which might result from the reduced reciprocal inhibition and the recruitment of additional cortical-spinal pathways connected to biceps. Based on FuzzyEn and MI, this study provided a comprehensive understanding of the mechanisms underlying the aging-related changes in the coordination of agonist and antagonist muscles.

Keywords: aging; muscular coordination; fuzzy entropy; mutual information

1. Introduction

Compared with young individuals, elderly individuals usually exhibit deteriorations in movement performance, such as decreased mechanical output [1–3], slower movement speed [4], and increased movement error [4]. Such deteriorations in sensorimotor function were suggested to partly result from complex modifications in the neuromuscular system in response to neurodegeneration process [4]. Since the agonist and antagonist muscles are the primarily contributing muscles in the control of joints, the coordination of agonist and antagonist muscles during human movements has been widely studied for a better understanding of the degenerative sensorimotor function along

aging process. It was suggested that a decline in the joint torque during isometric maximal voluntary contraction (MVC) could be attributed to the decreased agonist activation with aging [3]. It has also been demonstrated that the reduced rate of motor learning with aging might be associated with different levels of antagonist activation between young and elderly adults [5]. Muscle co-activation, *i.e.*, the simultaneous contraction of agonist and antagonist muscles, was utilized to characterize aging-related changes. Increased antagonist co-activation with aging that was found during human movements, such as isometric MVC [1,2], walking [6], and balanced standing [7], was suggested to be related to declined maximal force capacity [1,2], increased metabolic cost [6], and greater movement variability [7]. Although aging-related changes in the coordination of agonist and antagonist muscles has been found in previous works [1–7], challenges still remain in interpreting the neurological mechanisms of these altered coordination patterns [2,4,7].

The activities of individual muscles are adopted to investigate muscular coordination. When investigating aging-related declined joint torque during isometric MVC, the root mean square (RMS) of surface electromyogram (EMG) signals was used to represent the agonist and antagonist muscle activities [1]. In the study of the leg-stiffness in relation to aging, the peak of RMS was regarded as the pre-activity of corresponding muscle during downward stepping [8]. The linear envelope of EMG signals is another important measure of the muscle activity. Greater variability of EMG linear envelopes during walking in elderly adults was suggested to indicate more instable control of muscle activities with aging [9]. Recently, the entropy-based measures, such as sample entropy (SamEn), approximate entropy (ApEn), and fuzzy entropy (FuzzyEn) were introduced to reflect non-linear features of muscle activities. Zhang and Zhou [10] proposed SamEn in the analysis of EMG signals for detecting the onset of muscle activity. SamEn analysis of surface EMG signals has been used to estimate the activities of respiratory muscles [11] and trunk muscles [12] against the electrocardiography (ECG) interference and was found to be more robust than RMS [11,12]. ApEn analysis of surface EMG signals has been adopted to evaluate the function and behavior of muscles in patients with neuromuscular disorders [13,14]. FuzzyEn was first developed by Chen *et al.* [15]. The application of FuzzyEn in analyzing the surface EMG signals in our previous efforts [16,17] suggested that the decreased FuzzyEn in elderly subjects and post-stroke subjects might be attributed to the aging- and stroke- induced reduction of firing rate and number of active motor units [16,17]. In addition, the comparisons of SamEn, ApEn and FuzzyEn analysis of both simulated and real surface EMG signals demonstrated that FuzzyEn is a more robust and consistent measure [16].

Another aspect, inter-muscular coupling, is also important in describing muscular coordination, which could reflect the mechanisms of neuromuscular control [18]. Cross-correlation is a traditional measure for quantifying inter-muscular coupling in the temporal domain. In the study of the aging effects on the anticipatory postural control, cross-correlation analysis between trunk flexor and extensor muscles was adopted to demonstrate a transition from the reciprocal activation pattern to a more co-activation pattern [19]. Coherence was introduced to quantify coupling in the frequency domain. Coherent activities of hand muscles were analyzed to gain insight into how aging influences common oscillatory drive during index finger abduction and pinch grip [20]. As neuromuscular activities are inherently non-linear [17,21], non-linear measures of coupling are important to investigate aging-related alterations in muscular coordination. Mutual information (MI) is a non-linear measure derived from information entropy, which was widely used to study the coupling in neuronal network [22]. Svendsen *et al*. [23] used MI to reflect the inter-muscular coupling of four forearm muscles during static and dynamic tracking tasks. Madeleine *et al.* [24] adopted MI to depict the functional connectivity among three sub-parts of fatiguing trapezius. The studies of aging-related changes in muscular coordination rarely involved MI analysis. This non-linear measure might potentially extend the interpretation of the inter-muscular coupling to the information domain.

In this literature, we aimed to investigate aging-related changes in the coordination of agonist and antagonist muscles from the activities of individual muscles and the inter-muscular coupling. Within a myoelectric-controlled interface (MCI), subjects were required to modulate the agonist muscle activity

to track a target during voluntary isometric elbow flexion and extension. MCI is a visual feedback tool, which could help the subjects modulate the muscle activities finely [25]. Normalized muscle activation and FuzzyEn were applied to depict the activities of biceps and triceps. MI was utilized to measure the inter-muscular coupling between biceps and triceps. Based on FuzzyEn and MI, this study might provide a comprehensive understanding of aging-related changes in the coordination of agonist and antagonist muscles.

2. Methods

2.1. Subjects

Eighteen healthy subjects (10 males and 8 females; mean age: 23.7 ± 1.8 years) and 10 elderly subjects (5 males and 5 females; mean age: 55 ± 6.4 years) without any neurological or motor disorders volunteered to join in this study after signing written informed consent, which was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University ([2013]C-096, 28 February 2013). All the subjects were right-handed.

2.2. Apparatus and Procedure

The experiment apparatus was showed in Figure 1a. Subjects were asked to sit in an adjustable chair with their dominant arm rested horizontally on the armrest. The armrest positioned the subjects with the elbow in 90° flexion and the shoulder in 90° abduction [26]. Subjects were asked to grasp a handle connected to the armrest. After the skin was shaved and cleaned with alcohol, two circular silver-silver chloride (Ag-AgCl) electrodes (diameter 10 mm, center-to-center distance 20 mm) were attached to the bellies of biceps and triceps. EMG signals were recorded by a customized EMG amplifier with a gain of 5000, sampled at 1000 Hz with 16-bit resolution (DAQ USB-6341, National Instrument Corporation, Austin, TX, USA) and processed and stored by a custom LabVIEW™ (LabVIEW 2012, National Instruments Corporation, Austin, TX, USA) program.

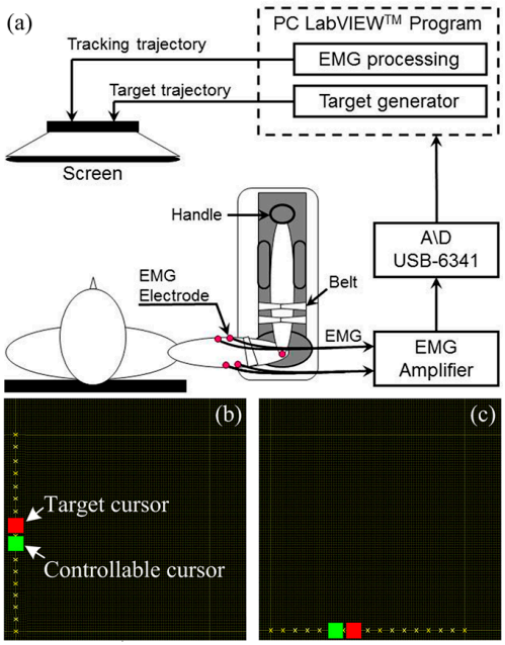

Figure 1. (**a**) Schematic diagram of the experimental setup; (**b**) Myoelectric-controlled interface during the elbow flexion task, in which the green square represented the controllable cursor, the red square represented the target cursor, and the yellow dashed line indicated target trajectory during elbow flexion; (**c**) Myoelectric-controlled interface during the elbow extension task, in which the yellow dashed line indicated target trajectory during elbow extension.

During the experiment, each subject was firstly required to perform isometric submaximal elbow flexion and extension several times. Then, three times of 5-s isometric MVC were performed for both elbow flexion and extension. The rest period between each trial was 2 min. The maximal EMG amplitude of biceps and triceps recorded during MVCs were stored to normalize the EMG signals of each muscle, respectively.

After MVC, subjects were required to modulate their agonist muscle activity to track a target during isometric elbow flexion and extension within a MCI. MCI was displayed in a screen in front of the subjects, in which there were two square cursors, a controllable cursor and a target cursor, displayed in a two-dimensional plane (Figure 1b,c). Activation of biceps and triceps were mapped to the Y-axis and X-axis of the MCI. The Y-coordinate of the controllable cursor represented the normalized biceps activation, and the X-coordinate of the controllable cursor represented the normalized triceps activation. During elbow flexion, biceps is agonist muscle and triceps is antagonist muscle. During elbow extension, triceps is agonist muscle and biceps is antagonist muscle. During tracking, the controllable cursor could reflect the normalized agonist activation and move along a single axis at a time, with the X-coordinate set at 0 in the elbow flexion task and the Y-coordinate set at 0 in the elbow extension task (Figure 1b,c). The target trajectory was designed as follows. In the elbow flexion task, target cursor moved at a constant speed along the Y-axis from the origin to the point (0, 15%), then returned to the origin in 10 s as a trial, and repeated this trial for three times in one performance. In the elbow extension task, target cursor moved at a constant speed along the X-axis from the origin to the point (15%, 0), then returned to the origin in 10 s as a trial, which was repeated for three times in one performance, too. In this study, 15% of the maximal EMG amplitude was picked to avoid muscle fatigue [25], and the desired mean activation level of agonist muscle during the tracking task was 7.5%. Each tracking task was performed 5 times, and a total of 10 performances were randomly arranged. There was at least a 30 s rest between two consecutive performances.

2.3. Data and Statistical Analysis

In the present study, in order to eliminate the individual differences [27], the normalized EMG linear envelopes were adopted to represent the normalized agonist and antagonist activation. EMG signals were band-pass filtered from 20 to 450 Hz, full-wave rectified, and low-pass filtered at 2 Hz [28], and finally normalized to the maximal EMG amplitude observed during the MVCs in LabVIEW^{TM}. FuzzyEn values of agonist and antagonist EMG, and MI were analyzed off-line in MATLAB (Matlab R2014a, MathWorks Inc., Natick, MA, USA).

FuzzyEn of a N sample time series $\{u(i)\colon 1 \leqslant i \leqslant N\}$ is computed as follows:

Given m, an m dimensional vector sequence could be formed as follows:

$$X_i^m = \{u(i), u(i+1) \cdots, u(i-m+1)\} - u_0(i), \ (i = 1, 2, \cdots, N-m+1;) \tag{1}$$

where the baseline of the vector sequence is $u_0(i) = \frac{1}{m}\sum_{j=0}^{m-1} u(i+j)$.

For every X_i^m, the distance d_{ij}^m between the two vectors X_i^m and X_j^m is defined as:

$$d_{ij}^m = max_{k\in(0,m-1)} \left| u(i+k) - u_0(j) - u(j+k) - \tfrac{1}{m}\sum_{j=0}^{m-1} u(i+j) \right|, \ (i, j = 1, 2, \cdots, N-m+1;\ i \neq j) \tag{2}$$

The definition of similarity degree between two vectors X_i^m and X_j^m is:

$$D_{ij}^m(n, r) = exp\left(-\left(\frac{d_{ij}^m}{r}\right)^n\right) \tag{3}$$

where r and n in Equation (3) determine the width and gradient of the boundary, respectively.

Define the function $\phi^m(n,r)$ as:

$$\phi^m(n,r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} ln(\frac{1}{N-m+1}\sum_{j=1,j\neq i}^{N-m+1} D_{ij}^m) \quad (4)$$

FuzzyEn is computed according to an equation as follows:

$$\text{FuzzyEn}(m,n,r,N) = ln\phi^m(n,r) - ln\phi^{m+1}(n,r) \quad (5)$$

Setting a suitable N, m, n and r is important for the calculation of FuzzyEn. According to our previous work [16,17], N = 1000, n = 2 and m = 2 were set in this study, and r = 0.15 was set as a fixed tolerance value that was dependent on the global standard deviation of the entire segment data, and this r value would not change among different analysis windows [11]. As the sampling rate of EMG data was 1000 Hz, mean FuzzyEn values of 10 s EMG data in a trial was calculated by averaging the FuzzyEn values of EMG data of each second.

MI was estimated between 10 s EMG data recorded from biceps and triceps. The data were normalized to (0, 1) and used to estimate MI through the following equation:

$$\text{MI} = \sum_{x_i,\, y_i}^{N} f_{XY}(x_i,\, y_i)\, log\frac{f_{XY}(x_i,\, y_i)}{f_X(x_i)\, f_Y(y_i)} \quad (6)$$

where f_{XY} was the joint cumulative density function of variables X (triceps EMG) and Y (Biceps EMG), and f_X and f_Y were the marginal cumulative density functions of X and Y. f_{XY} was estimated in kernel estimation, in which the scale kernel was $h^2 = [\frac{(N+1)}{N^{1.25}\sqrt{12}}]^2$ (let N = 10,000) [29].

The normalized agonist and antagonist activation, FuzzyEn values of agonist and antagonist EMG, and MI were averaged over five performances in each subject. The statistical analysis was conducted with SPSS21.0 (SPSS Inc., Chicago, IL, USA). All variables were reported as means ± standard deviation (SD) in the text and as means ± standard error (SE) in the figures. Two-way (group (young *vs.* elderly) × direction of contraction (flexion *vs.* extension)) analysis of variance (ANOVA) with repeated measures on the factor direction of contraction was performed for each variable. If the interaction between the group and the direction of contraction was significant, post-hoc analysis was then made between elbow flexion and elbow extension in each group, and between the young and elderly subjects for each direction of contraction, using t-tests. The significance level was set at 0.05.

3. Results

3.1. Normalized Agonist and Antagonist Activation

A graphical representation of the exemplar surface EMG signals of biceps and triceps recorded during the elbow flexion and extension task were showed in Figures 2 and 3, respectively. Figure 4a illustrated the mean normalized agonist activation during elbow flexion and extension in young and elderly subjects. Results showed the main effect of the group, with the normalized agonist activation being significantly higher in young subjects than in elderly subjects (F = 9.363, df = (1,26); p = 0.005; mean: 6.966 ± 0.117 % *vs.* 6.293 ± 0.157 %), while there was no main effect of direction, showing non-significant difference in the normalized agonist activation between elbow flexion and extension (F = 2.351, df = (1,26); $p > 0.25$; mean: 6.760 ± 0.139 % *vs.* 6.500 ± 0.139 %), and no significant interaction between group × direction of contraction (F = 0.374, df = (1,26); $p > 0.25$).

Figure 4b demonstrated the comparisons of the normalized antagonist activation during elbow flexion and extension between young and elderly subjects. Results showed the main effect of the group, with significantly lower normalized antagonist activation in young subjects than in elderly subjects (F = 43.428, df = (1,26); $p < 0.001$; mean: 1.182 ± 0.229 % *vs.* 3.925 ± 0. 307 %), while there was also a main effect of direction, showing significantly lower normalized antagonist

activation during elbow flexion than during elbow extension (F = 63.385, df = (1,26); $p < 0.001$; mean: 1.173 ± 0.271 % *vs.* 3.934 ± 0.271 %). The analysis on the normalized antagonist activation demonstrated a significant interaction between group × direction of contraction (F = 34.470, df = (1,26); $p < 0.001$). Post-hoc analysis showed that the normalized antagonist activation was significantly lower in young subjects than in elderly subjects during both elbow flexion (t = −3.080, df = 26; $p = 0.005$; mean: 0.820 ± 0.461 % *vs.* 1.528 ± 0.760 %) and elbow extension (t = −6.538, df = 26; $p < 0.001$; mean: 1.545 ± 0.931 % *vs.* 6.323 ± 2.877 %), and the normalized antagonist activation was significantly lower during elbow flexion than during elbow extension in both young subjects (t = −2.808, df = 17; $p = 0.012$; mean: 0.820 ± 0.461 % *vs.* 1.545 ± 0.931 %) and elderly subjects (t = −5.874, df = 9; $p < 0.001$; mean: 1.528 ± 0. 760 % *vs.* 6.323 ± 2.877 %).

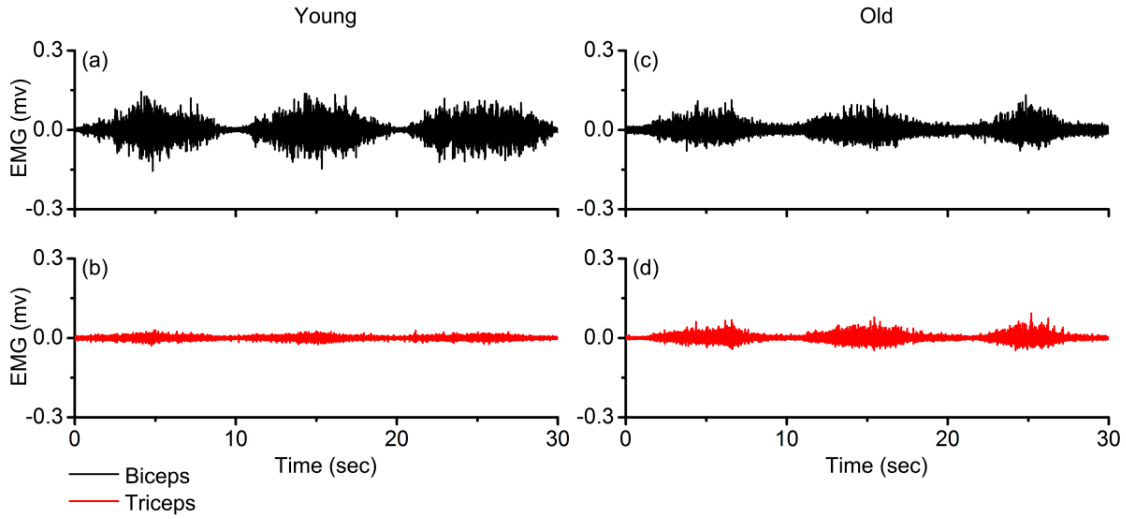

Figure 2. Typical electromyogram (EMG) data of biceps and triceps recorded during the elbow flexion task in one performance. Each performance contained three trials. (**a**) Biceps EMG of a young subject; (**b**) Triceps EMG of a young subject; (**c**) Biceps EMG of an elderly subject; (**d**) Triceps EMG of an elderly subject. Notes: Young, young subjects; Old, elderly subjects.

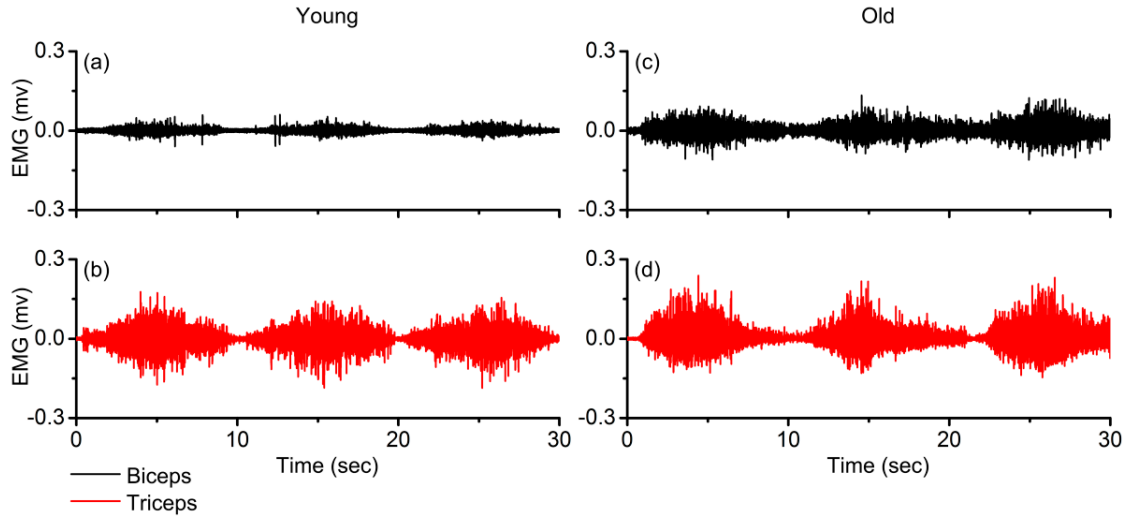

Figure 3. Typical EMG data of biceps and triceps recorded during the elbow extension task in one performance, each performance contained three trials. (**a**) Biceps EMG of a young subject; (**b**) Triceps EMG of a young subject; (**c**) Biceps EMG of an elderly subject; (**d**) Triceps EMG of an elderly subject. Notes: Young, young subjects; Old, elderly subjects.

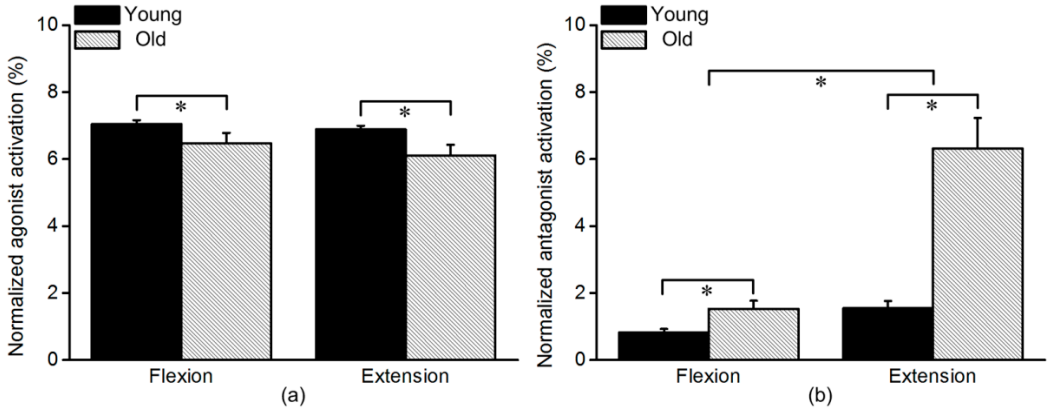

Figure 4. Mean normalized agonist (**a**) and antagonist (**b**) activation during elbow flexion and extension. Notes: Young: young subjects; Old: elderly subjects. * Statistically significant difference ($p < 0.05$).

3.2. FuzzyEn Values of Agonist and Antagonist EMG

Figure 5a showed the mean FuzzyEn values of agonist EMG during elbow flexion and extension in young and elderly subjects. Results demonstrated no main effect of the group, showing non-significant difference in FuzzyEn values of agonist EMG between young and elderly subjects (F = 2.921, df = (1,26); $p = 0.099$; mean: 0.269 ± 0.017 *vs.* 0.212 ± 0.023). Besides, there was no main effect of direction, showing non-significant difference in FuzzyEn values of agonist EMG between elbow flexion and extension (F = 3.504, df = (1,26); $p = 0.073$; mean: 0.220 ± 0.020 *vs.* 0.263 ± 0.020), and no significant interaction between group × direction of contraction (F = 0.011, df = (1,26); $p = 0.916$).

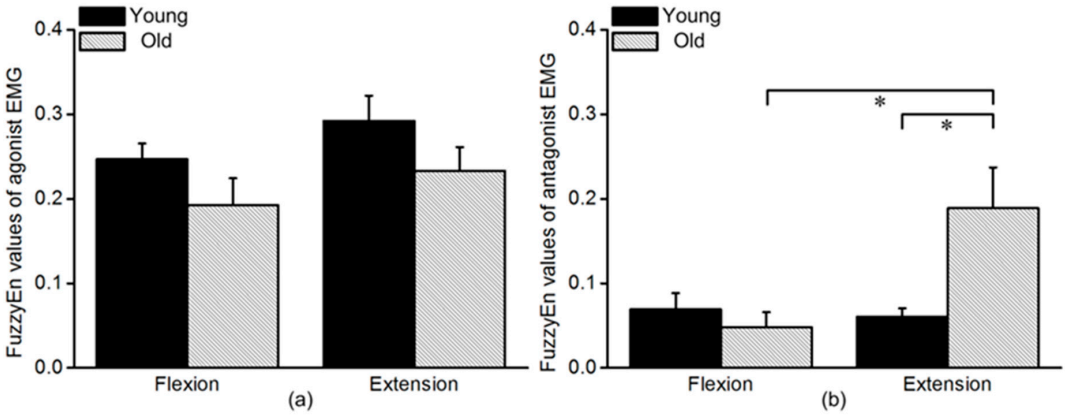

Figure 5. Mean FuzzyEn values of agonist (**a**) and antagonist (**b**) EMG during elbow flexion and extension. Notes: Young: young subjects; Old: elderly subjects. * Statistically significant difference ($p < 0.05$).

As in Figure 5b, there was no main effect of the group on FuzzyEn values of antagonist EMG, showing non-significant difference in FuzzyEn values of antagonist EMG between young and elderly subjects (F = 3.397, df = (1,26); $p = 0.077$; mean: 0.065 ± 0.014 *vs.* 0.118 ± 0.019). Moreover, there was a main effect of direction on FuzzyEn values of antagonist EMG, showing FuzzyEn values of antagonist EMG significantly lower during elbow flexion than during elbow extension (F = 15.135, df = (1,26); $p = 0.001$; mean: 0.058 ± 0.017 *vs.* 0.125 ± 0.017). In addition, there was a significant interaction between group × direction of contraction (F = 19.418, df = (1,26); $p < 0.001$). Post-hoc analysis demonstrated that FuzzyEn values of antagonist EMG were significantly lower in young subjects than in elderly subjects during elbow extension (t = −3.384, df = 26; $p = 0.002$; mean: 0.060 ± 0.042 *vs.* 0.189 ± 0.153),

and were significantly lower during elbow flexion than during elbow extension in elderly subjects (t = −4.350, df = 9; $p = 0.002$; mean: 0.048 ± 0.056 *vs*. 0.189 ± 0.153). There was no significant difference in FuzzyEn values of antagonist EMG between young and elderly subjects during elbow flexion, and between elbow flexion and extension in young subjects.

3.3. Mutual Information

As in Figure 6, there was no main effect of the group on MI, showing non-significant difference in MI between young and elderly subjects (F = 4.153, df = (1,26); $p = 0.052$; mean: 0.097 ± 0.009 *vs*. 0.066 ± 0.012). There was also no main effect of direction on MI, indicating the similar MI between elbow flexion and extension (F = 2.619, df = (1,26); $p = 0.118$; mean: 0.069 ± 0.011 *vs*. 0.094 ± 0.011). A significant interaction between group × direction of contraction was found (F = 7.647, df = (1,26); $p = 0.010$). Post-hoc analysis indicated that MI was significantly higher in young subjects than in elderly subjects during elbow extension (t = 2.654, df = 26; $p = 0.013$; mean: 0.132 ± 0.088 *vs*. 0.057 ± 0.010), and was significantly lower during elbow flexion than during elbow extension in young subjects (t = −3.039, df = 17; $p = 0.007$; mean: 0.062 ± 0.034 *vs*. 0.132 ± 0.088). No significant difference was found in MI between young and elderly subjects during elbow flexion, and between elbow flexion and extension in elderly subjects.

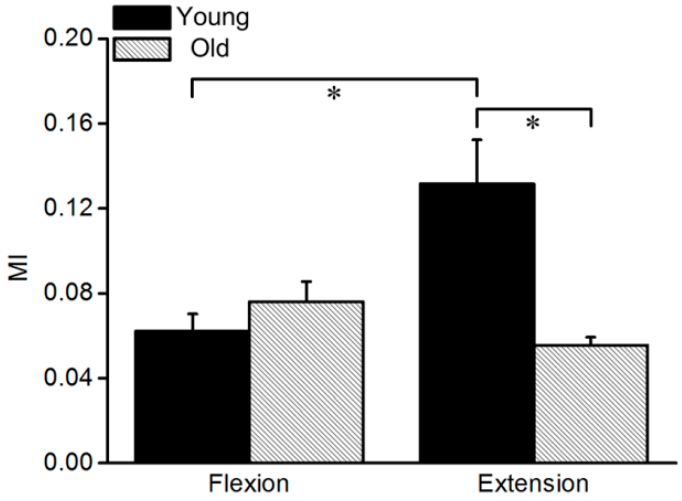

Figure 6. Mean value of MI during elbow flexion and extension. Notes: Young: young subjects; Old: elderly subjects. * Statistically significant difference ($p < 0.05$).

4. Discussion

The primary goal of this study was to investigate aging-related changes in the coordination of agonist and antagonist muscles. To describe the changes in muscular coordination, the normalized muscle activation and FuzzyEn were used to analyze the activities of biceps and triceps, and MI was adopted to reflect the changes of inter-muscular coupling.

The significantly reduced agonist activation with aging demonstrated in Figures 2c, 3d and 4a suggested that the mean activation level of agonist muscle in elderly subjects deviated more from the desired mean activation level (7.5%), which indicated a poorer tracking performance. This deterioration in tracking accuracy with aging was in agreement with previous studies [4], and was suggested to result from the motor unit remodeling and increased variability of motor unit discharge rate in elderly subjects [4].

Despite the significantly reduced agonist activation, the antagonist activation increased significantly during elbow flexion and extension in elderly subjects, indicating increased antagonist co-activation with aging. This finding was in line with previous studies [30–32]. Increased antagonist

co-activation was found in elderly adults during isometric elbow flexion and extension [30]. In investigating the aging-related changes of elbow angle variability during a quasistatic elbow flexion task, the elderly adults demonstrated higher antagonist co-activation than young adults [31]. Increased antagonist co-activation with aging was also found in the pre-movement phase during a rapid elbow extension task [32]. The coordination of agonist and antagonist muscle was supposed to be modulated at spinal level by the central nervous system (CNS), via regulating the excitation of motoneuron pools through the common drive [33], or activating Ia inhibitory interneurons through the disynaptic reciprocal inhibition [34]. The altered common drive and reduced reciprocal inhibition in elderly subjects might be attributed. Nevertheless, conflicting findings were exhibited during elbow flexion. In the study of torque–angular velocity relationships in elbow flexion, the antagonist co-activation was found to be similar between the young and elderly adults during isometric, concentric, and eccentric contractions [35]. In the study of the maximal power of biceps during maximal ballistic actions, there was also an absence of significant difference between two age groups in the activity of antagonist triceps [36]. As discussed by Klass *et al*. [2], these conflicting findings might result from the differences in the motor task that is performed, characteristics of the study population, and the methods adopted to assess muscle activity. Due to the presence of greater skinfold thickness in elderly subjects, Klass *et al*. [2] suggested that the comparisons of muscle activities between young and elderly subjects through comparing surface EMG amplitude could be misleading.

The similar FuzzyEn values of agonist and antagonist EMG and the similar MI between young and elderly subjects indicated that the coordination of agonist and antagonist muscles might not change with aging during elbow flexion. The significantly higher normalized antagonist activation and MI during elbow extension compared to flexion in young subjects indicated that there was more dependence on using the antagonist muscle during elbow extension than flexion, which might result from less skill in controlling the agonist muscle during elbow extension than flexion. This finding was in accordance with previous studies [37,38]. It was suggested that the significantly lower antagonist muscle activation during elbow flexion than extension might be attributed to a different involvement of biceps and triceps during daily movement [37]. The biceps had to work against gravity during daily movement, while the triceps did not, which could lead to a reduction in antagonist co-activation in favor of a better control of biceps than triceps [37]. Amarantini and Bru [38] have also demonstrated that strength training would improve the control of muscle activation and lead to a reduction in the antagonist co-activation. Therefore, the coordination of agonist and antagonist muscles during elbow flexion might not change with aging due to a frequent training of biceps to work against gravity in daily activities.

The similar FuzzyEn values of agonist EMG between young and elderly subjects and the significantly higher FuzzyEn values of antagonist EMG in elderly subjects indicated increased antagonist co-activation with aging during elbow extension. Moreover, the significantly decreased MI in elderly subjects implied decreased inter-muscular coupling with aging during elbow extension. The reduced inter-muscular coupling suggested that the activation of antagonist biceps was less relevant to the activation of agonist triceps in elderly subjects. Therefore, the common drive, which modulated the activation of antagonist muscles by co-activation and reciprocal activation [33], might not be account for the increased antagonist co-activation with aging during elbow extension. The reduced reciprocal inhibition, which would lead to the reduction of intermediated information flow between agonist and antagonist muscles, could be observed. In the study of inhibitory reflexes, it showed that the reciprocal inhibition between soleus muscle and tibialis anterior muscle decreased with aging [39]. A previous study also suggested that there might be additional cortical-spinal pathways connected to the antagonist, which could be recruited for compensation in elderly subjects in response to the degeneration process [4]. Our results suggested that increased antagonist co-activation during elbow extension might be also due to the recruitment of additional cortical-spinal pathways connected to biceps, which would not influence the inter-muscular coupling.

Based on FuzzyEn and MI, a comprehensive understanding of aging-related changes in the coordination of agonist and antagonist muscles was given in this study. Intramuscular EMG has long been used to investigate aging-related changes in the coordination of agonist and antagonist muscles [2]. Compared with intramuscular EMG, surface EMG is a simpler and non-invasive tool for the assessment of muscle activities, but surface EMG amplitude could be easily influenced by many factors such as electrode location, electrode-skin contact impedance, movement artifacts, thickness of skinfold and adipose tissue. Although FuzzyEn values will be affected by the range of signal amplitudes, FuzzyEn demonstrates better consistency of measurements than RMS and linear envelope to characterize the internal randomness of signals [11]. MI is robust to linear noise, and could be used as a measure to infer the common neural input of two muscles from surface EMG signals. As for non-linear measures, FuzzyEn and MI analysis could also be applied in a clinic to characterize other physiological signals that contain non-linear features, such as electroencephalograms (EEG) and ECG signals. A limitation of this study is that we did not perform the experiment under well-controlled conditions, since several related factors, such as sex, % body fat, and muscle strength could also influence the surface EMG signals [3]. In future work, it is necessary to control these factors well, or use the simulation data to verify the effect of each factor, thus providing further evidence of aging-induced changes in muscular coordination.

5. Conclusions

In this study, the normalized muscle activation, FuzzyEn and MI were used to investigate aging-related changes in the coordination of agonist and antagonist muscles during voluntary isometric elbow flexion and extension. It was found that there were increased antagonist co-activation and decreased inter-muscular coupling with aging during elbow extension, which might be due to the reduced reciprocal inhibition and the recruitment of additional cortical-spinal pathways connected to biceps. The findings in this study could help gain comprehensive insight into the mechanisms underlying aging-related changes in the coordination of agonist and antagonist muscles, and FuzzyEn and MI have the potential to be applied in clinics to investigate neurological mechanisms underlying muscle activities.

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Abbreviations

The following abbreviations are used in this manuscript:

EMG	Electromyogram
ECG	Electrocardiography
EEG	Electroencephalograms
MVC	Maximal voluntary contraction
MCI	Myoelectric-controlled interface
SamEn	Sample entropy
ApEn	Approximate entropy
FuzzyEn	Fuzzy entropy
MI	Mutual information
CNS	Central nervous system

References

1. Macaluso, A.; Nimmo, M.A.; Foster, J.E.; Cockburn, M.; McMillan, N.C.; de Vito, G. Contractile muscle volume and agonist–antagonist coactivation account for differences in torque between young and older women. *Muscle Nerve* **2002**, *25*, 858–863. [CrossRef] [PubMed]
2. Klass, M.; Baudry, S.; Duchateau, J. Voluntary activation during maximal contraction with advancing age: A brief review. *Eur. J. Appl. Physiol.* **2007**, *100*, 543–551. [CrossRef] [PubMed]
3. Billot, M.; Duclay, J.; Simoneau-Buessinger, E.M.; Ballay, Y.; Martin, A. Is co-contraction responsible for the decline in maximal knee joint torque in older males? *Age* **2014**, *36*, 899–910. [CrossRef] [PubMed]
4. Hortobágyi, T.; Devita, P. Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. *Exerc. Sport. Sci. Rev.* **2006**, *34*, 29–35. [CrossRef] [PubMed]
5. Chen, Y.T.; Kwon, M.; Fox, E.J.; Christou, E.A. Altered activation of the antagonist muscle during practice compromises motor learning in older adults. *J. Neurophysiol.* **2014**, *112*, 1010–1019. [CrossRef] [PubMed]
6. Peterson, D.S.; Martin, P.E. Effects of age and walking speed on coactivation and cost of walking in healthy adults. *Gait Posture* **2010**, *31*, 355–359. [CrossRef] [PubMed]
7. Laughton, C.A.; Slavin, M.; Katdare, K.; Nolan, L.; Bean, J.F.; Kerrigan, D.C.; Phillips, E.; Lipsitz, L.A.; Collins, J.J. Aging, muscle activity, and balance control: Physiologic changes associated with balance impairment. *Gait Posture* **2003**, *18*, 101–108. [CrossRef]
8. Hortobágyi, T.; DeVita, P. Muscle pre-and coactivity during downward stepping are associated with leg stiffness in aging. *J. Electromyogr. Kinesiol.* **2000**, *10*, 117–126. [CrossRef]
9. Kang, H.G.; Dingwell, J.B. Dynamics and stability of muscle activations during walking in healthy young and older adults. *J. Biomech.* **2009**, *42*, 2231–2237. [CrossRef] [PubMed]
10. Zhang, X.; Zhou, P. Sample entropy analysis of surface EMG for improved muscle activity onset detection against spurious background spikes. *J. Electromyogr. Kinesiol.* **2012**, *22*, 901–907. [CrossRef] [PubMed]
11. Estrada, L.; Torres, A.; Sarlabous, L.; Jane, R. Improvement in neural respiratory drive estimation from diaphragm electromyographic signals using fixed sample entropy. *IEEE J. Biomed. Health Inform.* **2016**, *20*, 476–485. [CrossRef] [PubMed]
12. Zhang, X.; Ren, X.; Gao, X.; Chen, X.; Zhou, P. Complexity analysis of surface EMG for overcoming ECG interference toward proportional myoelectric control. *Entropy* **2016**, *18*. [CrossRef]
13. Giannasi, L.C.; Matsui, M.Y.; Politti, F.; Batista, S.R.F.; Caldas, B.F.; Amorim, J.B.; de Oliveira, L.V.; Oliveira, C.S.; Gomes, M.F. Test–retest reliability of electromyographic variables of masseter and temporal muscles in patients with cerebral palsy. *Arch. Oral Biol.* **2014**, *59*, 1352–1358. [CrossRef] [PubMed]
14. Xiong, A.; Zhao, X.; Han, J.; Liu, G. Application of the chaos theory in the analysis of EMG on patients with facial paralysis. *Adv. Intell. Syst. Comput.* **2014**, *274*, 805–819.
15. Chen, W.; Wang, Z.; Xie, H.; Yu, W. Characterization of surface EMG signal based on fuzzy entropy. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2007**, *15*, 266–272. [CrossRef] [PubMed]
16. Ao, D.; Sun, R.; Tong, K.Y.; Song, R. Characterization of stroke- and aging-related changes in the complexity of EMG signals during tracking tasks. *Ann. Biomed. Eng.* **2014**, *43*, 990–1002. [CrossRef] [PubMed]
17. Sun, R.; Song, R.; Tong, K.Y. Complexity analysis of EMG signals for patients after stroke during robot-aided rehabilitation training using fuzzy approximate entropy. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2014**, *22*, 1013–1019. [CrossRef] [PubMed]
18. Power, H.A.; Norton, J.A.; Porter, C.L.; Doyle, Z.; Hui, I.; Chan, K.M. Transcranial direct current stimulation of the primary motor cortex affects cortical drive to human musculature as assessed by intermuscular coherence. *J. Physiol.* **2006**, *577*, 795–803. [CrossRef] [PubMed]
19. Asaka, T.; Wang, Y. Effects of aging on feedforward postural synergies. *J. Hum. Kinetics* **2009**, *20*, 63–70. [CrossRef]
20. Keenan, K.G.; Massey, W.V.; Walters, T.J.; Collins, J.D. Sensitivity of EMG-EMG coherence to detect the common oscillatory drive to hand muscles in young and older adults. *J. Neurophysiol.* **2012**, *107*, 2866–2875. [PubMed]
21. Jin, S.H.; Lin, P.; Hallett, M. Linear and nonlinear information flow based on time-delayed mutual information method and its application to corticomuscular interaction. *Clin. Neurophysiol.* **2010**, *121*, 392–401. [PubMed]
22. Jung, T.I.; Vogiatzian, F.; Har-Shemesh, O.; Fitzsimons, C.P.; Quax, R. Applying information theory to neuronal networks: From theory to experiments. *Entropy* **2014**, *16*, 5721–5737.

23. Svendsen, J.H.; Samani, A.; Mayntzhusen, K.; Madeleine, P. Muscle coordination and force variability during static and dynamic tracking tasks. *Hum. Mov. Sci.* **2011**, *30*, 1039–1051. [PubMed]
24. Madeleine, P.; Samani, A.; Binderup, A.T.; Stensdotter, A.K. Changes in the spatio-temporal organization of the trapezius muscle activity in response to eccentric contractions. *Scand. J. Med. Sci. Sports* **2011**, *21*, 277–286. [PubMed]
25. Gordon, K.E.; Ferris, D.P. Proportional myoelectric control of a virtual object to investigate human efferent control. *Exp. Brain Res.* **2004**, *159*, 478–486. [PubMed]
26. Missenard, O.; Mottet, D.; Perrey, S. The role of cocontraction in the impairment of movement accuracy with fatigue. *Exp. Brain Res.* **2008**, *185*, 151–156. [CrossRef] [PubMed]
27. Burden, A. How should we normalize electromyograms obtained from healthy participants? What we have learned from over 25 years of research. *J. Electromyogr. Kinesiol.* **2010**, *20*, 1023–1035. [CrossRef] [PubMed]
28. Canning, C.G.; Ada, L.; O'Dwyer, N.J. Abnormal muscle activation characteristics associated with loss of dexterity after stroke. *J. Neurol. Sci.* **2000**, *176*, 45–56. [CrossRef]
29. Moon, Y.I.; Rajagopalan, B.; Lall, U. Estimation of mutual information using kernel density estimators. *Phys. Rev. E.* **1995**, *52*, 2318–2321. [CrossRef]
30. Klein, C.S.; Rice, C.L.; Marsh, G.D. Normalized force, activation, and coactivation in the arm muscles of young and old men. *J. Appl. Physiol.* **2001**, *91*, 1341–1349. [PubMed]
31. Gordon, M.T. Effect of Age, Elbow Muscle Co-Contraction Level, and Elbow Moment Loading Characteristics on Elbow Angle Positional Variability in Postural Tasks by Positional Variability in Postural Tasks. Ph.D. Thesis, University of Michigan, Ann Arbor, MI, USA, 2012.
32. Bautmans, I.; Vantieghem, S.; Gorus, E.; Grazzini, Y.R.; Fierens, Y.; Pool-Goudzwaard, A.; Mets, T. Age-related differences in pre-movement antagonist muscle co-activation and reaction-time performance. *Exp. Gerontol.* **2011**, *46*, 637–642. [CrossRef] [PubMed]
33. De Luca, C.J.; Mambrito, B. Voluntary control of motor units in human antagonist muscles: coactivation and reciprocal activation. *J. Neurophysiol.* **1987**, *58*, 525–542. [PubMed]
34. Nielsen, J.; Kagamihara, Y. The regulation of presynaptic inhibition during co-contraction of antagonistic muscles in man. *J. Physiol.* **1993**, *464*, 575–593. [CrossRef] [PubMed]
35. Pousson, M.; Lepers, R.; Van Hoecke, J. Changes in isokinetic torque and muscular activity of elbow flexors muscles with age. *Exp. Gerontol.* **2001**, *36*, 1687–1698. [CrossRef]
36. Valour, D.; Ochala, J.; Ballay, Y.; Pousson, M. The influence of ageing on the force-velocity-power characteristics of human elbow flexor muscles. *Exp. Gerontol.* **2003**, *38*, 387–395. [CrossRef]
37. Bazzucchi, I.; Riccio, M.E.; Felici, F. Tennis players show a lower coactivation of the elbow antagonist muscles during isokinetic exercises. *J. Electromyogr. Kinesiol.* **2008**, *18*, 752–759. [CrossRef] [PubMed]
38. Amarantini, D.; Bru, B. Training-related changes in the EMG-moment relationship during isometric contractions: Further evidence of improved control of muscle activation in strength-trained men? *J. Electromyogr. Kinesiol.* **2015**, *25*, 697–702. [CrossRef] [PubMed]
39. Kido, A.; Tanaka, N.; Stein, R.B. Spinal excitation and inhibition decrease as humans' age. *Can. J. Physiol. Pharmacol.* **2004**, *82*, 238–248. [CrossRef] [PubMed]