The Switching Mechanism of Muscle Synergies for Lower Limb Control

(下肢制御における筋シナジーの切替機序)

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Acknowledgements

Dr. Jun Ishibashi raised my awareness as a sole proprietor, and Prof. Tetsuya Amino watched the progress of my early work as a historian, and my supervisor Prof. Senshi Fukashiro has helped my career as a scientist.

Dr. Shinsuke Yoshioka taught me biomechanics. Dr. Dai Yanagihara and Dr. Kazutoshi Kudo imparted basic knowledge about the muscle synergy and uncontrolled manifold hypotheses to me, respectively. Prof. Kimitaka Nakazawa framed my thoughts about the size principle.

Prof. Shu Takagi gave me critical advice. Dr. Junichi Ushiyama, who was introduced by Dr. Kentaro Chino, and Dr. Ryuta Kinugasa told me research methods. I could focus on my work, with the support of Dr. Yuki Inaba, Mr. Yuta Kawamoto, Dr. Kohei Shioda, Dr. Rintaro Ogane, Mr. Shimpei Kubo, Obara Shiraume Scholarship Foundation, RIKEN, and Japan Society for the Promotion of Science.

I say a few words in a scientific manner, which is about selecting uncontradicted evidence; thank you.

Takahito Suzuki
A history of the muscle-synergy concept

Since ancient times, humans have been interested in the mechanics of human body. The Edwin Smith Papyrus provides evidence that ancient Egyptians investigated human anatomy at least as early as the 17\textsuperscript{th} century B.C. (Breasted 1930a, 1930b). In the second century A.D., Galen reported human anatomy in detail. For example, he separated 14 muscles around the ankle (Goss 1963). These ancient anatomists wondered why one joint had multiple muscles that had a similar function, and how these muscles were controlled.

Galen grouped muscles and termed them agonists and antagonists (Goss 1968). In the 17\textsuperscript{th} century, Descartes proceeded with this idea, and proposed that the agonist and antagonist were connected by nerves and were alternately activated (Descartes 1972). In such a manner, ancient to early-modern scholars had conceived some kind of muscle grouping based on function as one of the ways in which muscles around a certain joint were controlled.

From the late 17\textsuperscript{th} century, the research for muscle activation mechanics rapidly developed (Cobb 2002). Swammerdam discovered that nerve irritation, in which electrical stimulation might have been induced by a brass hook and silver wire (Cobb 2002), leads to contraction of a single muscle in the frog (Swammerdam 1758). In 1791, Galvani observed that electrical nerve stimulation induced contraction of multiple muscles in the frog limb (Galvani 1791). In 1870, Fritsch and Hitzig confirmed functional localization of the motor cortex of the dog by electrical stimulation (Fritsch and Hitzig 1870). Because electrical stimulation to the nerve or cortex induced simultaneous or cooperative activity of muscles, these observers believed in the integrative control of multiple muscles. Consequently, Sherrington used the term
‘synergy’ to describe cooperative activity of muscles, although what was “cooperative” was somewhat ambiguous (Sherrington 1906). In the middle part of the 20th century, Bernstein defined the ancient question regarding the control of multiple muscles as the ‘degrees of freedom problem’ (Bernstein 1967).

Evidence for the existence of muscle synergies

Even assuming the integrative control of multiple muscles, it was difficult to identify the physiological systems that function as muscle synergies. One of the possible sites was the motor cortex (Fritsch and Hitzig 1870). Cortical interneurons and corticospinal and corticomotoneuronal cells could represent muscle synergies (Huntley and Jones 1991). In 1991, Bizzi and colleagues observed that microstimulation of a site in the frog lumbar spinal cord elicited a leg force pattern that was related to several muscles, and simultaneous stimulation of two spinal sites summed two corresponding sets of leg forces (Bizzi et al. 1991). Since 1991, many studies have confirmed the ability of spinal interneurons to simultaneously control multiple muscles in various animals, such as the frog (Hart and Giszter 2010; Mussa-Ivaldi et al. 1994; Roh et al. 2011) and monkey (Takei and Seki 2010). Because spinal interneurons are close to motoneurons, they likely compose a large part of muscle synergies.

Similar to the difficulties experienced clarifying the physiological entity of muscle synergies, it has not been easy to investigate the way muscle synergies are recruited during voluntary movements (Lee 1984). Although correlation between the electromyographic activities of several muscles was observed during a single-joint movement (Bouisset et al. 1977; Buchanan et al. 1986), a mathematical tool that can decompose the mixed electromyographic activity to the recruitment of each muscle synergy was hard to find. In 1999, Tresch and colleagues applied a non-negative least-squares algorithm, which is a computational decomposition technique, to the electromyographic activity of frog limb muscles (Tresch et al.
3

1999). After this study, computational decomposition techniques for electromyographic activities spread widely among researchers in the field of motor control, and many studies have reported the existence of muscle synergies during a variety of voluntary movements (Cappellini et al. 2006; d'Avella et al. 2003; Roh et al. 2011; Torres-Oviedo et al. 2006).

Challenge to the dependence of human motor control on muscle synergies

The stimulation and behavioral approaches have provided enormous physiological and behavioral evidence of muscle synergies. Nevertheless, the muscle synergy hypothesis has been difficult to strictly prove or falsify (Kutch and Valero-Cuevas 2012; Tresch and Jarc 2009). Doubt has been cast on whether the stimulation approach can elicit the complete repertoire of muscle activation patterns (Kutch and Valero-Cuevas 2012). Even though interneurons are available for the synchronous control of multiple muscles, the specific control of single muscles might be learned and used by the motor cortex (Moritz et al. 2008). Of course, the behavioral approach can examine all practical muscle activation patterns, but it is affected by task constraints that reduce feasible activation patterns, independent of neural control (Buchanan et al. 1986; Kutch and Valero-Cuevas 2012; Lee 1984; Tresch and Jarc 2009). For example, previous studies reported that muscle activities during walking were grouped in a synergy-like manner (Cappellini et al. 2006; Clark et al. 2010; Dominici et al. 2011), but such a grouped muscle activity was roughly predicted by computer simulation that developed around the end of the 20th century (Anderson and Pandy 2001), based on an objective function (Flash and Hogan 1985; MacConaill 1966) unrelated to muscle synergies. Such reduced activation patterns could be misinterpreted as muscle synergies, which are neural constraints. Therefore, the study to prove the muscle synergy hypothesis should distinguish muscle synergies from non-neural muscle activation patterns constrained by a task.

In the 21st century, studies on the variability of the exerted force or muscle activation
have provided evidence against the dependence on muscle synergies during human motor control (Kutch et al. 2008; Tresch and Jarc 2009; Valero-Cuevas et al. 2009). Valero-Cuevas and colleagues applied the uncontrolled manifold approach (Schöner 1995), which has been used to reveal large, task-irrelevant variability of joint kinematics (Scholz and Schöner 1999) and kinetics (Scholz et al. 2002), to muscle activation, and reported that the variability of index finger muscle activities that affected the fingertip force was smaller than their task-irrelevant variability (Valero-Cuevas et al. 2009). One interpretation (Tresch and Jarc 2009) is that this small variability suggests that each muscle was independently controlled and activity that did not affect the task (i.e., the fingertip force) was uncontrolled. This interpretation emphasizes the independent control of muscle activities and somewhat contradicts the hypothesis that muscle activities are simultaneously controlled by muscle synergies (Tresch et al. 1999).

Further evidence is necessary to verify the dependence of human motor control on muscle synergies, and this evidence must be obtained in an experiment that clarifies the mechanical constraints and the variability of muscle activities in a given task.

**Thesis Contents**

In the thesis, a muscle synergy is defined as a synchronous synergy, i.e., one in which all muscles are activated with no temporal delay (Tresch and Jarc 2009). The purpose of the thesis is to confirm the dependence of lower limb control on muscle synergies and propose the muscle synergy recruitment strategy. For these purposes, the research is presented in four chapters: II–V. Because knee extensor activation at the fully extended position can induce a change in plantar flexor activity at the constant mechanical constraint on plantar flexor muscles, plantar flexor activity during isometric plantar flexion with or without isometric knee extension is analyzed by two-piece linear regression (Chapter II), non-negative matrix factorization (Chapters II, III, and IV), uncontrolled manifold approach (Chapter III), and interpolated twitch technique.
The aim of the study reported in Chapter II was to reveal the dependence of plantar flexor muscles on muscle synergies and the difference in this dependence between low and high plantar flexion torques. The mechanical constraint that reduces the feasible muscle activity patterns was carefully controlled, and the results presented in Chapter II showed that knee extensor activation systematically induced a change in plantar flexor activity in the absence of a change in the mechanical constraint on plantar flexor muscles. The existence of muscle synergies was necessary to explain this phenomenon clearly.

The results presented in Chapter II showed that the dependence on muscle synergies is clearer with low-intensity plantar flexion than with high-intensity plantar flexion; therefore, the aim of the studies reported in Chapter III was to reveal ways in which muscle synergies are recruited at low-intensity plantar flexion. Chapter III is divided into two sections. The results of the study presented in Section I were already published (Suzuki et al. 2014), and confirmed that a change in knee extensor activation induced a drastic change in plantar flexor activity during low-intensity plantar flexion. The aim of the study reported in Section II was to resolve the discrepancy between the muscle synergy hypothesis and the uncontrolled manifold hypothesis at the muscle activation level and provide a valuable insight into the recruitment of muscle synergies. To achieve this aim, the study reported in Section II applied the uncontrolled manifold approach to the variability of plantar flexor activity and muscle synergy recruitment during plantar flexion with and without knee extensor activation.

Although the results of the study represented in Chapter II did not show a clear change in activation ratio between plantar flexor muscles at high-intensity plantar flexion, the activity of the soleus and medial gastrocnemius muscles increased with knee extensor activation. Therefore, the aim of the study reported in Chapter IV was to evaluate the effect of the interaction between plantar flexor and knee extensor muscles on the generation of maximum
plantar flexion torque.

Chapter II deals with plantar flexion torques ranging from low to maximum levels, Chapter III is focused on low-intensity plantar flexion, and Chapter IV examines the supramaximal plantar flexion. Chapter V provides a general discussion on the research, and proposes ways in which muscle synergies are recruited.
Chapter II

Plantar flexor activities are non-mechanically constrained with knee extensor activation

This study will be published elsewhere within five years.
**Section I of Chapter III**

*Gastrocnemius and soleus are selectively activated when adding knee extensor activity to plantar flexion*

**Introduction**

Most activities of daily living involve multi-joint movements. For example, simultaneous motions of ankle and knee joints are required for many activities, including standing (Horak and Nashner 1986), running (Duysens et al. 1991), swimming (Troup 1999), and cycling (Andrews 1987; De Marchis et al. 2013). During these multi-joint movements, biarticular muscles, such as the gastrocnemius, have direct effects on two joints at the same time (Lombard 1903), and these effects depend on task constraints, including the movement direction, joint displacement, and external force (Andrews 1987; Zajac 1993). Therefore, control of biarticular muscles is complex and important to multi-joint movements.

The gastrocnemius, a biarticular muscle that crosses the ankle and knee, functions as both a plantar flexor and a knee flexor. Partly because of this anatomical characteristic, the muscle activation level of the gastrocnemius increases when voluntary knee flexion is added to voluntary isometric plantar flexion (Gravel et al. 1987). However, in a situation where both plantar flexion and knee extension are required, it is possible that the activity of the gastrocnemius, which is an antagonist during knee extension, would be depressed. Such depression of antagonist activity is induced by agonist activity through neural pathways, an action called reciprocal inhibition. This well-known phenomenon has been carefully investigated in the ankle (Nielsen and Pierrot-Deseilligny 1996) and elbow (Katz et al. 1991). Previous studies, however, had little concern about reciprocal inhibition at the human knee (Bayoumi and Ashby 1989; Hamm and Alexander 2010; Kudina 1980), and they did not deal with the gastrocnemius as a knee flexor. Therefore, it is unclear how voluntary activation of
knee extensors influences gastrocnemius activity. If activation of knee extensors causes gastrocnemius activity to decrease while satisfying the total demand of plantar flexion torque, the activities of monoarticular plantar flexors, such as the soleus (Sol), are increased, changing the load share among plantar flexors.

In this study, it was hypothesized that gastrocnemius activity is depressed and Sol activity is increased during simultaneous motion of plantar flexion and knee extension. To test this hypothesis, we investigated activation of triceps surae when voluntary isometric knee extension was added to voluntary isometric plantar flexion.

**Methods**

*Subjects*

Ten male volunteers participated in the experiment. Their ages, heights, and body masses (mean ± SD) were 25.3 ± 3.6 years, 173.0 ± 5.3 cm, and 68.2 ± 8.7 kg, respectively. They had no medical history or signs of a neurological disorder. All subjects gave their written informed consent for the study after receiving a detailed explanation for the purposes, potential benefits, and risks associated with participation in the study. The Human Research Ethics Committee at the Department of Life Sciences, The University of Tokyo, approved all of the procedures used in the study.

*Force and electromyography recordings*

For all of the trials, each subject was required to maintain a prone posture with no joint angle changes. A knee was fully extended on a bed with pads that elevated the knee to avoid contact of the bed with the electrode on the rectus femoris (RF). The ankle was fixed at 0° (neutral position), and the right foot was tightly strapped to a plate of a dynamometer (VTF-002; VINE
Bionic Systems, Tokyo, Japan) with a strain gauge (LTZ-500KA; Kyowa, Tokyo, Japan) amplified by a strain amplifier (CDV-700A; Kyowa) or a torque-measuring system (Biodex System 3; Biodex Medical Systems, Shirley, NY, USA) (Fig. 1). The angles of the right ankle and knee were carefully fixed to remove any influence of angular variations on the electromyography (EMG) tracings of the triceps surae (Cresswell et al. 1995). The constancy of the knee angle was checked by a goniometer (SG150; Biometrics, Gwent, UK) for seven subjects, and the goniometer was taken off to immobilize the knee as strictly as possible for three subjects. In the pilot study, we had confirmed that isometric knee extension with no plantar flexor activation had no effect on the torque signal of the present experimental setup.

Surface EMGs were recorded from the RF, biceps femoris (BF), tibialis anterior (TA), MG, lateral gastrocnemius (LG), and Sol using two Ag-AgCl electrodes with diameters of 10 mm and an inter-electrode distance of 20 mm. After carefully abrading and cleaning the skin with alcohol, the electrodes were placed over distal parts of the RF and BF; the bellies of the TA, MG, and LG; and a medial protrusion of the Sol. The ground electrode was placed on the tuberositas tibiae. The EMG signals were amplified using a standard biosignal recording system (model 365, NEC Medical Systems, Tokyo, Japan; or Bagnoli Desktop EMG Systems, Delsys, Boston, MA, USA), with filtering at a bandwidth of 5 Hz to 1 kHz. All electrical signals were stored with a sampling frequency of 2 kHz on the hard disk of a personal computer using a 16-
bit analog-to-digital converter (PowerLab 16/30; ADInstruments, Sydney, Australia).

**Experimental protocol and data analyses**

Before the experiment, the subjects practiced until they could generate the targeted torque. For the maximum voluntary contraction (MVC) trials, they performed isometric MVCs for knee extension, knee flexion, plantar flexion, and dorsiflexion. They gradually increased the contraction level to a maximum to avoid a short-time burst on the EMG at the initial rise. Each trial lasted for > 3 s and was conducted twice. Rest periods between trials lasted a few minutes. The EMGs were recorded during all trials, but torque was measured only for plantar flexion.

The data obtained during the MVC trials were processed as follows. The 1-s analyzed window was moved through the recorded time in 1/2000-s steps. For the MVC trial of plantar flexion, the torque was averaged over each window. The maximum voluntary isometric plantar flexion (PFMVC) torque was defined as the largest among all the mean torque values obtained from all of the windows of two trials. The average rectified values (ARVs) of the EMGs of the MG, LG, and Sol were calculated at the same window where the PFMVC was obtained. This analysis depended on the widespread definition that the EMG during the MVC corresponded to the MVC torque in the same moment (Disselhorst-Klug et al. 2009). For the above-mentioned MVC trial for knee extension, knee flexion, or dorsiflexion, the 1-s window was shifted in 1/2000-s steps, and the ARV was calculated over each 1-s window. Because the produced torques were not measured during the MVC trials (except for plantar flexion), the ARVs of the RF, BF, and TA during MVCs were determined as the largest among the ARVs obtained from all windows of two MVC trials for each muscle.

After a rest period of a few minutes following the MVC trials, the subjects undertook the main trials. They performed constant isometric plantar flexion at 10%, 20%, and 30% of the PFMVC (%PFMVC), in random order. These levels were chosen because almost all bursts of
triceps surae EMG activity were less than 30% MVC in activities of daily living (Shirasawa et al. 2009). The resulting plantar flexion torque and target torque levels were displayed on an oscilloscope in front of the subject to provide visual feedback. They performed each plantar flexion once at each level. They were asked to set the plantar flexion torque as close as possible to the target level during the first 15 s. After the first 15 s, they were asked to add knee extensor activity to the plantar flexion. The knee extension levels were set at 0%, 50%, and 100% of the maximum voluntary isometric knee extensor activation (%KEMVC). They were asked to press a plate in a same manner at all knee extension conditions. Because the root mean square value of the EMG of the RF was proportional to the knee extension torque at any portion of the muscle (Watanabe et al. 2012), the KEMVC was determined not by the torque but by RF ARV, which was equivalent to the root mean square value in a practical application (Clancy et al. 2002). Knee extension for 15 s at each level was randomly added while maintaining constant plantar flexion torque (Fig. 1). The knee extension level was fed back to the subjects auditorily (not visually) because it was difficult for them to handle two visual feedbacks simultaneously. To obtain the brief ARV of the RF for the auditory feedback, the EMG of the RF was full-wave-rectified and low-pass-filtered at a cutoff frequency of 10 Hz online using LabChart software (ADInstruments, Sydney, Australia). During each trial, if this processed signal went beyond or fell below the range of the target level ± 10% of the corresponding value during the MVC (%MVC), the subjects received auditory feedback until the processed signal returned to the target range. At 100% KEMVC, the subjects were encouraged to perform maximum voluntary knee extensions, which were monitored by the processed signal. A few minutes of rest was allowed between trials at each plantar flexion level.

The data obtained in the main trials were processed as follows. The analysis program searched the 5-s window, where it obtained the minimum value of the absolute difference in the ARV of the RF between the target level and the produced value by moving the window through
the recorded time in 1/2000-s steps. The averaged torque and the ARVs of all muscles were calculated over the chosen window and were expressed as % MVC. These processes were completed using Matlab 2007a software (Mathworks, Natick, MA, USA).

**Statistics**

The statistical significances for the ARVs (expressed as % MVC) of the RF, MG, LG, and Sol were tested by two-way analysis of variance (ANOVA) with repeated measures (three plantar flexion levels × three knee extension levels). Shaffer’s post-hoc test was conducted to examine the difference between the knee extension levels. If the interaction between the plantar flexion level and the knee extension level was significant, the post-hoc test included a multiple comparison for simple effects. The Greenhouse–Geisser degrees of freedom correction (ε) was used to correct for violation of the sphericity assumption. Eta-squared ($\eta^2$) and the power (1-β) were calculated to provide an indication of the adequacy of the sample size. The ANOVA, post-hoc test, and power test were performed with statistical software (SPSS 12.0J; SPSS Japan, Tokyo, Japan). The level of significance for all comparisons was set at $P < 0.05$.

**Results**

A typical example of the plantar flexion torque and the EMGs of all muscles during the 20% PFMVC trial is shown in Figure 2. The plantar flexion torque would be constant at all knee extension levels. Although the RF activity at 100% KEMVC seemed to fluctuate, the activation level was higher than that at 50% KEMVC. The MG showed tonic activation during isometric plantar flexion without knee extension, but its amplitude drastically decreased when isometric knee extension was added to the task. With MG activity depression, Sol activity was increased. LG activity did not show the modulation seen with MG activity. These observations were confirmed as follows.
Table 1 shows group results of the controlled factors at all conditions. The errors between the target level and the produced torque were $< 1\%$ PFMVC under any of the conditions. At 50\% and 100\% KEMVC, the ARVs of the RF were about 40\% and 80\% MVC, respectively. Although they were somewhat lower than the target levels, the post-hoc test revealed that the ARV of the RF significantly increased with increasing knee extension level from 0\% to 50\%, from 50\% to 100\%, and from 0\% to 100\% KEMVC ($P < 0.001$ for each comparison). For all conditions, the ARVs of the BF and TA were $< 10\%$ and $< 5\%$ MVC, respectively.

![Fig. 2. Typical plantar flexion (PF) torque and electromyograms (EMGs). Left. Rectified EMGs during maximum voluntary contraction (MVC) trials for each muscle. Right. Torque and rectified EMGs during the 20\% of plantar flexion MVC (%PFMVC) trial. EMGs were obtained from the rectus femoris (RF), biceps femoris (BF), tibial anterioris (TA), medial gastrocnemius (MG), lateral gastrocnemius (LG), and soleus (Sol). Knee extension (KE) levels were set at 0\% KEMVC (relaxation), 50\% KEMVC, 0\% KEMVC, and 100\% KEMVC at 15-s intervals. Shaded areas represent the 5-s windows where the mean torque and average rectified values of EMG activities were calculated.](image)
Table 1. Plantar flexion torque and average rectified values for electromyographic activity of the controlled muscles under all conditions

<table>
<thead>
<tr>
<th>%PFMVC</th>
<th>%KEMVC</th>
<th>Torque</th>
<th>RF</th>
<th>BF</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0</td>
<td>10.0 (0.3)</td>
<td>2.7 (2.1)</td>
<td>2.0 (2.1)</td>
<td>3.1 (3.2)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>10.2 (0.2)</td>
<td>38.9 (6.6)</td>
<td>6.5 (2.8)</td>
<td>2.7 (3.1)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>10.2 (0.4)</td>
<td>72.2 (14.9)</td>
<td>9.1 (4.2)</td>
<td>4.2 (4.7)</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>20.1 (0.6)</td>
<td>2.6 (2.1)</td>
<td>2.6 (2.6)</td>
<td>3.7 (3.7)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>20.4 (0.6)</td>
<td>37.9 (7.5)</td>
<td>5.9 (2.6)</td>
<td>4.0 (3.8)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>20.5 (0.8)</td>
<td>74.0 (15.8)</td>
<td>9.0 (4.2)</td>
<td>3.2 (2.9)</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>29.9 (0.8)</td>
<td>2.5 (1.6)</td>
<td>3.2 (2.3)</td>
<td>3.4 (3.1)</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>29.8 (0.9)</td>
<td>38.9 (7.0)</td>
<td>6.1 (3.2)</td>
<td>4.1 (3.3)</td>
</tr>
<tr>
<td></td>
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<td>30.7 (0.9)</td>
<td>74.8 (19.0)</td>
<td>9.6 (4.2)</td>
<td>3.9 (3.2)</td>
</tr>
</tbody>
</table>

MVC: maximum voluntary contraction; %PFMVC: target level of plantar flexion torque; %KEMVC: target level of average rectified value of electromyographic activity of rectus femoris; RF: rectus femoris; BF: biceps femoris; TA: tibial anterioris. The RF, BF, and TA were controlled in this study. The value in each cell is the mean (standard deviation). All values are represented as a percentage of the corresponding value during the MVC (%MVC).

The ARV of the MG significantly differed among the plantar flexion levels ($F_{2,18} = 18.5, \varepsilon = 0.953, \eta^2 = 0.24, 1-\beta = 0.99, P < 0.001$) and among the knee extension levels ($F_{2,18} = 15.8, \varepsilon = 0.549, \eta^2 = 0.19, 1-\beta = 0.95, P = 0.002$) (Fig. 3). The interaction between the plantar flexion level and the knee extension level was not significant ($F_{4,36} = 0.7, \varepsilon = 0.454, \eta^2 = 0.00, 1-\beta = 0.14, P = 0.502$). Shaffer’s post-hoc test revealed that the ARV of the MG significantly decreased with increasing knee extension level from 0% to 50% KEMVC ($P = 0.002$) and from 0% to 100% KEMVC ($P = 0.005$). There was no significant difference between 50% and 100% KEMVC ($P = 0.529$).

The ARV of the LG significantly differed among the plantar flexion levels ($F_{2,18} = 22.2, \varepsilon = 0.647, \eta^2 = 0.38, 1-\beta = 0.99, P < 0.001$) but not among the knee extension levels ($F_{2,18} = 0.3, \varepsilon = 0.523, \eta^2 = 0.00, 1-\beta = 0.08, P = 0.596$) (Fig. 3). The interaction was not significant ($F_{4,36} = 0.9, \varepsilon = 0.471, \eta^2 = 0.00, 1-\beta = 0.17, P = 0.415$).

The ARV of the Sol significantly differed among the plantar flexion levels ($F_{2,18} = 68.9, \varepsilon = 0.674, \eta^2 = 0.39, 1-\beta = 1.00, P < 0.001$) and among the knee extension levels ($F_{2,18} = 42.9,$
\[ \varepsilon = 0.740, \eta^2 = 0.30, 1-\beta = 1.00, P < 0.001 \] (Fig. 3). The interaction was not significant \( (F_{4,36} = 2.8, \varepsilon = 0.473, \eta^2 = 0.03, 1-\beta = 0.46, P = 0.091) \). Shaffer's post-hoc test revealed that the ARV of the Sol significantly increased with increasing knee extension level from 0% to 50% KEMVC \((P < 0.001)\), from 50% to 100% KEMVC \((P = 0.001)\), and from 0% to 100% KEMVC \((P < 0.001)\).

**Discussion**

*Influence of knee extensor activation on the activities of plantar flexors*

The main finding of the present study was that MG activity was depressed and Sol activity was increased when knee extension was added to plantar flexion. This finding suggests that knee extensor activity is related to selective activation of plantar flexor synergists.

Studies about voluntary single-joint movements suggested that knee extension with no
intended ankle motion were followed by unconscious activation of dorsiflexors (not plantar flexors), and conversely, dorsiflexion induced knee extensor activity (Aruin 2001; Dimitrijevic et al. 1992; Hwang and Abraham 2001). However, the results of the present study about voluntary multi-joint movements revealed not only the coupling of knee extensors and plantar flexors but also the differences in coupling patterns among plantar flexors. In this study, because the MG is a biarticular plantar flexor acting as an antagonist for knee extension, knee extensor activation resulted in reduced MG activity, which is seemingly in line with the concept of reciprocal inhibition, and increased activation of the Sol, which is a monoarticular plantar flexor. These results seem to be unique to multi-joint movements and depend on anatomical differences.

Selective activation among the synergists has been observed during sustained isometric plantar flexion without activation of knee extensors (McLean and Goudy 2004; Sirin and Patla 1987; Tamaki et al. 1998, 2011). For example, a previous study reported that Sol activity occasionally substituted other plantar flexors and increased to, at most, 30% MVC during 1 h of isometric plantar flexion at 10% PFMVC (McLean and Goudy 2004). In the present study, the ARV of the Sol increased to more than 30% MVC at 10% PFMVC concurrently with knee extension (Fig. 3). Especially at 30% PFMVC, the ARV of the Sol startlingly increased to 70% MVC with knee extension at 100% KEMVC (Fig. 3). These quantified amounts suggest that activation of knee extensors serves as a trigger to place a heavy load on the Sol.

Physiological mechanisms

The physiological mechanisms underlying the observed influence of knee extension on triceps surae activity may be explained by the activity at both the central and peripheral levels. The MG functions not only as a plantar flexor but also as a knee flexor. Thus, when voluntary knee extension is added to plantar flexion, the central drive for knee extension reduces MG activity because it works as an antagonist during knee extension. To compensate for the torque loss
induced by MG activity depression, the activation level of the Sol must increase. To this end, a greater central drive is provided to the Sol motoneuron pool. Additionally, the peripheral neural network from the quadriceps to the triceps surae would be related to the observed change in the triceps surae activation pattern. The reciprocal, or heteronymous, inhibition (Bayoumi and Ashby 1989; Hamm and Alexander 2010; Kudina 1980; Meunier et al. 1994) from the quadriceps could then inhibit knee flexor activity, including that of the MG.

There is another possible explanation—that increased Sol activity is followed by MG activity depression. A facilitatory heteronymous connection from the quadriceps to the Sol is so fundamental that it exists not only in human subjects, who have a number of transjoint neural pathways (Meunier et al. 1993), but also in certain animals, such as the cat and baboon, which have few transjoint neural pathways between the ankle and knee (Eccles et al. 1957; Hongo et al. 1984). For human movements requiring simultaneous motion of plantar flexion and knee extension, it has been reported that neural pathways from the quadriceps to the Sol are selected for task requirements (Barbeau et al. 2000; Kawashima et al. 2006; Lamy et al. 2008). For example, during the early stance phase of human walking, the stretch reflex from the quadriceps had a facilitatory effect on Sol activity (Kawashima et al. 2006), and heteronymous inhibition from the quadriceps to the Sol was reduced (Lamy et al. 2008). Partly because of selecting such facilitatory connections, quadriceps activation induces increased Sol activity. To maintain constant plantar flexion torque, MG activity would have to decrease with heteronymous inhibition from the Sol to the MG (Meunier et al. 1994).

As mentioned above, the peripheral neural pathways could provide a simple explanation for the observed selective activation. However, MG activity was not decreased with increasing knee extensor activation from 50% to 100% KEMVC. Although the inhibitory effect of knee extensor activation on MG activity would be saturated at low-intensity plantar flexion, Chapter II revealed that knee extensor activation at any levels had a facilitatory effect on MG
activity at high-intensity plantar flexion. To explain these phenomena through the peripheral neural pathways from the quadriceps muscles, various situation-dependent effects of these pathways are necessary. Alternatively, the muscle synergy hypothesis allows a better view that planar flexor activities are changed by recruited plantar flexor synergies depending on the presence of knee extensor activation. If the recruitment of plantar flexor synergies is determined by the presence of knee extensor activation as observed in Chapter II, it is understandable that MG activity is not drastically changed with increasing knee extensor activation from 50% to 100% KEMVC. Although the present study could not definitively identify which neural pathways to the MG and Sol are used during simultaneous motion of plantar flexion and knee extension, explanation based on muscle synergies is simpler and suitable for the observed selective activation.

Practical significance

The observed selective activation, wherein MG activity was depressed and Sol activity was increased during plantar flexion with simultaneous knee extension, allowed smooth straightening of the leg. Leg straightening—requiring simultaneous plantar flexion, knee extension, and hip extension—is a component of various daily and sporting activities, including jumping (Barbeau et al. 2000) and walking (Anderson and Pandy 2001; Franz and Kram 2012; Hof et al. 2005; Lamy et al. 2008). During leg straightening, MG activity would conflict with knee extensor activity because of its knee-flexing function. Conversely, the Sol is a monoarticular plantar flexor, so its activity directly increases push-off force. Some previous studies reported that MG activity was weaker than Sol activity at the early stance phase of walking, where knee extensors are strongly activated (Franz and Kram 2012; Hof et al. 2005). A simulation study also predicted coactivation of knee extensors and the Sol without MG activity at this phase (Anderson and Pandy 2001). Because of the anatomical difference, the Sol
is preferable to the MG for leg straightening.

The observed selective activation is consistent with the anatomical decision, but its practical significance in multi-joint movements could not be explained by anatomical function alone. Knee extensors could pull on the calcaneus as a result of the action of biarticular plantar flexors—so-called energy transfer (Bobbert et al. 1986; Prilutsky and Zatsiorsky 1994). If biarticular plantar flexors do not generate knee flexion torque, knee extensors could not act to accelerate the ankle to plantar flexion through these biarticular muscles, and the knee angle would reach the limit too early to perform the maximum mechanical work (van Ingen Schenau et al. 1987). Taking into account these mechanical characteristics of biarticular muscles, an adequate amount of MG activity is required in particular situations. Therefore, the anatomically reasonable activation may disturb the above-mentioned mechanical functions of the MG in some situations. Although the present study reveals selective activation depending on anatomical function, it is necessary to assess in which situation this phenomenon occurs and is effective.

Taking into consideration the physiological difference, there are effective situations, which is another significant practical aspect of this phenomenon. The MG is more easily fatigued than the Sol (Kawakami et al. 2000) because its ratio of type II fibers is three times that in the Sol (Johnson et al. 1973). It is possible that the observed substitution for muscle activation reduces the load on the MG, thereby delaying its exhaustion during prolonged multi-joint exercise, such as walking (Cronin et al. 2013), which requires plantar flexion and simultaneous knee extension. For example, during 1-h walking, the fascicle length at the ground contact and the range of its change through a stride decreased in the MG whereas those of the Sol were not significantly changed (Cronin et al. 2013). From the perspective of the force-length relationship, Sol activity would compensate for the loss of the force-generating capacity of the MG in a fatigue condition. This compensation would be facilitated by the observed substitution.
Moreover, a previous study reported that some knee extensor synergists alternated during sustained knee extension at 2.5% MVC for 1 h (Kouzaki and Shinohara 2006). The frequency of the alternation during muscle activity among the synergists negatively correlates with the amount of reduction in the MVC force (Kouzaki and Shinohara 2006). Although the generation mechanism underlying the substitution for muscle activation during a multi-joint movement should differ somewhat from that during a single-joint movement, it is possible that the observed substitutions among the plantar flexor synergists have a similar functional ability to reduce fatigue during a strenuous task. Therefore, knee extensor activation changes load sharing not only between the ankle and knee (Monaco et al. 2009) but also among plantar flexors, thereby potentially managing fatigue during a multi-joint exercise that requires leg straightening.

**Limitations**

There were two problems in the study regarding the physiological explanation of the attained results. First, although the MG and LG cross the ankle and knee and have almost the same muscle fiber composition (Johnson et al. 1973), LG activity was not depressed with knee extension—unlike MG activity (Figs. 1, 2). Earlier studies also reported that LG and MG activity occasionally had different responses to the same motion (Nardone and Schieppati 1988; Tamaki et al. 1998, 2011). For example, during eccentric isotonic plantar flexion against a 100-N load, the LG displayed high activation, whereas the MG showed little activity (Nardone and Schieppati 1988). Moreover, a previous study indicated the possibility that the MG and LG are differently controlled by neural pathways from the same origin (Duysens et al. 1996). The sural nerve stimulation had a facilitatory effect on the MG and an inhibitory effect on the LG during the middle and late stance phase of walking (Duysens et al. 1996). Therefore, LG activity could be regulated separately from the MG for the task used in the study although the characteristics of neural circuits from the quadriceps have been unclear.
Second, the change in the ARV of the MG was not always proportional to that of the Sol. For example, increasing the knee extension level from 50% to 100% KEMVC resulted in the ARV of the MG remaining at almost the same level, whereas that of the Sol significantly increased (Fig. 3). The physiological cross-sectional area (PCSA), the total cross-sectional area of all of the muscle fibers at right angles to their long axes, is known to be a good predictor of the generation capacity of muscle force (Fukunaga et al. 2001). The Sol has a larger PCSA than the MG (Friederich and Richard 1990). Taking into consideration the difference in the PCSA between these muscles, the estimated torque increase induced by the increased Sol activity was larger than the decrease in the plantar flexion torque induced by MG activity depression. However, the MG has a three times higher ratio of type II fibers than the Sol (Johnson et al. 1973), and type II fibers generate more force than type I fibers. The difference in muscle fiber composition reduces the estimated torque increase by the Sol.

In another aspect, recent studies reported that muscle activities were different in several portions of a single muscle, such as the MG and RF. Additionally, the surface EMG technique recorded muscle activity only at the relatively narrow area underneath the electrode (Hodson-Tole et al. 2013; Watanabe et al. 2012). For example, recorded EMG activity was different at each electrode in the MG, and the distal portion of the MG was mainly activated during standing (Hodson-Tole et al. 2013). Although the depression of MG activity detected was small in this study, there was the potential for a greater decrease in muscle activity in other portions of the MG. Additionally, other small plantar flexors (e.g., peroneus brevis, posterior tibialis) contribute at least 20% of the plantar flexion torque (Murray et al. 1976). Because there is an inhibitory pathway from the quadriceps to the peroneus brevis (Meunier et al. 1994), it is possible that simultaneous knee extensor activation causes the activity of such small muscles to decrease. (The activities of these muscles can barely be measured by surface EMG.) When we take into consideration the combined decreased activation of the MG, the activity spatial
difference within the MG, and the small plantar flexors, the torque increase by the Sol was not excessive.

Conclusions

The present study revealed that when knee extensor activity is added to plantar flexion MG activity is depressed and Sol activity is increased. The quantified amounts of change indicate that knee extensor activation has an important influence on load sharing among plantar flexors. The results suggest that monoarticular plantar flexors (not biarticular plantar flexors, which also function as knee flexors) are selectively activated depending on the preference of their anatomical characteristics for simultaneous knee extension.
Section II of Chapter III

*Plantar flexor activities depend on muscle synergies with varying in task-irrelevant subspace*

This study will be published elsewhere within five years.
Chapter IV

Voluntary activation of triceps surae muscles depends on the presence of knee extensor activation

This study will be published elsewhere within five years.
Chapter V

General Discussion

*Dependence of human motor control on muscle synergies*

The main purpose of the thesis is to confirm the dependence of human motor control on muscle synergies. For this purpose, various patterns of plantar flexor activities at the mechanically same condition were quantified.

In the behavioral approach based on computational decomposition techniques, such as the non-negative matrix factorization (Lee and Seung 1999), previous studies evaluated muscle activities during various movements (Cappellini et al. 2006; d'Avella et al. 2003; Roh et al. 2011; Tresch et al. 1999) or a dynamic movement which included tonic and silent periods of individual muscle activities, such as walking (Clark et al. 2010; Dominici et al. 2011). These studies extracted muscle synergies from resultant muscle activities, based on the premise that various muscle activation patterns were feasible for these movements. However, a given movement largely reduces feasible muscle activation patterns (Kutch and Valero-Cuevas 2012; Tresch and Jarc 2009). Partly because of reduction in feasible patterns at a given movement, computer simulation studies based on minimizing an objective function, such as the metabolic energy (Anderson and Pandy 2001) or the weighted squared sum of muscle forces (Xiao and Higginson 2008), predicted synergy-like grouped muscle activities regardless of no assumption to muscle synergies. In another aspect, the electromyographic analysis is difficult to evaluate the dynamic movements, which many synergy studies have investigated, because of the signal nonstationarity, the shift of the electrodes relative to muscle fibers, and the changes in the conductivity properties of the tissues separating electrodes and muscle fibers (Farina 2006). Even though previous studies aimed to extract a relatively small number of grouped muscle
activities from various patterns, feasible muscle activation patterns that the mechanical constraints reduced might be misinterpreted as muscle synergies because the actual number of feasible activation patterns was unknown at a given movement. This lack of information prevented previous studies in the behavioral approach from strictly examining the dependence of human motor control on muscle synergies.

In contrast to previous studies, isometric plantar flexion with or without isometric knee extension in this research clearly required only one mechanical constraint. Because the mechanical constraint of this research was plantar flexion torque only and was not affected by knee extension at fully extended knee position, the mechanical constraint was same under a given plantar flexion torque regardless of knee extensor activation. When the slope of regression line, which suggested a muscle synergy (Lee 1984), between plantar flexor activities was drastically changed with knee extensor activation (Chapter II, and Section II of Chapter III), the number of constrained muscle activation patterns exceeded that of mechanical constraints. Therefore, this result suggests that plantar flexor activation is non-mechanically constrained.

Non-mechanical constraints correspond to not only muscle synergies but also the peripheral neural pathways between knee extensor and plantar flexor muscles (Meunier et al. 1993, 1994). For example, the heteronymous connection from the quadriceps muscles to the soleus muscle (Meunier et al. 1993) would increase the soleus activity with adding knee extensor activation to plantar flexion, and then, the activation ratio between the soleus muscle and other plantar flexor muscles, such as medial and lateral gastrocnemius, and peroneus longus and brevis muscles, must change to maintain the targeted torque. Certainly, knee extensor activation at low-intensity plantar flexion induced an increase in the soleus activity and a decrease in the medial gastrocnemius activity (Section I of Chapter III).

The results presented here will be published elsewhere within five years.
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Uncontrolled manifold hypothesis at the muscle synergy level

A recent study had applied the uncontrolled manifold approach to the muscle activation level and reported that the variability of index finger muscle activities that affected the fingertip force was smaller than their task-irrelevant variability (Valero-Cuevas et al. 2009). One interpretation
(Tresch and Jarc 2009) is that this small variability suggests that each muscle was independently controlled and its activity that did not affect the task (i.e., fingertip force) was uncontrolled. This interpretation emphasizes the independent control of muscle activities and seemingly contradicts the muscle synergy hypothesis (Tresch et al. 1999). However, Section II of Chapter III revealed that the uncontrolled manifold hypothesis does not contradict the muscle synergy hypothesis.

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Previous studies have revealed the physiological entity for linear muscle activation and linear combination of activation, which were premised by the muscle synergy hypothesis. The orderly recruitment of motoneurons depending on the size principle (Henneman et al. 1965) would result in linear muscle activation. Motoneurons innervating a given muscle would be divided into termed task groups (Loeb 1985), and the size principle is held within each task group (Riek and Bawa 1992). A task group would be formed across different muscles (Sokoloff
et al. 1999; Wyman et al. 1974), through a spinal interneuron (Bizzi et al. 1991; Takei and Seki 2010) or a cortical interneuron with corticomotoneuronal cells (Huntley and Jones 1991). A muscle synergy could be expressed as such a task group. Summation of recruitments of muscle synergies enables linear combination of muscle activation. Although muscle synergies could correspond to the above-mentioned physiological systems, the recruitment strategy of muscle synergies remained unclear (Sokoloff et al. 1999). The uncontrolled manifold analysis for the muscle synergy recruitment provided a new insight into this physiologically unsolved problem for the muscle synergy hypothesis.

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**Perspective for human movements**

Muscle synergies could reduce the degrees of freedom of lower limb muscles or motor units. Especially, the central pattern generator could generate locomotion (Grillner and Zangger 1975) by using such simplified modules (Taga et al. 1991). If the number of plantar flexor synergies is one as in the case of previous muscle synergy studies that set the arbitrary criterion for determining the number of muscle synergies (Cappellini et al. 2006; Clark et al. 2010; Dominici et al. 2011), the lower limb control is simplest. However, the present research suggested that more than one plantar flexor synergy left the degrees of freedom and the recruitment strategy
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To accomplish the task goal during a human voluntary movement, the central nervous system tries to correct the joint motion only if the motion error affects the task performance, and if not, the error from the desired trajectory is neglected. According to the uncontrolled manifold principle, the central nervous system optimally uses the feedback information that involved in the task performance, for modulating the recruitments of muscle synergies. This modulation induces successive changes at the muscle activation level (Fig. 3; Valero-Cuevas et al. 2009), the kinetics level (Scholz et al. 2002), and the joint kinematics level (Diedrichsen 2007; Scholz et al. 1999, 2000). Because the uncontrolled manifold principle is fundamentally held at the muscle synergy level (Fig. 5 in Section II of Chapter III), this principle would appear
at these secondary levels.

Conclusions

The present research confirmed the dependence of human motor control of plantar flexor activities on muscle synergies, with clarifying the mechanical constraint and suggested that the muscle synergy recruitment strategy within a task corresponds to the uncontrolled manifold principle, leading to the uncontrolled manifold principle at the muscle activation level and other secondary levels.
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