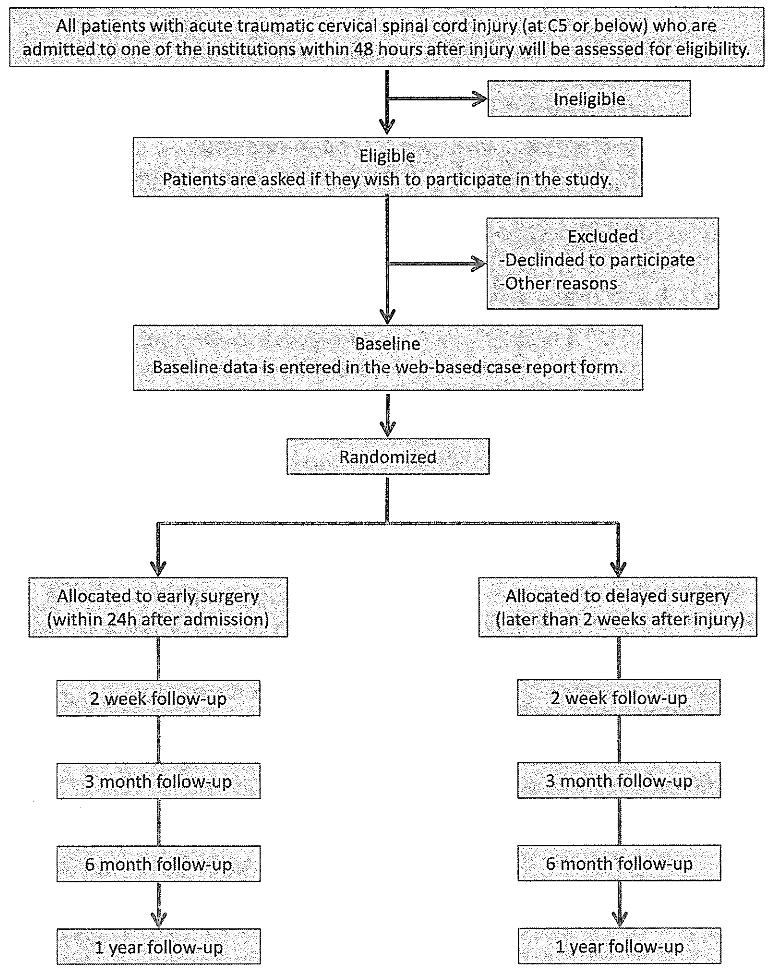

Figure 1 Study flowchart.

including plain radiographs, magnetic resonance imaging (MRI) and computed tomography (CT).

Inclusion criteria

Subjects will be eligible for inclusion if they satisfy the following inclusion criteria:

- aged 20 to 79 years
- without bone injury (spinal fracture or dislocation)
- American Spinal Injury Association (ASIA) impairment Grade C
- cervical canal stenosis due to preexisting conditions, such as spondylosis and ossification of the posterior longitudinal ligament (OPLL)

The presence of cervical canal stenosis will be confirmed by physicians based on the MRI findings obtained on admission. The presence of OPLL will be determined by using plain radiographs or CT. The thickness of the OPLL must be 20% or more of the spinal canal.

Exclusion criteria

Subjects will be excluded from enrollment if they meet any of the following conditions:

- unstable medical status
- unable to undergo surgery within 24 hours after admission
- impaired consciousness or mental disorder that precludes neurological examination
- difficulty in obtaining informed consent in Japanese

Randomization

We will adopt the web-based allocation system using the University Medical Information Network (UMIN), which is one of the data centers that run as a public institution in Japan. By entering the information about the patient, investigators will be able to know the allocation results immediately.

The allocation table, which was created by stratified block randomized by the trial statistician, is registered in the UMIN. The block size is concealed to all investigators involved in this study. We have adopted stratification factors as follows:

- the presence of ossification of the posterior longitudinal ligament (OPLL) (yes/no)
- implementation of high-dose methylprednisolone treatment according to the NASCIS2 protocol (yes/no)
- preexisting gait disturbance due to myelopathy
- degree of canal compromise (50% or more/less than 50% canal compromise)

Preexisting gait disturbance due to myelopathy will be determined by the attending spine surgeon before randomization, based on thorough patients' history and available medical record. Gait disturbance attributable to other causes (for example, trauma, osteoarthritis, and paralysis after stroke) will be excluded.

Presence of severe canal compromise (50% or more canal compromise) will be assessed by the attending spine surgeon based on mid-sagittal MR images obtained at admission. For patients presented with OPLL, mid-sagittal reconstruction CT images or plain radiographs of the cervical spine will be used to calculate the degree of canal compromise.

Interventions

Patients will be randomly allocated to undergo either early surgery or delayed surgery.

Early surgery

Patients allocated to early surgery will undergo surgery within 24 hours after admission. The time when they enter the operating room will be used as a reference. The principal goal of surgery is to achieve decompression of the spinal cord. The choice of anterior or posterior approach will be left to the surgeon's discretion. The use of spinal instrumentation will be permitted when needed. The surgery will be performed by or under supervision of a board-certified orthopedic surgeon. The details of the surgical treatment and any perioperative adverse events will be recorded in a web-based predefined form. All patients will receive intensive rehabilitation tailored to the individual and injury-specific factors immediately after surgery.

Delayed surgery

Patients allocated to the delayed surgery group will receive conservative treatment consisting of early mobilization and intensive rehabilitation for at least two weeks after the injury. Surgical decompression will be performed by the same team as in the early surgery group at any time later than two weeks after the injury when the physician thinks the timing is appropriate. Physicians will be allowed to treat patients non-surgically as long as the patients can achieve independent ambulation.

Other treatments

Apart from the surgical management, all patients will receive appropriate medical support, including permissive or induced hypertensive therapy (mean blood pressure > 85 mmHg) [13]. High-dose methylprednisolone will be used per the discretion of the treatment team according to the NASCIS-2 protocol [1,14,15]. The use or lack of high-dose methylprednisolone must be determined and entered into the web-based database prior to the randomization. Physicians will not be allowed to change or discontinue the administration of methylprednisolone after randomization.

Primary and secondary outcomes

Participants will be evaluated two weeks, three months, six months and one year after randomization. Table 1 provides an overview of the outcomes that will be used in this study. Physicians and research nurses who are not involved in the patient's care will assess the outcome at each follow-up examination before the patients see their doctors.

Primary outcomes

The primary outcome is a recovery in motor function one year after injury. The assessment will include: 1) the change from baseline to one year after the admission in the ASIA motor score; 2) the total score of the Spinal Cord Independence Measure (SCIM) version 3 and 3) the proportion of patients who regained the ability to walk 100 meters without human assistance.

The ASIA motor score is a 100-point score based on ten pairs of key muscles, each given a five point rating. The SCIM is a validated 100-point disability scale developed specifically for patients with SCI, with an emphasis on daily tasks grouped into three subscales: self-care (20 points), respiration and sphincter management (40 points) and mobility (40 points) [16-18].

Secondary outcomes

The secondary outcomes will include: 1) the health-related quality of life as measured by the Medical Outcomes Study Short Form 36 (SF-36) [19,20] and the EuroQol 5 Dimension (EQ-5D) [21]; 2) the neuropathic pain at the injured level and below as assessed by the Neuropathic Pain Symptom Inventory (NPSI) [22] and 3) the walking status as evaluated with the Walking Index for Spinal Cord Injury (WISCI) II [23].

The scores on the SF-36 will be used as a generic measure of the patient health status. The SF-36 comprises eight

Table 1 The timeline of the outcome measures to be collected

	Admission	Follow-up			
		2 weeks	3 months	6 months	1 year
Visit	X[a]	X	X	X	X
Informed consent	X[a]				
Baseline clinical characteristics	X[a]				
Blood analyses	X[a]	X	X	X	X
Magnetic resonance imaging	X[a]				X
Computed tomography	X[a]				
Plain radiographs	X[a]	X			X
Neurological assessment including the ASIA motor score and ASIA impairment scale	X[a]	X	X	X	X
Evaluation of adverse events					
SCIM version 3		X	X	X	X
WISCI II		X			X
SF-36		X			X
EQ-5D		X	X	X	X
NPSI		X			X

X[a]: obtained prior to enrollment; ASIA: American Spinal Injury Association; EQ-5D: EuroQol 5 Dimension; NPSI, Neuropathic Pain Symptom Inventory; SCIM: Spinal Cord Independence Measure; SF-36: Medical Outcomes Study Short Form 36; WISCI: Walking Index for Spinal Cord Injury.

single subscale scores associated with physical and mental health.

The NPSI is a self-questionnaire specifically designed to evaluate the different symptoms of neuropathic pain. It includes 12 items, each of which is quantified on a (0 to 10) numerical scale. The pain associated with SCI is classified into two categories: at-level pain and below-level pain. Participants will be asked to complete the NPSI separately for pain in the upper extremities (at-level pain) and in the trunk and lower extremities (below-level pain). The WISCI II is a valid 21-level hierarchical scale of walking based on physical assistance, the need for braces and devices, with an ordinal range from 0 (unable to walk) to 20 (walking without assistance for at least 10 meters).

Adverse events

The occurrence of pre-specified adverse events will be also assessed. Adverse events will be gathered from patients themselves and from the patient record review. The *a priori* defined adverse events are: worsening of paralysis in the upper extremities, worsening of paralysis in the lower extremities, reoperation, use of a respirator (more than one week), tracheostomy, sepsis, pneumonia, acute respiratory distress syndrome, atelectasis, other respiratory complications, wound infection (superficial), wound infection (deep), urinary tract infection, other infections, gastrointestinal bleeding, peptic ulcer, ileus, acute myocardial infarction, other cardiac events, pulmonary embolism, cerebrovascular complication, liver dysfunction/disease, renal dysfunction/disease, delirium, depression, other complications and death.

Sample size

For this exploratory trial, the sample size was determined primarily based on feasibility. We assumed that it is feasible to enroll approximately 100 patients (50 patients per group) during the planned study period. As there is no valid data to indicate the optimal endpoint to evaluate the neurological and functional recovery of SCI patients, we selected three candidate endpoints as the primary endpoint: 1) the change from the baseline to one year after the admission in the ASIA motor score; 2) the proportion of patients who regained the ability to walk 100 meters without human assistance and 3) the total score of the Spinal Cord Independence Measure (SCIM) version 3.

We need 45 patients per group when the difference to be detected in the ASIA motor score between the groups is 12 points and the common standard deviation is 20. Additionally, we expect that the percentage of ambulatory patients one year after the injury will increase from 50% to 80%. To detect this difference, we need 39 patients for each group. With regard to the SCIM, there are few data that can be used as a basis for sample size calculation. For the reasons above, we set the sample size to be 50 patients per group. All calculations assume an 80% power at a two-tailed significance level of 0.05.

Statistical methods

All analyses will be based on an intention-to-treat principal, and will be performed with two-sided *P*-values considered significant when they are below 0.05. For a detailed analysis, the statistician will make a statistical analysis plan before the data lock, as indicated below:

1) Primary endpoint:
  - ASIA motor score
    Calculate the difference one year after the baseline, and compare the two groups using a *t*-test
  - The proportion of patients who regained the ability to walk
    Calculate the rate of patients who can walk one year after the baseline, and compare the two groups using the chi-square test
  - SCIM
    Compare the differences in the SCIM after one year.

2) Secondary endpoint:
   Compare the differences in the WISCI II, SF-36 and EQ-5D. For the SF-36, we plan to use only the total points, and not to compare each domain.
3) Safety:
   We will compare the rates of adverse events between the groups. In particular, in patients that are moved out of the surgical standby group, we will compare the ratio of the occurrence of adverse events with those in the patients in the early operation group.

Planned subgroup analyses

Predefined subgroup analyses will be performed in patients with or without OPLL. These will include high-dose methylprednisolone treatment, preexisting gait disturbance and severe canal compromise (> 50% canal compromise). Based on our previous study, we hypothesize that early surgical decompression will be beneficial in patients with preexisting gait disturbance and those with severe canal compromise.

Ethical issues

The study protocol was approved by the local ethics committees of all participating hospitals and will be done in accordance with the Declaration of Helsinki. The study will be overseen by an independent safety monitoring board. All participants will give written informed consent before entry.

Ethical approval was obtained from all participating hospitals. The results will be disseminated via the usual scientific forums, including peer-reviewed publications and presentations at international conferences.

Discussion

Despite intensive basic and clinical research, an effective treatment for cervical SCI has not been established. In the presence of preexisting canal stenosis, the role of surgical decompression and its optimal timing continue to be subjects of intense debate. Addressing the issue of the timing of surgical intervention is critical in that, if the timing of surgery has no effect on the patient's outcome, then all patients can initially be treated non-surgically and surgery can be delayed for weeks or even months after the injury without compromising the patient's recovery [6]. On the other hand, if early surgical decompression is proven to be beneficial, drastic changes in the medical service system, including logistics, should be made to ensure that all SCI patients receive early surgery.

In conducting clinical studies on SCI, the heterogeneity of the study population can be a major obstacle, especially in the acute phase. SCI patients vary greatly in the severity of paralysis and neurological prognosis. Clinical studies including patients with various degrees of neurological injury may have insufficient power. Therefore, in this study, we will focus on patients with ASIA C status. In a recent review, the consensus of experts was that it is reasonable to consider early surgical decompression in patients with profound neurologic deficit (ASIA C) and spinal canal stenosis without fracture or instability. On the other hand, those with a less severe deficit (ASIA D) can be treated with initial observation with surgery potentially performed at a later date [6]. We will exclude patients with ASIA B status, because these patients are often difficult to distinguish from ASIA A patients at the time of admission.

The information available regarding the window of opportunity or therapeutic window in human SCI is imprecise [24] and the definition of 'early surgery' has not yet been well established. Although the ideal cutoff time at which surgery provides potential neuroprotection is not known, the most intensively investigated times in the prior studies were 24 and 72 hours. In this study, we have adopted a cutoff at twenty-two hours after admission mainly for practical and logistic reasons. Twenty-four hours after admission is considered to be necessary and sufficient to safely perform the initial evaluation of patients and summon the operating team for emergency surgery. In this study, we adopted the time of admission as a reference, since the time of injury sometimes remains conjectural.

The OSCIS study is designed to provide evidence of the potential benefit of early surgical decompression over a wait-and-see strategy. We believe that the results of this trial will have a substantial impact on the management of cervical SCI.

Trial status

The trial was registered in the UMIN register on 1 December, 2011. The first patient was randomized on 3 December, 2011. The trial is currently open for recruitment.

Additional file

Additional file 1: List of participating hospitals with approval from local ethical boards (as of 6 August, 2013).

Abbreviations

AIS: ASIA Impairment Scale; ASIA: American Spinal Injury Association; CT: Computed tomography; EQ-5D: EuroQol 5 Dimension; MRI: Magnetic resonance imaging; OPLL: Ossification of the posterior longitudinal ligament; SCI: Spinal cord injury; SCIM: Spinal Cord Independence Measure; SF-36: Medical Outcomes Study Short Form 36; UMIN: University Medical Information Network; WISCI: Walking Index for Spinal Cord Injury.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HC, HO, TO, SS, MS, MM, and YT participated in the conception and design of the study. YK will participate in the monitoring and quality control of the data. HC drafted the manuscript. All authors read, commented on and approved the manuscript.

Acknowledgement

This study is being performed with the aid of the Investigation Committee on the Ossification of the Spinal Ligaments of the Japanese Ministry of Health, Labor and Welfare. This study is also supported by the JOA-Subsidized Science Project Research 2012-2.

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Received: 27 April 2013 Accepted: 31 July 2013
Published: 7 August 2013

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doi:10.1186/1745-6215-14-245
Cite this article as: Chikuda *et al.*: Optimal treatment for Spinal Cord Injury associated with cervical canal Stenosis (OSCIS): a study protocol for a randomized controlled trial comparing early versus delayed surgery. *Trials* 2013 14:245.

Exp Brain Res (2014) 232:1–11
DOI 10.1007/s00221-013-3702-2

RESEARCH ARTICLE

Modulation between bilateral legs and within unilateral muscle synergists of postural muscle activity changes with development and aging

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Received: 17 October 2012 / Accepted: 3 September 2013 / Published online: 10 November 2013

Abstract The effect of development and aging on common modulation between bilateral plantarflexors (i.e., the right and left soleus, and the right and left medial gastrocnemius) (bilateral comodulation) and within plantarflexors in one leg (i.e., the right soleus and the right medial gastrocnemius) (unilateral comodulation) was investigated during bipedal quiet standing by comparing electromyography–electromyography (EMG) coherence among three age groups: adult (23–35 years), child (6–8 years), and elderly (60–80 years). The results demonstrate that there was significant coherence between bilateral plantarflexors and within plantarflexors in one leg in the 0- to 4-Hz frequency region in all three age groups. Coherence in this frequency region was stronger in the elderly group than in the adult group, while no difference was found between the adult and child groups. Of particular interest was the finding of significant coherence in bilateral and unilateral EMG recordings in the 8- to 12-Hz frequency region in some subjects in the elderly group, whereas it was not observed in the adult and child groups. These results suggest that aging affects the organization of bilateral and unilateral postural muscle activities (i.e., bilateral and unilateral comodulation) in the plantarflexors during quiet standing.

Keywords Aging · Development · Postural muscle activities · Common modulation

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Introduction

During human quiet standing, the ankle is the primary joint regulating the position of the body, as the non-moving feet are the only contact with the external environment. In addition, human bipedal standing is a task that requires bilateral activities of postural muscles. Therefore, many studies have addressed how the activities between bilateral plantarflexors are organized by assessing time- and frequency-domain characteristics (e.g., Gibbs et al. 1995; Mochizuki et al. 2006). So far, it has been found that common input to individual motor units in the bilateral soleus muscles (SOL) is greater during postural tasks than during voluntary isometric tasks (Mochizuki et al. 2006, 2007).

Boonstra et al. (2008a) recently reported that coherence between bilateral SOLs during quiet standing was statistically significant in two distinct frequency regions (i.e., 0–4 and 8–12 Hz) when coherence was assessed by rectified surface electromyography (EMG). The result in the former frequency region was consistent with the previous report in which coherence was assessed by motor units (Mochizuki et al. 2006, 2007). On the other hand, the latter frequency region was not observed in the study of motor units. The reason for these differences was unclear, but it could be attributed to differences in the methods. Coherence between rectified surface EMGs quantifies common input to the net activity of two motoneuron pools (Boonstra et al. 2008a), whereas coherence between motor units is likely to reflect the correlated activity of two focal motoneurons. Regarding the origin of correlated activity in the latter frequency region, they suggested that it would be related to bilateral common input from the reticulospinal tract, as alcohol ingestion resulted in a decrease of coherence in this frequency region.

While bilateral common input to the plantarflexors has been investigated to some extent for young adult individuals, the effects of development and aging on the organization of postural muscle activity between bilateral legs have rarely been investigated. Aging induces considerable change in the central nervous system as well as the neuromuscular system as related to postural balance (Horak et al. 1990; Maki and McIlroy 1996). As a consequence, postural sway increases more in the elderly than in young individuals due to a deterioration of the postural control system (Collins et al. 1995; Laughton et al. 2003; Masani et al. 2007). In contrast, postural stability keeps improving during childhood in the course of development (Figura et al. 1991; Hatzitaki et al. 2002; Rival et al. 2005; Olivier et al. 2008). Given these changes of standing posture, it may be expected that development and aging also affect the organization of bilateral coupling between homologous plantarflexors.

In the present study, we investigated the effects of development and aging on the common modulation between bilateral homologous plantarflexors during quiet standing by comparing EMG–EMG coherence among three age groups: adult (23–35 years), child (6–8 years), and elderly (60–80 years). EMG–EMG coherence was assessed by surface EMG between (1) bilateral SOL and (2) bilateral medial gastrocnemius (MG) muscles. In the previous studies of motor units, it was reported that common modulation of one leg was also greater during postural tasks than during voluntary tasks (Mochizuki et al. 2006). Therefore, we also examined EMG–EMG coherence between unilateral SOL and MG muscles. Eyes-closed (EC) and eyes-open (EO) conditions were applied in the present study, since it is known that visual information affects the strength of EMG–EMG coherence (Boonstra et al. 2008a).

Methods

Subjects

Subjects included 23 healthy adults (13 males and 10 females) from 23 to 35 years of age, 21 healthy children (11 boys and 10 girls) ranging from 6 to 8 years, and 22 healthy elderly (14 males and 8 females) ranging from 60 to 80 years. Informed consent to participate in the experimental procedures was obtained from the subjects and, in the case of the children, their parents; the experimental procedures were approved by the local ethics of the National Rehabilitation Center for Persons with Disabilities, Tokorozawa, Japan.

Measurements

Surface EMG activities were recorded from both sides of the SOL, MG, and tibialis anterior (TA) muscles. The EMG signals were recorded by surface EMG sensors with an inter-electrode distance of 10 mm (DE-2.1, DELSYS, Boston, MA, USA); the sensors were connected to a differential amplifier with a filter bandwidth of 20–450 Hz (Bagnoli-8, DELSYS, Boston, MA, USA). All signals were digitalized at a sampling frequency of 1 kHz by a 16-bit A/D converter (PowerLab, ADInstruments, Sydney, Australia).

The subjects were required to stand quietly on a platform for 125 s with their feet parallel in a natural stance. They were asked to hold both arms comfortably at their sides under EO or EC conditions. In the adult and elderly groups, the displacement of the center of pressure (COP) was measured using a force platform (type 9281B, Kistler, Zurich, Switzerland). In the child group, COP was measured by another force platform (EFP-S-1.5KNSA13, Kyowa, Tokyo, Japan) due to technical reasons.

EMG–EMG coherence

Spectral coherence is a statistic that can be used to identify common oscillations between two signals across a broad range of frequencies. This statistic has been applied to two EMG signals recorded above different muscles to investigate the strength of comodulation of the spinal motoneurons of the plantarflexors (i.e., EMG–EMG coherence). EMG–EMG coherence among (1) bilateral SOL (right and left SOLs: rSOL–lSOL), (2) bilateral MG (right and left MGs: rMG–lMG), and (3) unilateral (right) SOL and MG (rSOL–rMG) muscles was calculated using two steps in accordance with the previous study of Farmer et al. (2007).

First, 125 s of data in each EMG signal was rectified and divided into 15 segments (no overlapping), each with 2^{13} data points. Then, the auto-spectra of two EMG signals (f_{xx} and f_{yy}) and the cross-spectra (f_{xy}) were estimated by averaging the discrete Fourier transforms from the segments. The squared coherence function ($|R_{xy}(\lambda)|^2$) was estimated with the following equation (1):

$$|R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda)f_{yy}(\lambda)}, \quad (1)$$

where λ is the frequency. The phase function was calculated as the phase angle of the cross-spectral estimate.

Second, the pooled coherence function was estimated to summarize the correlation structure in each group of subjects. For population analysis, all rectified EMG signals were normalized to have unit variance. The pooled coherence function ($|\hat{R}_{xy}(\lambda)|^2$) was estimated with the following equation (2):

$$\left|\hat{R}_{xy}\right|^2 = \left|\frac{\sum_{i=1}^{k} L_i R_{xy}^i(\lambda)}{\sum_i^k L_i}\right|^2, \tag{2}$$

where R_{xy}^i is the individual coherency, L_i is the number of segments required to estimate individual coherence, and k is the number of records (i.e., subjects).

In the present study, all confidence limits were set at 99 %.

Statistical analysis

The COP signal was low-pass filtered using a fourth-order Butterworth filter with a cutoff frequency of 20 Hz. Then, the speed of the COP was calculated by dividing the sum of the anterior/posterior (A/P) COP displacement by the sampling time. This measure has been reported to be valid for assessing age-related alterations of postural sway (Maki et al. 1990; Olivier et al. 2008).

For a statistical comparison of the amount of coherence among the groups, the coherence estimates for each pair of EMG signals were normalized into *z*-scores (Rosenberg et al. 1998). These *z*-scores were determined for individual subjects. Special focus was given to two frequency regions, the 0- to 4-Hz and 8- to 12-Hz regions. The former frequency region corresponds to postural sway related to EMG modulation (Gatev et al. 1999; Masani et al. 2003) and the latter to the motor unit discharge frequency (Kouzaki and Masani 2012).

The differences in the mean *z*-scores at the 0- to 4-Hz and 8- to 12-Hz regions among groups and between visual conditions were tested using a mixed-design (between and within factors) two-way (age × visual condition) repeated-measures ANOVA. When statistical significance was encountered, Tukey's post hoc comparisons were applied.

In the present study, the incidence of significant coherence in the 0- to 4-Hz and 8- to 12-Hz regions was calculated to show how many subjects reached the confidence limit in each group and for each EMG pair and visual condition. The statistical differences in incidence were tested using the χ^2 test at each EMG pair, frequency, and visual condition. Post hoc comparisons using Marascuilo's method were applied to determine the statistical differences in incidence among the groups.

A Pearson's product-moment correlation (i.e., a simple linear regression) was calculated between the speed of the A/P COP displacement and the coherence *z*-score (0- to 4-Hz or 8- to 12-Hz frequency regions) in each group and for each EMG pair and visual condition. The significance level was set at $P < 0.05$.

Results

The mean values of the speed of the A/P COP displacement for each age group and visual condition are shown in Fig. 1. As already reported in the previous studies, the speed of the A/P COP displacement was larger in the elderly and child subjects than in the adult subjects. A two-way ANOVA revealed the main effect of age and visual condition (age: $F_{(2,63)} = 47.677$, $P < 0.001$; visual condition: $F_{(1,63)} = 7.977$, $P < 0.001$). Since the interaction between age and visual condition was also significant ($F_{(2,63)} = 5.687$, $P = 0.005$), post hoc analysis was performed. The results show that the speed of the A/P COP displacement was significantly larger in the elderly and child groups than in the adult group (EO condition: $P < 0.001$ for the child group; EC condition: $P = 0.012$ for the elderly; and $P = 0.037$ for the child groups). A significant difference in visual conditions was found only in the elderly group ($P = 0.029$).

Typical examples of rectified surface EMGs, the corresponding auto-spectral density functions, and the coherence functions with the phase functions for rSOL–lSOL muscles in the EO condition are shown in Fig. 2. Peaks in the auto-spectral density functions were commonly observed in the 8- to 12-Hz frequency region for adult, child, and elderly subjects (Fig. 2, middle panels). However, coherence analysis revealed different patterns for the three age groups. The coherence functions showed significant values in the 8- to 12-Hz frequency region only in the elderly subject, but for all three age groups in the 0- to 4-Hz frequency region (Fig. 2, right panels).

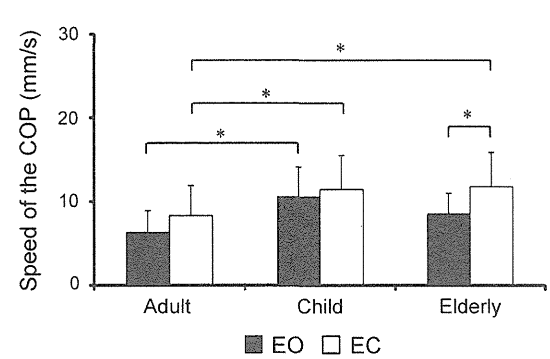

Fig. 1 Mean and standard deviation of the speed of the A/P COP displacement among adult, child, and elderly groups in the EO and EC conditions. *Asterisk* significant difference ($P < 0.05$)

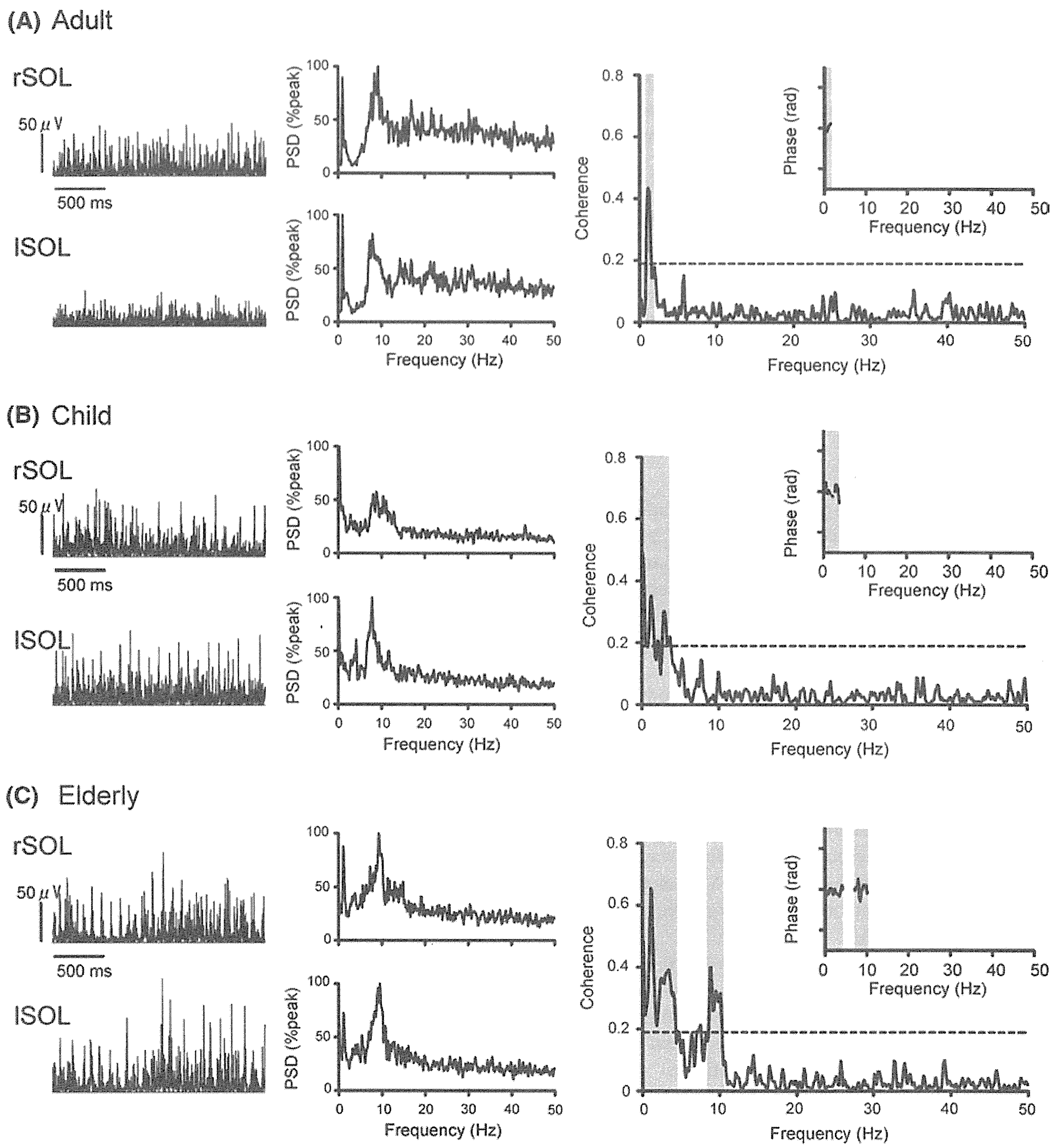

Fig. 2 Typical examples of rectified surface EMGs (*right*), autospectral density functions (*middle*) in the *right* (*upper part*) and *left* (*lower part*) SOL, and their coherence function with phase function as an inset (*right*) in the EO condition for an adult (**a**), a child (**b**), and an elderly (**c**) subject. The 99 % confidence level for each example is presented with *horizontal lines*. The frequency region where the corresponding coherence was significant is shown by *shading*

The pooled coherence and phase plots are shown in Figs. 3 and 4 to describe the features of each group. The pooled coherence values (Fig. 3) around the 0- to 4-Hz frequency region were statistically significant in all groups for all muscle pairs (bilateral muscles and unilateral muscles) in EO and EC conditions. Coherence between bilateral muscles around the 8- to 12-Hz frequency region was significant only in the elderly group; however, coherence between

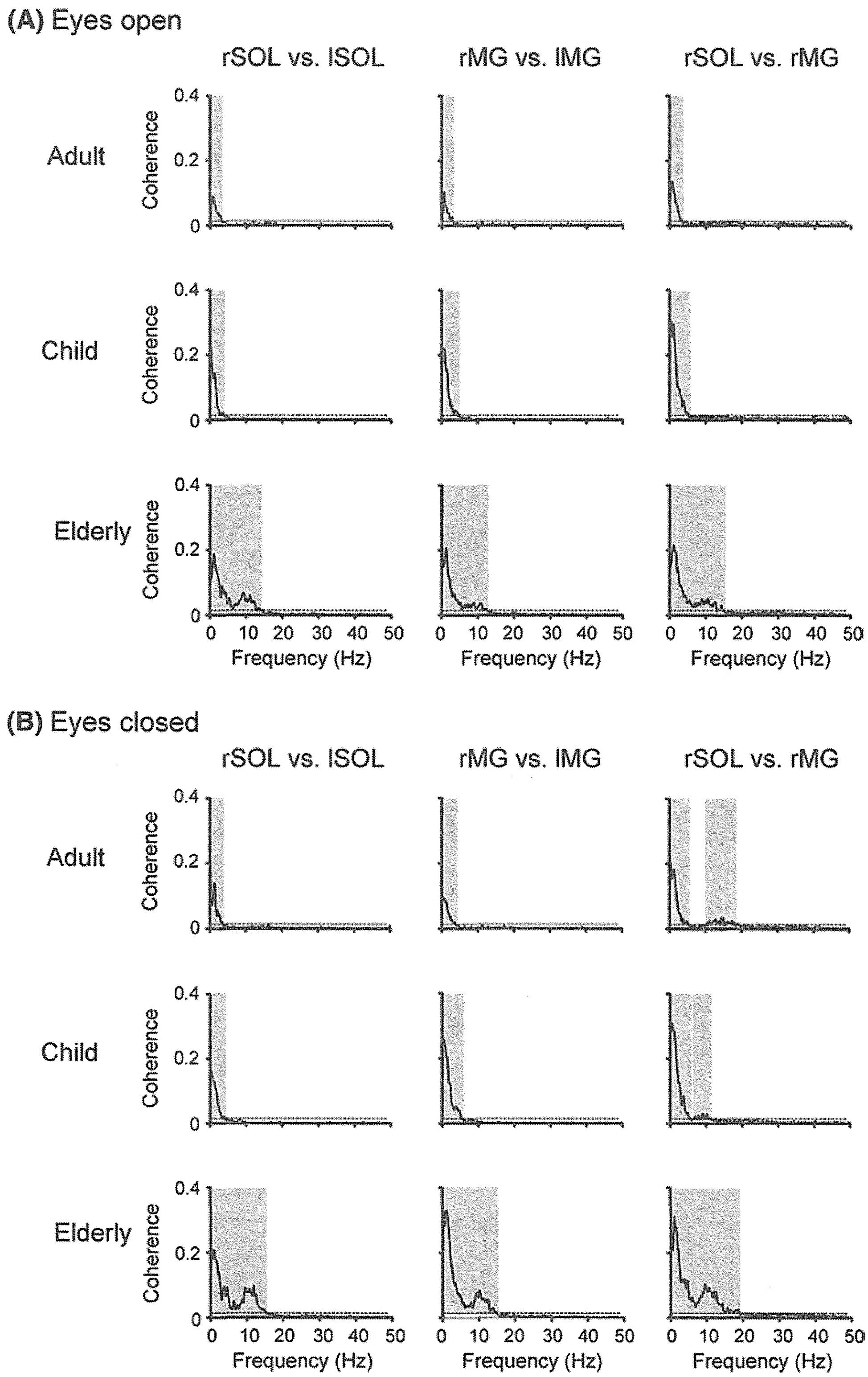

Fig. 3 Pooled coherence plot for three age groups in all muscle pairs (i.e., rSOL–lSOL, rMG–lMG, and rSOL–rMG) in the EO (**a**) and EC (**b**) conditions. The 99 % confidence level is presented with *horizontal lines*. The frequency region where the corresponding coherence was significant is shown by *shading*

unilateral muscles was significant in all groups in the EC condition. In the frequency region, where the corresponding pooled coherence was significant, the phase–frequency plots were almost flat and around 0 rads for all groups in all muscle pairs in the EO and EC conditions (Fig. 4).

The mean values of coherence *z*-scores for the 0- to 4-Hz and 8- to 12-Hz frequency regions are shown in Fig. 5 for statistical purposes. In the 0- to 4-Hz frequency region (Fig. 5, upper panels), the coherence *z*-scores between all muscle pairs were greater in the elderly group than in the adult group.

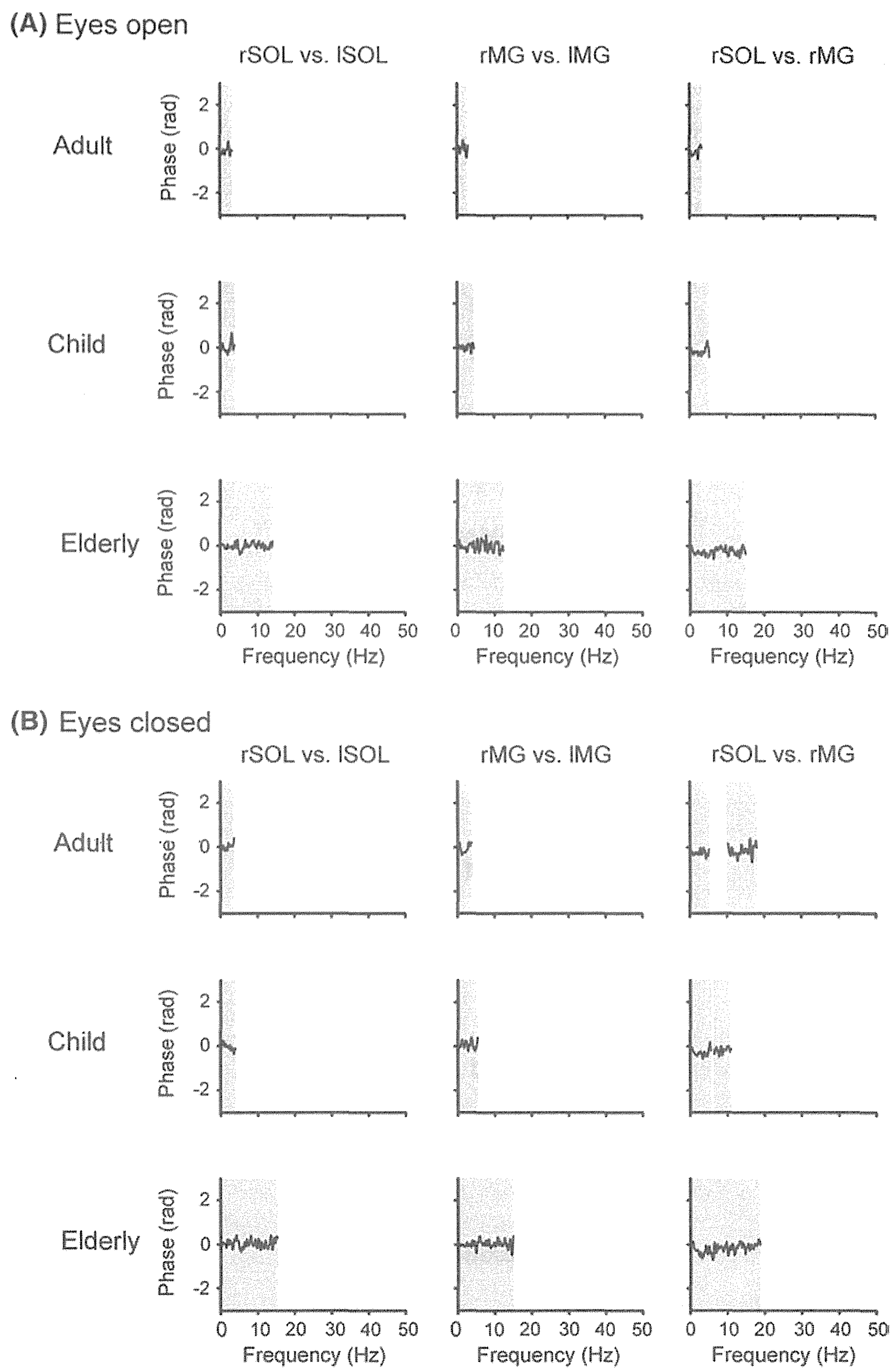

Fig. 4 Pooled phase plot for three age groups in all muscle pairs (i.e., rSOL–lSOL, rMG–lMG, and rSOL–rMG) in the EO (**a**) and EC (**b**) conditions. The *phase plot* is shown for the frequency region where the corresponding pooled coherence was significant

A two-way ANOVA revealed the main effect of age and visual condition in the rSOL–lSOL muscles (age: $F_{(2,63)} = 5.668$, $P = 0.005$; visual condition: $F_{(1,63)} = 4.089$, $P = 0.047$), the rMG–lMG muscles (age: $F_{(2,63)} = 7.449$, $P < 0.001$; visual condition: $F_{(1,63)} = 19.375$, $P < 0.001$), and the rSOL–rMG muscles (age: $F_{(2,63)} = 4.330$, $P = 0.017$; visual condition: $F_{(1,63)} = 15.989$, $P < 0.001$). Tukey's post hoc analysis revealed significant differences between the adult and elderly groups in the rSOL–lSOL muscles ($P = 0.004$) and the rSOL–rMG muscles ($P = 0.022$). In the rMG–lMG muscles, a difference between the adult and elderly groups was found only in the EC condition ($P < 0.001$).

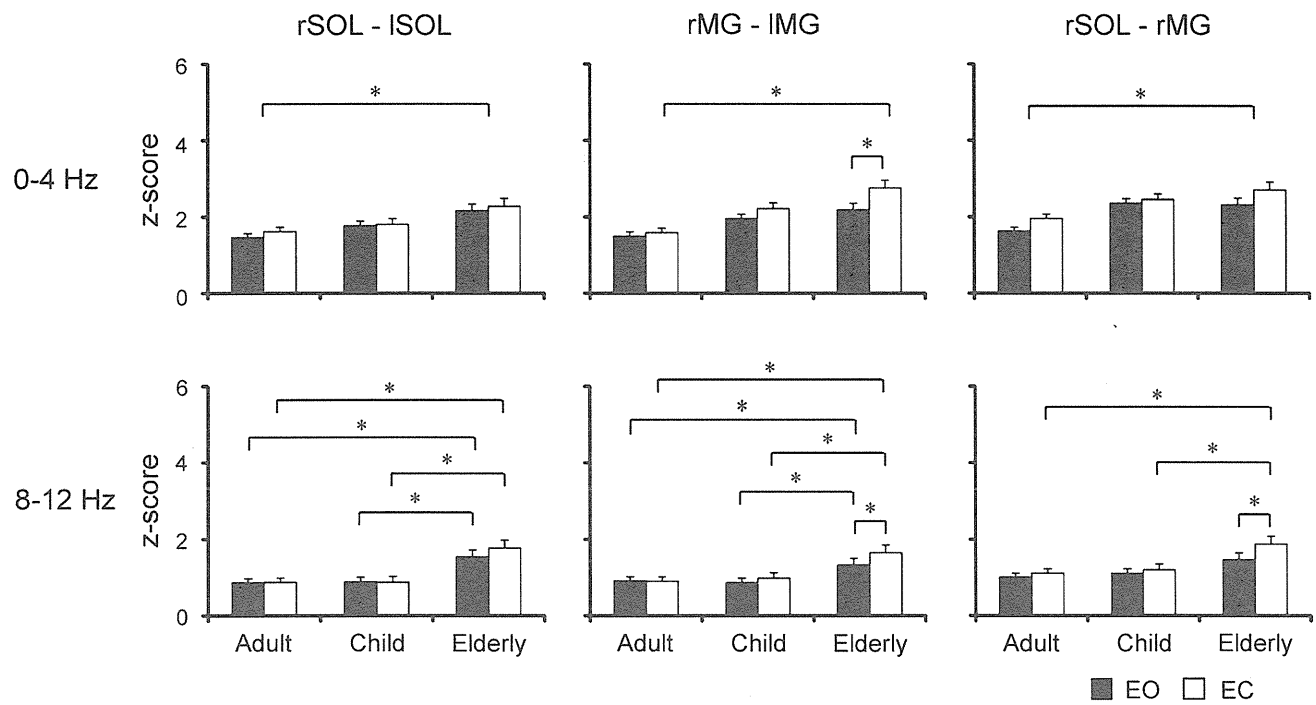

Fig. 5 Comparisons of the mean coherence *z*-scores among three age groups in the 0- to 4-Hz and 8- to 12-Hz frequency regions in each muscle pair in the EO and EC conditions. *Asterisk* significant difference ($P < 0.05$)

In the 8- to 12-Hz frequency region (Fig. 5, lower panels), group differences were found not only between the adult and elderly groups but also between the child and elderly groups. The coherence *z*-scores between all muscle pairs were greater in the elderly group than in the adult and child groups. A two-way ANOVA revealed a main effect of age and visual condition as well as significant interaction in the rSOL–lSOL muscles (age: $F_{(2,63)} = 25.086$, $P < 0.001$; visual condition: $F_{(1,63)} = 8.552$, $P = 0.005$; age × visual condition: $F_{(2,63)} = 7.551$, $P < 0.001$), the rMG–lMG muscles (age: $F_{(2,63)} = 15.318$, $P < 0.001$; visual condition: $F_{(1,63)} = 33.651$, $P = 0.005$; age × visual condition: $F_{(2,63)} = 15.376$, $P < 0.001$), and the rSOL–rMG muscles (age: $F_{(2,63)} = 7.224$, $P < 0.001$; visual condition: $F_{(1,63)} = 25.904$, $P = 0.005$; age × visual condition: $F_{(2,63)} = 6.583$, $P = 0.003$). In the rSOL–lSOL and the rMG–lMG muscles, differences between the adult and elderly groups as well as between the child and elderly groups were found in both the EO and EC conditions (all pairs, $P < 0.001$) but in the rSOL–rMG muscles only in the EC condition ($P = 0.001$ for adult vs. elderly and $P = 0.004$ for child vs. elderly).

In the 0- to 4-Hz and 8- to 12-Hz frequency regions, the coherence functions for each EMG pair reached significant levels more frequently in the elderly subjects than in the other two subject groups. Therefore, the incidence of significant coherence in each group and for each EMG pair was calculated (Table 1). In the 0- to 4-Hz frequency region (Table 1a), the χ^2 test revealed a significant difference between the groups in the rMG–lMG muscles (EO: $\chi^2 = 6.6137$, $P = 0.037$; EC: $\chi^2 = 12.3607$, $P = 0.002$) and

Table 1 The incidence of significant coherence in the (a) 0- to 4-Hz and (b) 8- to 12-Hz frequency regions for each EMG pair

(a) 0-4Hz

	rSOL - lSOL	rMG - lMG	rSOL - rMG
EO			
Adult	34.8% (8/23)	34.8% (8/23)] *	39.1% (9/23)] *
Child	61.9% (13/21)	57.1% (12/21)	57.1% (12/21)
Elderly	63.6% (14/22)	72.7% (16/22)]	77.3% (17/22)]
EC			
Adult	30.4% (7/23)	26.1% (6/23)] *	69.6% (16/23)
Child	47.6% (10/21)	57.1% (12/21)	66.7% (14/21)
Elderly	50.0% (11/22)	77.3% (17/22)]	77.3% (17/22)

(b) 8-12Hz

	rSOL - lSOL	rMG - lMG	rSOL - rMG
EO			
Adult	0.0% (0/23)] *	0.0% (0/23)	4.3% (1/23)
Child	0.0% (0/21)] *	0.0% (0/21)	9.5% (2/21)
Elderly	36.4% (8/22)]	18.2% (4/22)	18.2% (4/22)
EC			
Adult	0.0% (0/23)] *	0.0% (0/23)] *	8.7% (2/23)
Child	0.0% (0/21)] *	0.0% (0/21)] *	9.5% (2/21)
Elderly	45.5% (10/22)]	36.4% (8/22)]	36.4% (8/22)

* Significant difference ($P < 0.05$)

in the rSOL–rMG muscles (EO: $\chi^2 = 6.6996$, $P = 0.035$). Post hoc analysis showed that the elderly group exhibited significantly greater incidence than the adult groups ($P = 0.022$ for the rMG–lMG muscles in the EO condition; $P < 0.001$ for the rMG–lMG muscles in the EC condition; $P = 0.019$ for the rSOL–rMG muscles in the EO condition).

In the 8- to 12-Hz frequency region, the coherence functions between bilateral muscles reached significant levels only in the elderly subjects (Table 1b). The χ^2 test revealed a significant difference between the groups in the rSOL–lSOL muscles (EO: $\chi^2 = 18.2069$, $P < 0.001$; EC: $\chi^2 = 23.5714$, $P < 0.001$) and the rMG–lMG muscles (EC: $\chi^2 = 23.5714$, $P < 0.001$). Post hoc analysis showed that the elderly group exhibited significantly greater incidence than the adult ($P = 0.002$ for the rSOL–lSOL muscles in the EO condition; $P < 0.001$ for the rSOL–lSOL muscles in the EC condition; $P = 0.002$ for the rMG–lMG muscles in the EO condition) and child groups ($P = 0.002$ for the rSOL–lSOL muscles in the EO condition; $P < 0.001$ for the rSOL–lSOL muscles in the EC condition; $P = 0.002$ for the rMG–lMG muscles in the EO condition).

To investigate the relationship between EMG–EMG coherence and the amount of postural sway, coherence in the 0- to 4-Hz and 8- to 12-Hz frequency regions was compared with the speed of the A/P COP displacement. The coefficients of determination (r^2) values are shown in Table 2. The strength of the association was weak as a whole. A significant correlation was observed only in the 0- to 4-Hz frequency region in the child (rSOL–lSOL in both visual conditions, $P < 0.05$) and elderly groups (rMG–lMG and rSOL–rMG in the EC condition, $P < 0.05$).

Table 2 The coefficient of determination (r^2) value between the amount of postural sway and EMG–EMG coherence in the (a) 0- to 4-Hz and (b) 8- to 12-Hz frequency regions for each EMG pair

	rSOL–lSOL	rMG—lMG	rSOL–rMG
(a) 0–4 Hz			
EO			
Adult	0.06	0.03	0.03
Child	0.28*	0.00	0.06
Elderly	0.01	0.03	0.04
EC			
Adult	0.03	0.00	0.08
Child	0.34*	0.00	0.01
Elderly	0.04	0.23*	0.21*
(b) 8–12 Hz			
EO			
Adult	0.07	0.00	0.08
Child	0.00	0.00	0.05
Elderly	0.01	0.04	0.00
EC			
Adult	0.12	0.05	0.01
Child	0.04	0.01	0.01
Elderly	0.02	0.03	0.03

* Significant correlation ($P < 0.05$)

Discussion

The main findings of the present study were that there was a prominent comodulation between bilateral plantarflexors (bilateral comodulation) and with plantarflexors in one leg (unilateral comodulation) in the 0- to 4-Hz frequency region in all three age groups and in both visual conditions. This comodulation was stronger in the elderly group than in the adult group, while no difference was found between the adult and child groups. Of particular interest was that, in the elderly group, there was clear bilateral and unilateral comodulation in the 8- to 12-Hz frequency region in some subjects. Such bilateral comodulation was not observed in the adult and child groups, although a few subjects showed unilateral comodulation in these groups. These results suggest that the common oscillatory drive to the homologous plantarflexors and with plantarflexors in one leg became stronger in the elderly group in the two distinct frequency regions (0–4 and 8–12 Hz).

Coherence in the 0- to 4-Hz frequency region

We found significant coherence between bilateral plantarflexors and within plantarflexors in one leg in the 0- to 4-Hz frequency region in all three age groups; we also found that the strength of coherence for each bilateral plantarflexor was different among the age groups. The result for the adult group was consistent with the previous studies that reported comodulation between bilateral plantarflexors in the motor unit discharges (Mochizuki et al. 2006, 2007) and surface EMG recordings (Boonstra et al. 2008a). In addition, we found significant coherence between unilateral SOL and MG muscles in this frequency region, and the strength of these coherences was different among the age groups.

In quiet standing, the bilateral homologous plantarflexors synergistically modulate the ankle joint torque in a coordinated manner, which contributes to maintaining body balance. Our current finding and the previous findings (Mochizuki et al. 2006, 2007; Boonstra et al. 2008a) clearly quantify this synergistic activity of bilateral homologous plantarflexors during quiet standing. This comodulation should be realized via a common input to the motoneuron pools of those muscles. Mochizuki et al. (2007) suggested that a common somatosensory and/or supraspinal input concurrently modulates the motoneuron pools of both legs during a postural task that requires integrated muscle activities in bilateral legs.

The unilateral EMG–EMG coherence of plantarflexors during standing was reported here for the first time. Both the SOL and MG are synergistic muscles for the postural control of bipedal standing (Basmajian and De Luca 1964). Masani et al. (2003) showed that each correlates with postural sway, which agrees with the current results indirectly. It should be noted that bilateral and unilateral EMG–EMG coherences should reflect a different neural control mechanism. Bilateral EMG–EMG coherence may reflect organized inputs for homologous plantarflexors to maintain bipedal standing, while unilateral EMG–EMG coherence may reflect functional coupling of inputs for synergist plantarflexors.

Significant bilateral EMG–EMG coherence in the 0- to 4-Hz frequency region is most likely observed between homologous plantarflexors during postural control tasks involving both legs (Mochizuki et al. 2006; Boonstra et al. 2008a) but not between elbow muscles (Boonstra et al. 2006) or quadriceps muscles (Boonstra et al. 2008b). In this frequency region, the muscle activity in the plantarflexors correlates with the postural sway (Masani et al. 2003). Therefore, we expected that bilateral EMG–EMG coherence in the 0- to 4-Hz frequency region is related to postural stability during quiet standing. In the elderly and child groups, a positive correlation between EMG–EMG coherence and the speed of the A/P COP displacement was observed in some conditions. However, it seemed to lack consistency: the child group showed significant correlation between the right and left SOL both in EO and EC conditions, whereas the elderly group showed it in other muscle pairs (i.e., rMG–lMG and rSOL–rMG) in the EC condition. These results suggest that the causal relationship between the strength of the plantarflexors' coherence and the amount of postural sway was lacking, although they may imply the essential difference in the neural mechanism for controlling plantarflexors between development and aging.

Coherence in the 8- to 12-Hz frequency region

In all groups, a marked frequency component in the SOL EMG was found in the 8- to 12-Hz frequency region (Fig. 2, middle panels). This result is consistent with the previous studies (Mori 1973, 1975; Kouzaki and Masani 2012). Most motor units in the SOL muscle are reported to discharge at a frequency of 8–10 Hz (Mori 1973), and those activities are synchronized within a muscle (Mori 1975). More recently, it has also been reported that the frequency spectrum of the mechanomyogram obtained from the SOL muscle shows oscillatory activity in the same frequency region (Kouzaki and Masani 2012).

Previously, Boonstra et al. (2008a) reported that bilateral EMG–EMG coherence between the plantarflexors in the 8- to 12-Hz region was observed during quiet standing with eyes open and eyes closed in adult subjects. This stands in contrast to our present finding that adult subjects did not show significant bilateral EMG–EMG coherence between the plantarflexors. This difference could be attributed to differences in the methods used to estimate coherence. Therefore, we tried to estimate coherence using the same method previously used (i.e., Welch's periodogram method with Hamming windows of 2,048 samples' length, 1,024-sample overlap, and corresponding confidence limits). However, our results did not change; no adult subjects showed significant coherence in the plantarflexors in both eyes-open and eyes-closed conditions. It remains unclear what causes this difference, but the present result at least demonstrates that coherence in the 8- to 12-Hz region was stronger in the elderly subjects than in the adult subjects.

We found a clear difference related to aging: bilateral and unilateral EMG–EMG coherences in this frequency region were prominent only in the elderly. Coherence analysis identifies comodulation of muscle activity across a broad range of frequencies (Mochizuki et al. 2006). Therefore, these results suggest that, in the elderly subjects, common oscillation was enhanced among the plantarflexors in the 8- to 12-Hz region. The increase in EMG–EMG coherence around 10 Hz has been reported between bilateral arm muscles, between quadriceps muscles, and within quadriceps muscles during fatiguing contractions in an isometric force production task (Boonstra et al. 2006, 2008b). It has also been reported that bilateral EMG–EMG coherence increased between finger muscles during bilateral precision grip tasks when the force output changed from an increasing to a stable-state contraction (Boonstra et al. 2009). Considering these results, it can be speculated that the enhancement of common oscillation in the 8- to 12-Hz frequency region is one neural strategy that stabilizes the force output to maintain the required position when the force output produced by inter-limb and/or intra-limb muscles becomes unstable. Thus, the results from the elderly group imply that some elderly subjects adopt this strategy to counteract larger postural sway.

The 8- to 12-Hz frequency region corresponds to that of physiological tremor (McAuley and Marsden 2000, for a review); in this region, the elderly show more oscillation in the SOL (Kouzaki and Masani 2012). It is well known that periodic common input to motoneuron pools may arise from various levels of the nervous system (McAuley and Marsden 2000, for a review), but most research seems to agree that it arises at a supraspinal level (Farmer et al. 1993; Grosse et al. 2002; Semmler 2002). The subcortical mechanisms may be related to an increase in bilateral modulation of the plantarflexors in the 8- to 12-Hz frequency region. Extrapyramidal tracts, such as the reticulospinal and vestibulospinal tracts, should be considered as the neural pathways that could produce synchronous input to bilateral motoneuron pools. Animal studies have revealed that these pathways innervate both sides of the spinal cord (Shinoda et al. 1986; Jankowsaka et al. 2003). Furthermore, in the reticulospinal tract, it has been reported that stimulation of reticular formation evokes bilateral muscle movements in monkeys (Davidson et al. 2007). These pathways have strong connections with the cerebellum, and thus the present result may reflect age-related alteration of the cerebellum activity. For example, cerebellar Purkinje cells exhibit significant changes in both morphology and function during the normal aging process (Zhang et al. 2010, for a review). It is known that Purkinje cells in the cerebellar vermis inhibit the fastigial nuclei, which in turn projects bilaterally to the brain stem reticular formation and lateral vestibular nuclei.

The corticospinal pathway should also be considered. In general, corticomuscular coherence (i.e., the coherence between motor cortical field potentials and EMG) at around 10 Hz is rarely observed (Conway et al. 1995; Kilner et al. 2000). However, a recent study has reported that corticomuscular coherence at the alpha region (8–14 Hz) was increased in the elderly with the major influence of an additional cognitive task (Johnson and Shinohara 2012). This result suggests that the motor cortex can account for the origin of unilateral and bilateral EMG–EMG comodulation in the 8- to 12-Hz frequency region. Bilateral coupling may arise from the cortical network between bilateral motor cortexes through the corpus callosum (Franz et al. 1996; de Oliveira et al. 2001). Although it is difficult to determine the origin of this common input from the present study, the age-related alteration in the supraspinal mechanism may be attributed to the peculiar unilateral and bilateral comodulations observed in elderly subjects.

The present study recruited only healthy elderly people with no known neuromuscular disorders. However, many aspects of motor system function are known to change with normal aging in a variety of manners. It is quite likely that some elderly subjects who participated in the present study had undetectable levels of motor dysfunction. Additional experimental approaches, for example, recruiting elderly subjects with a variety of gross motor function levels and diagnoses, might provide further insights into the significance of age-related alternations of EMG–EMG coherence and explain variability within the group.

In the child subjects, no significant change was observed in EMG–EMG coherence in the 8- to 12-Hz frequency region as compared to the adult group. In the previous studies, a number of reports demonstrated changes in brain structures during human development. For example, immaturity of the corpus callous and the presence of ipsilateral corticospinal projection have been reported until early adolescence (Eyre et al. 2001; Carson 2005), indicating bilateral projection of brain to spinal motoneuron pools in children. Thus, it remains possible that an increase in EMG–EMG coherence in the 8- to 12-Hz frequency region can be observed in children younger than those we examined in this study. Whether the absence of 8–12 Hz EMG–EMG coherence is innate or acquired is still an open question. Further studies are required to investigate a relation to maturation in this frequency region.

Effects of visual conditions

It is known that there is a tight coupling between postural control and visual information, especially in the elderly (Lucy and Hayes 1985). In the present study, we demonstrate that the oscillatory EMG activity in the low- (0–4 Hz) and high (8–12 Hz)-frequency regions is affected by visual conditions only in the elderly. As described above, increased coherence of the low-frequency region would contribute to a synergistic control of body sway. The present results indicate that visual input in elderly subjects modulates two different common inputs.

Adult and child subjects were not affected by visual conditions. However, the underlying neural mechanism might be different. In adult subjects, the weak effect of the visual condition could be attributed to the high capacity of the postural control system. On the other hand, in child subjects, the different development of the sensory systems for postural control would be related. It has been reported that the proprioceptive system maturates at 3–4 years of age, whereas the visual and vestibular system continues to develop until 15 or 16 years of age (Steindl et al. 2006). This indicates that proprioceptive information plays a dominant role for postural control in children. Thus, visual conditions would have a weak effect on oscillatory muscle activity in children.

Conclusion

In conclusion, we have demonstrated that common oscillatory input to bilateral homologous plantarflexors and unilateral plantarflexors in one leg was enhanced in elderly subjects in the 0- to 4-Hz and 8- to 12-Hz frequency regions. The common oscillatory input in the latter frequency region was specific to the elderly group. The present result suggests that aging affects the organization of bilateral and unilateral postural muscle activities in the plantarflexors during quiet standing.

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Predictive control of ankle stiffness at heel contact is a key element of locomotor adaptation during split-belt treadmill walking in humans

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J Neurophysiol 111:722-732, 2014. First published 13 November 2013; doi:10.1152/jn.00497.2012

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First published November 13, 2013; doi:10.1152/jn.00497.2012.

Predictive control of ankle stiffness at heel contact is a key element of locomotor adaptation during split-belt treadmill walking in humans

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Submitted 11 June 2012; accepted in final form 12 November 2013

Ogawa T, Kawashima N, Ogata T, Nakazawa K. Predictive control of ankle stiffness at heel contact is a key element of locomotor adaptation during split-belt treadmill walking in humans. *J Neurophysiol* 111: 722–732, 2014. First published November 13, 2013; doi:10.1152/jn.00497.2012.—Split-belt treadmill walking has been extensively utilized as a useful model to reveal the adaptability of human bipedal locomotion. While previous studies have clearly identified different types of locomotor adaptation, such as reactive and predictive adjustments, details of how the gait pattern would be adjusted are not fully understood. To gain further knowledge of the strategies underlying split-belt treadmill adaptation, we examined the three-dimensional ground reaction forces (GRF) and lower limb muscle activities during and after split-belt treadmill walking in 22 healthy subjects. The results demonstrated that the anterior component of the GRF (braking force) showed a clear pattern of adaptation and subsequent aftereffects. The muscle activity in the tibialis anterior muscle during the early stance phase was associated with the change of braking force. In contrast, the posterior component of GRF (propulsive force) showed a consistent increase/decrease in the fast/slow leg during the adaptation period and was not followed by subsequent aftereffects. The muscle activity in the gastrocnemius muscle during the stance phase gradually decreased during the adaptation phase and then showed a compensatory reaction during the washout phase. The results indicate that predictive feedforward control is required to set the optimal ankle stiffness in preparation for the impact at the heel contact and passive feedback control is used for the production of reflexively induced propulsive force at the end of the stance phase during split-belt treadmill adaptation. The present study provides information about the detailed mechanisms underlying split-belt adaptation and should be useful for the construction of specific rehabilitation protocols.

electromyography; gait adaptation; ground reaction force; locomotion; motor learning

HUMAN BIPEDAL LOCOMOTION IS flexible enough to accommodate environmental demands. To achieve rhythmic and stable steps in various situations, two types of control strategies, reactive and predictive adjustments, take place. Reactive action is rapidly elicited based on the automatically induced vestibulospinal and spinal reflex system utilizing sensory feedback (Dietz 1992; Sinkjaer et al. 1996). Predictive action can be accomplished over minutes to hours using trial-and-error-based learning, which presumably involves the cerebellar process (Bastian 2006).

Split-belt treadmill walking has been utilized as a useful model to reveal the adaptability of human bipedal locomotion and has been studied extensively over the last decade from the perspective of locomotor adaptation (Prokop et al. 1995; Reisman et al. 2005, 2007, 2009, 2010; Morton and Bastian 2006; Choi and Basitan 2007; Choi et al. 2009; Vasudevan and Bastian 2010; Malone and Bastian 2010; Torres-Oviedo and Bastian 2010; Vasudevan et al. 2011; Musselman et al. 2011). As subjects walk in this novel environment, in which two belts are driven independently of one another, adaptive changes of the gait motion are evident, as are the aftereffects upon return to a "tied" speed (Reisman et al. 2005). Previous studies have demonstrated that some variables, such as step length and double support time, showed clear adaptation and subsequent aftereffects, while other variables, such as stride length and stance time, showed merely reactive adjustment at the beginning of the adaptation period (Reisman et al. 2005). These findings indicate that the two distinct types of adjustments, feedback (short term, reactive) and feedforward (longer term, predictive) adjustments, coexists within the same task. Regarding the mechanisms underlying split-belt locomotor adaptation, Morton and Bastian (2006) revealed that cerebellar function is important in predictive but not in reactive adjustments. This is quite reasonable, because the results can be attributed to the well-established notion of an internal model, which is the process for the recalibration of motor command with the new task demand, as originally demonstrated in reaching movements of the upper limbs (Kawato et al. 1987; Shadmehr and Mussa-Ivaldi 1994). Understanding the role of predictive and reactive feedback strategies in locomotor adaptations would give us important information to facilitate gait rehabilitation as well as to elucidate task-specific functional networks underlying human locomotion. While a series of previous studies using split-belt walking have provided plenty of information concerning locomotor adaptation, the details of how the gait pattern would be adjusted are not fully understood. To discuss the strategies underlying locomotor adaptations to split-belt walking, it is particularly important to address the biomechanical characteristics beyond spatiotemporal and kinematic parameters, that is, the behaviors involved in the kinetic variables and muscle activities. The purpose of this study was therefore to elucidate the role of predictive and reactive feedback strategies in locomotor adaptations to split-belt walking, based on the evaluation of ground reaction force (GRF) and electromyography (EMG) in the lower limb muscles.

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METHODS

Subjects. Twenty-two volunteers (between 21 and 40 yr of age; 21 men) with no known history of neurological or orthopedic disorders participated in the study. All the subjects gave their informed consent for participation in the experimental procedures, which were approved by the local ethics committee of the National Rehabilitation Center for Persons with Disabilities, Japan. All of the experimental procedures were performed in accordance with the Declaration of Helsinki.

Experimental protocol. In the present study, we used an experimental protocol established by Reisman et al. (2005) (the protocol shown in Fig. 1*A*) in their first of a series of studies exploring the split-belt locomotor adaptation.

Subjects walked on a split-belt treadmill (Bertec) with two belts (one under each foot; see the schematic in Fig. 1*B*), each driven by an independent motor. During the experiment, the treadmill was operated in either a "tied" (two belts moving at the same velocity) or "split" (at different velocities) pattern (Reisman et al. 2005), depending on the testing session. During the baseline period, the treadmill was tied and the velocity was set at 0.5 m/s for the slow and 1.0 m/s for the fast sessions. In the adaptation period, one belt speed was set at 0.5 m/s while the other was set at 1.0 m/s (1:2 ratio). The velocity of the belt underneath each leg was randomly assigned on a subject-by-subject basis. The leg on the fast belt during the adaptation period was defined as the "fast leg" and that on the slow belt was defined as the "slow leg." Following the adaptation period was the washout period, where the belt condition was again tied at 0.5 m/s. Between testing sessions, the belt condition was changed (continuously without stopping) by the experimenter with acceleration (deceleration) of 0.5 m/s^2. Subjects were informed about the changes in belt condition but not about whether the belts would be tied or split or whether the speed would be

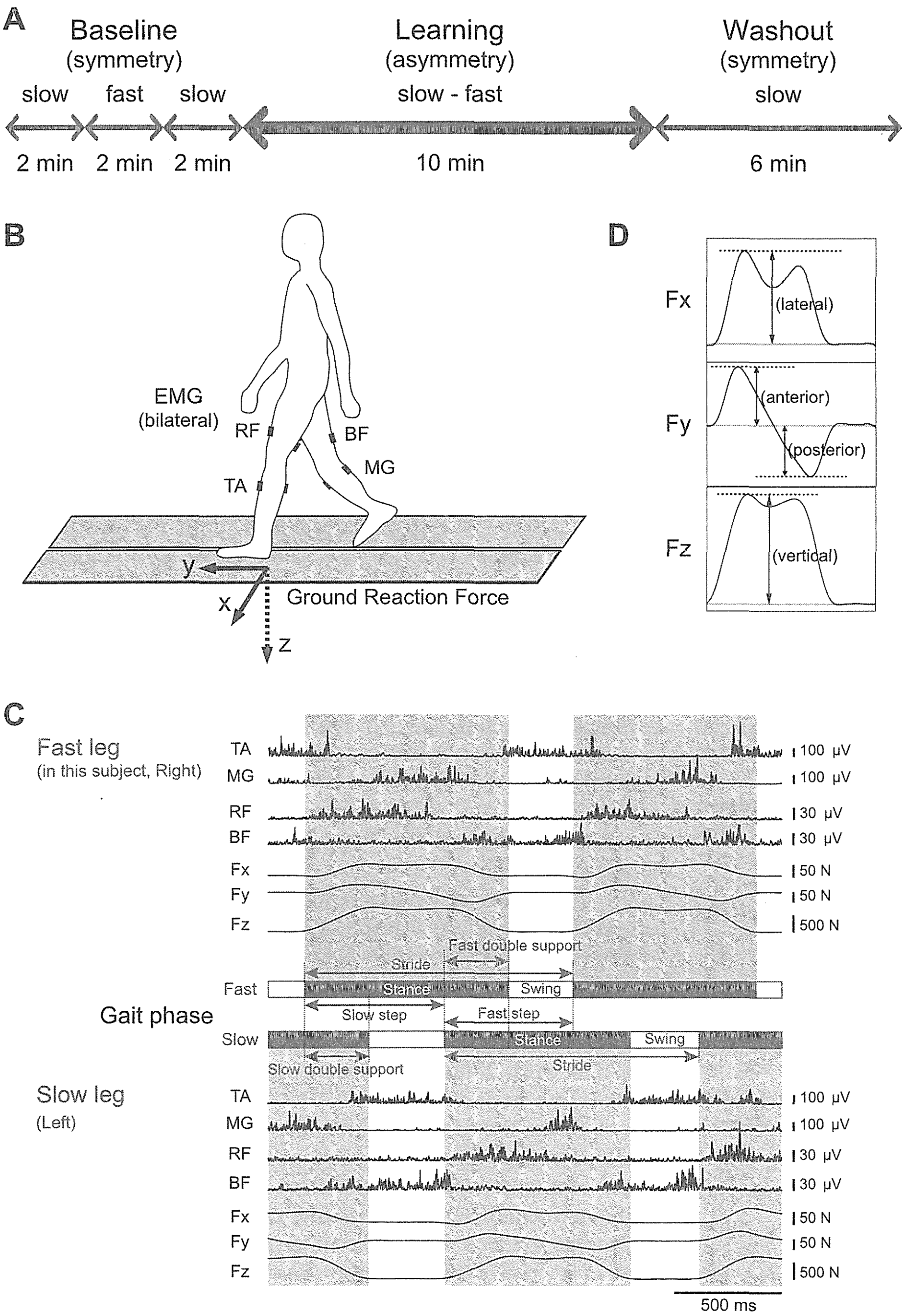

Fig. 1. *A*: time course of the experimental protocol. *B*: schematic of the experimental setup. The EMG activities in 4 muscles [medial head of the gastrocnemius (MG), tibialis anterior (TA), rectus femoris (RF), and biceps femoris (BF)] and the mediolateral (Fx), anteroposterior (Fy), and vertical (Fz) orthogonal ground reaction force (GRF) components were recorded bilaterally. *C*: representative waveforms of the EMG and the GRF during the slow baseline period in 1 subject, described bilaterally, and the description of the gait phases. *D*: description of the GRF data analysis: peak values during each stride cycle (indicated by red arrows) were taken.

increased or decreased. During the experiment, subjects were instructed to walk normally while watching a wall 3 m in front of them. They were told not to look down at the belts to avoid gaining any visual information about the belt conditions. For safety, one experimenter stood by the treadmill during the experiment, and the subjects could hold onto the handrails mounted on either side of the treadmill in case there was a risk of falling. In our test, all subjects completed the testing sessions without using the handrails.

Supplemental experiment (control condition). In addition, we performed a control experiment to determine whether the observed effects (if any) during and after walking in the given environment are derived specifically as a consequence of walking on the asymmetrically driven treadmill or are due simply to task complexity. We referred to an experimental protocol demonstrated by Jayaram et al. (2011). The subjects were 10 healthy men. The subjects walked for a total of 22 min on the same treadmill surface as that used in the main experiment, but the two belts were always operated in the tied condition. During the baseline period, the subjects walked at two different velocities (slow at 0.5 m/s^2, fast at 1.0 m/s^2, and again, slow at 0.5 m/s^2) for 2 min each. After the baseline period was an adaptation period in which the subjects were required to walk for 10 min at variable velocities [either slow, middle (0.75 m/s^2), or fast during the baseline] that changed every 10 s and were centered at the middle. The variable velocities were delivered in random order, and the subjects were thus not provided with information on the upcoming velocities. After the adaptation period, the velocities were returned to the slow speed and the subjects walked at the slow speed for 6 min.

Data recording. Force sensors mounted underneath each treadmill belt were used to determine three orthogonal GRF components: mediolateral (Fx), anteroposterior (Fy), and vertical (Fz). The force data were low-pass filtered at 4 Hz and were digitized at a sampling frequency of 1 kHz (Power Lab; AD Instruments). EMG activity of the medial head of the gastrocnemius (MG), tibialis anterior (TA), rectus femoris (RF), and biceps femoris (BF) muscles was recorded bilaterally using surface electrodes (Trigno Wireless System; DELSYS). Since the total number of EMG recordings was limited, we selected the pair of extensor and flexor muscles in each shank and thigh muscle. Before placement of the electrodes, the skin was lightly rubbed with very fine sandpaper and was cleaned with alcohol pads. The recorded EMG signals were amplified (with ×300 gain preamplifier), band-pass filtered (20–450 Hz), and digitized simultaneously with the signals from the two force plates.

Data analysis. The obtained GRF and EMG data were analyzed on a stride-by-stride basis for both the fast and slow legs, respectively. From the vertical Fz component of the force data, the moments of foot contact and toe-off were detected using a custom-written program (VEE pro 9.0; Agilent Technologies). On the basis of foot contact and toe-off, the following parameters were calculated as temporal characteristics of gait (see the schematic description in Fig. 1*C*). *1*) Stride time: the time between one foot contact and the subsequent foot contact in the same leg. *2*) Step time: the time between the foot contact of one leg and the subsequent foot contact of another leg (i.e., the step time on the fast side is calculated as the time between foot contact on the slow side and the following foot contact on the fast side and vice versa for the slow side). *3*) Stance time: the time spent in contact with the walking surface (computed for both fast and slow legs). *4*) Swing time: the time spent not in contact with the surface (computed for both fast and slow legs). *5*) Double support time: the time spent with both feet in contact with the surface (i.e., fast double support time between the foot contact of the slow side and the subsequent toe-off in the fast side and vice versa for the slow side).

The force signals were analyzed for the Fx, Fy, and Fz components as the peak values within every stride cycle (refer to Fig. 1*D*). For the anteroposterior (Fy) component, both the positive and the negative peaks were calculated to assess both the anterior braking component appearing immediately after the foot contact and the posterior propulsive component immediately before toe-off (Fig. 1*D*).

The EMG signal for each muscle was full-wave rectified after subtraction of the DC component. The integrated EMG (iEMG) for both stance phase and the swing phase was computed for every stride. We analyzed the muscle activities during the stance phase in more detail, where time series changes of the EMG activities in each muscle were separated into the early stance phase (0 to 50% of the stance phase) and the late stance phase (50 to 100% of the stance phase).

From the temporal parameters, the GRF, and the iEMG data, we excluded the values for the first stride of each testing session from the later analysis due to the acceleration (deceleration)-induced disturbance of gait stability upon the change of belt conditions. To allow intersubject comparison, all the data were normalized to averages of those during the baseline period, which we defined as the last 50 strides of the second slow baseline period. Even though the total time of gait session is identical among subjects, the total number of steps would be different due to the relative contribution between stride length and cadence. The normalized values were then divided into bins of 10 s each in duration. This process was important to consider the time-dependent nature of adaptive and de-adaptive processes, because the number of stride cycles taken was variable across subjects.

Statistics. Statistical analysis was performed for the changes in each variable (temporal parameters, GRFs, and iEMGs) among the different testing periods: the slow 1 period, the fast period, the slow 2 period during the baseline, the first 10 s of the adaptation, the last 10 s of the adaptation, the first 10 s of the washout, and the last 10 s of the washout. ANOVA for repeated measures was used. When repeated-ANOVA gave significant results, Bonferroni's post hoc comparisons were performed to test for differences between testing periods. Correlation coefficients were calculated to test the relationships among variables. Data are presented as the means ± SE. Significance was accepted at $P < 0.05$.

RESULTS

Temporal characteristics. Figure 2*A* portrays the time series variation of the temporal parameters throughout the experimental protocol. With exposure to the split belt condition, these parameters showed a general decrease (except for stance time and swing time in the fast leg) from those during the slow baseline (significant differences from the baseline are shown as filled circles), regardless of the leg (either fast or slow). During the 10-min adaptation phase, all the parameters gradually and only slightly increased toward the baseline. To characterize the "capability of adaptation," Fig. 2*B* compares the parameters at different time points (see METHODS). In some parameters, such as stance time ($P < 0.01$) and double support time ($P < 0.01$) in the fast leg, and step time ($P < 0.01$) and swing time ($P < 0.001$) in the slow leg, there were significant differences between the first and the last 10 s of the 10-min adaptation period (significant differences are shown as solid lines), indicating the capability of adaptation. In contrast, other parameters, such as stride time in the fast leg and stance time, double support time, and stride time did not show such changes. When the belt condition was returned to tied, all the subjects exhibited a pronounced limp despite the belt condition being identical to the baseline condition, as reported in a previous study (Reisman et al. 2005). There were significant differences from the baseline period in step time ($P < 0.05$) and swing time ($P < 0.05$) in the fast leg, while other parameters did not show such differences in either the fast or the slow leg. Early in the 6-min washout period (in the first 1–2 min), those initially modulated parameters converged almost to the baseline values.

Ground reaction force. The time series changes of the GRF were to a great extent different among the components (mediolateral, anterior, posterior, and vertical), and based on these