教 育 総 説

Review-Essentials

# 脊髄損傷後の歩行機能回復に向けた新しいビジョン —神経の再生・修復から機能回復まで—

## *A New Approach for the Restoration of Locomotor Function after Spinal Cord Injury*

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## はじめに

神経科学領域の近年の研究成果により，従来可塑的性質をもたないと考えられていた脊髄内の神経回路網がかなりの範囲でその機能を回復できることが明らかになってきた．Raineteau と Schwab[1]は，*Nature Review Neuroscience* 誌に寄せた総説論文の中で上記の脊髄可塑性に関し，受傷後の神経線維自体の可塑性（anatomical plasticity）と感覚刺激の繰り返し入力による可塑性（synaptic plasticity あるいは use-dependent plasticity）を分けて論じている（**Fig. 1**）．近年盛んに研究されている脊髄神経再生についての研究は医学的・解剖学的視座から前者を実現しようとする試みである一方で，歩行機能回復のためのリハビリテーションは機能的視座から後者を主眼に捉えた試みと位置づけることができる．本稿では，近年の神経科学・医学領域の進歩に呼応する形で今後大きな変化をみせるであろう脊髄損傷後のリハビリテーションについて，神経の再生・修復から歩行機能回復までを包括的視点から捉え，その全体像について概説する．

## 1．脊髄神経の再生と修復

脊髄再生研究の端緒ともいえる Aguayo ら[2]のラット脊髄切断モデルに対する肋間神経のケーブルグラフト移植の報告以来，脊髄再生の大きなテーマは皮質脊髄路の再建であった．動物実験でも再生の証明は主として皮質運動野に神経トレーサーを注入し，それが損傷部を超えて尾側で同定されるか，という組織学的検討がなされた．このような基礎研究の中で，皮質脊髄路の再生を阻害する要因の同定や，ニューロン自体を活性化する介入方法開発が進められ，中でも軸索再生阻害因子として同定された Nogo に対する抗体療法はすでにヨーロッパでの臨床治験が開始されている[3]．

また，損傷部に細胞を補うことで再生を誘導するいわゆる移植療法の研究も，iPS 細胞の発見と相まって近年目覚ましい成果を上げている．iPS 細胞の利用方法についてはいくつかの手法が考えられるが，その 1 つはあらゆる組織の細胞になりうる iPS 細胞を神経系統の幹細胞「神経幹細胞」まで誘導し，これを損傷部に移植する方法である．移植された細胞はニューロンおよびグリア（オリゴデンドロサイト・アストロサイト）に分化することで機能回復に寄与することが知られている[4]．神経線維の再構築という観点からは移植治療は 2 つの効果をもつと現時点では考えられている．1 つは移植された細胞がグリア系に分化し皮質脊髄路など long tract の再生の足場となって働く作用（**Fig. 2**①）で，もう 1 つはニューロンに分化し，これが脳からの神経線維とシナプスを形成し，そこから尾側へ新たな神経線維を伸ばし下肢機能を制御するという作用である（**Fig. 2**②）．臨床的な再生医療のトピックスとして，2012 年度から先進医療として大阪大学で開始された慢性期脊髄損傷に対する自家嗅粘膜組織移植が知られる[5]．これも嗅粘膜組織内に豊富に存在するグリア細胞を移植することで脊髄の下降路を再建することを意図したものと位置づけられる．

## 2．神経線維の再生と機能回復

こうした皮質脊髄路の再生誘導研究では，その多くでモデル動物において良好な後肢の運動機能回復が報告さ

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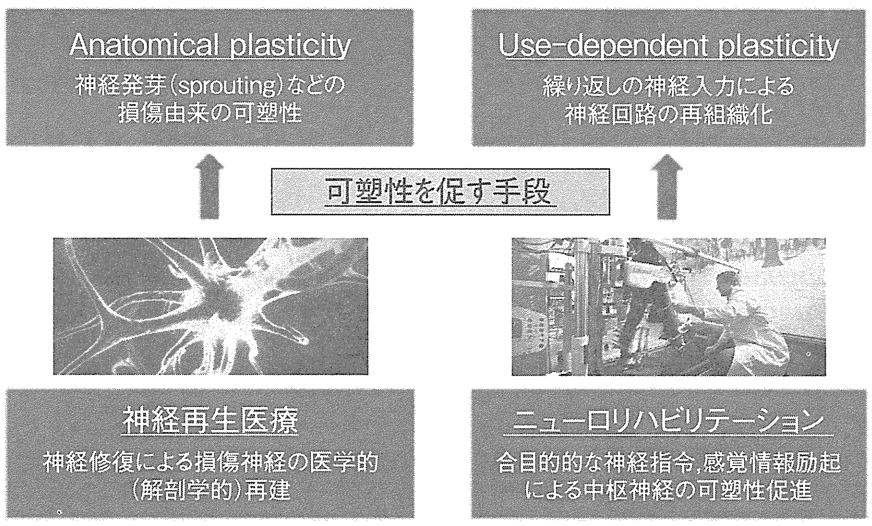


**Fig. 1　2 つの可塑性についての知見をベースとした歩行機能再獲得のための具体的戦略**

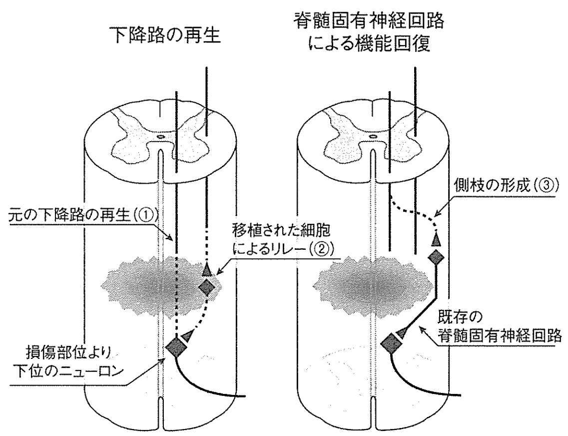


**Fig. 2　脊髄再生において想定される再生パターン**
脳と脊髄前角の運動ニューロンをつなぐ経路の再生には，下降路が損傷部を超えて再生するメカニズムが考えられる（①, ②）．一方で，再生神経線維（点線）が損傷部を超えなくても既存の脊髄内回路とそこへの側枝形成により機能回復が得られる可能性が報告されている（③）．

れているが，その一方で実際にどのような回路形成が機能回復につながったのか，という検証はまだ十分には進んでいない．末梢神経再生の場合は損傷の遠位側に細胞外マトリックスによるチューブ状の構造が残存しており，再生線維はそれに沿って進むことで，ターゲットである神経筋接合部に到達すると考えられている．一方で，脊髄には末梢神経のようなガイドとなるマトリックス構造はないため，損傷部を超えて再生した皮質脊髄路の線維がもとのターゲットである腰膨大部の脊髄前角ニューロンまで到達するのは容易でないことが想像される．したがって，皮質脊髄路が再生した場合であっても損傷遠位部では新たな神経回路が構築される必要があり，このことは移植細胞が神経伝達を中継するニューロンとして働く場合でも同様である．

一方で，損傷部を超える軸索再生がなくても機能回復が得られるとするモデルも提唱されている．マウスの脊髄において脳からの下降路を左右異なるレベルで切断した場合，切断部における再生がなくても後肢機能が回復するという現象が報告されている[6]．この回復過程には皮質→脊髄の経路ではなく，脊髄→脊髄の経路が関与することがわかっている．すなわち，もともと損傷を逃れて残存していた脊髄→脊髄経路（脊髄固有神経：propriospinal neuron）が損傷部頭側領域で皮質脊髄路から新たな入力を受け，一方で損傷部尾側では脊髄前角ニューロンあるいは歩行に関連する神経回路に信号を伝えることとなる（**Fig. 2**③）．この際の新しい経路は側枝の伸長(sprouting）と呼ばれ，そのメカニズムは損傷部を超える神経再生とは別個に考えられる．さらに，こうした側方向の新たな神経結合が，新たな神経線維（側枝）の形成によるものか（解剖学的な再構築），既存の結合の強化によるものか（機能的な再構築），を厳密に判定することは容易ではない．

このように，脊髄損傷後に神経線維が再生したとしても，実際の機能回復につながるためには機能を有する神経回路を形成する必要がある．そして機能的な神経回路を再組織化しようとするプロセスにおいて放出される神経栄養因子や，シナプス結合の強化といった現象自体が神経線維の再生に関与している可能性もあり，解剖学的

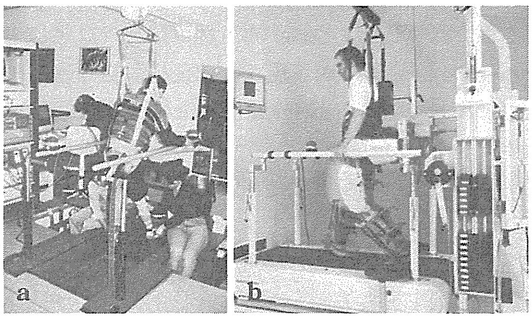

Fig. 3　理学療法士による徒手補助（a）およびロボティクス（b）による免荷歩行トレーニング

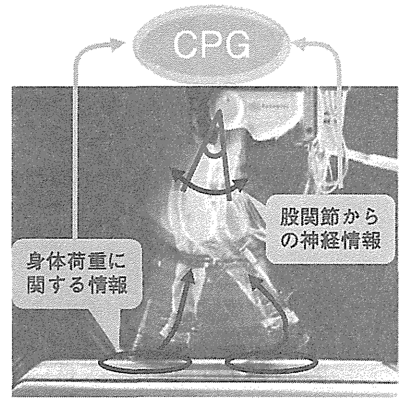


Fig. 4　脊髄 CPG の活動に影響する 2 つの求心性感覚情報

な再構築と機能的な再構築は密接な関係にあるという理解が妥当であろう．

したがって，脊髄損傷者の歩行機能回復を考える場合には，神経線維の再生誘導と神経回路再構築の誘導をバランスよく考慮する必要がある．皮質からの指令による運動が障害されている状態において神経回路の再組織化を誘導する 1 つの方法として，目的の運動に関連した感覚入力を加える手法があり，歩行機能訓練においては受動的歩行訓練（ステッピング運動）が臨床現場においても実践されてきた．次節ではこの方法について概説する．

## 3．脊髄神経回路の可塑性と歩行機能回復

他動的な体肢の動作（歩行を企図するならばステッピング運動）によって繰り返し生じる刺激-応答サイクルは，脊髄を中心とした歩行運動出力を発現させる神経回路を活性化し，中長期的なトレーニングの実施によって歩行能力改善の方向に誘導される，と考えられる[7]．換言すれば，免荷歩行トレッドミルトレーニングや各種ロボティクスによる歩行リハビリテーションは，繰り返しの神経入力によってもたらされる神経可塑性（use-dependent plasticity）を理論的背景とした神経リハビリテーション方法の 1 つとして位置づけることができよう．

脊髄損傷者の場合，麻痺領域への随意指令が残存している不全損傷者では脊髄より上位の中枢神経と脊髄間の連絡がわずかであっても残存しているため，歩行の基本的リズム発現を担う脊髄中枢パターン発生器（central pattern generator：CPG）の活動惹起とともに，脳と脊髄の間の機能的結合，高位中枢そのものの歩行に関連した神経活動の改善が想定できる．一方，脊髄完全損傷者に関していえば，ステッピング運動を行わせることで脊髄 CPG の活動を惹起できたとしても，現時点では歩行トレーニングを実施しても歩行機能を再獲得できる可能性は皆無に近い．しかし，動物実験において脊髄神経再生の実現可能性を膨らませるいくつかの有力な研究成果が得られている現状を考えれば，脊髄再生医療の実現を念頭に置いた先見的な研究はきわめて高い意義をもつものと考えられる．脊髄神経の再生は，神経の組織解剖学的な再建に加えて立位・歩行を含む機能面での回復を実現してこそ成功といえることから，神経修復についての研究の進歩に呼応して，修復後の効果的なリハビリテーション方法の検索に関しても多くの目が注がれるべきである．

## 4．免荷歩行トレーニングの理論と方法

体重を部分的に軽減したうえで補助者や装置による両脚のステッピング運動をアシストする，免荷歩行トレーニング（body weight supported treadmill training）は，歩行機能回復に有効な方法として広く認識されている．**Fig. 3 a** に示す例では，ハーネスを上方より牽引することで脊髄損傷者の体重を部分的に免荷したうえでトレッドミルに立たせ，理学療法士がベルトスピードに合わせて麻痺下肢の動作を補助し，他動的に左右交互のステッピングを行わせている．この免荷トレッドミルトレーニングは，荷重を支えるための過剰な筋活動や注意配分を免荷によって最小限に抑え，下肢のステッピング運動が表出しやすくなるようにする狙いがある．歩行中の立脚-遊脚期の切り替わりに伴う下肢への荷重，股関節の屈曲-伸展動作は，歩行機能の回復にきわめて重要である（**Fig. 4**）．なぜなら，脚全体に加わる荷重情報と股関節の伸展に関わる感覚情報は脊髄 CPG の活動を惹起するための最も重要な入力信号だと考えられているためで

ある[8~10]．受動的ステッピング運動中には多くの感覚受容器が刺激され，歩行運動の位相に応じた求心性感覚情報が，脊髄歩行中枢の活動を高めることになる[7,9,10,12,13]．脊髄不全損傷者を対象とした歩行リハビリテーションの効果を検証した大規模な無作為化比較試験（randomized controlled trial：RCT）によると，従来より行われてきた平行棒やロフストランド杖などを用いた歩行，免荷歩行という方法の違いによらず，歩行リハビリテーションを行うことで脊髄不全損傷者の多くが歩行能力改善の可能性をもつことが示されている[14~16]．

免荷歩行トレーニングでは，1人の患者に対し，2人以上の理学療法士が必要となる．さらに，ステッピング動作の補助はかなりの労力が必要であり，1人の理学療法士が続けて何人もの患者の補助をすることは現実的に不可能である．動力歩行装置 Lokomat（Hocoma 社，スイス：**Fig. 3 b**）はこれらの問題点，臨床場面での制約を克服するために，療法士によるステッピング補助を動力補助に代行させるべく開発されたものである[17]．Lokomat の基本機構は長下肢装具の膝と股関節部分に動力機構を取りつけた装具部，トレッドミル上に固定する固定部，および装具の動きを制御するコンピューターから成る．これらを免荷装置およびトレッドミルと組み合わせることで，これまで人間の手で行っていたステッピングの補助を，機械を用いて代替することが可能となった．さらに，補助者の疲労という制限因子が克服されたため，徒手では困難であった長時間のトレーニングも可能となった．Lokomat は装置自体の有用性や基本的なリハビリテーション効果についての検証段階は終えており，すでに世界数カ国の施設間ネットワークの中で臨床試験を行っている．今後テクノロジーの発達とともに，同様の機器開発がますます加速されるのは必然的流れであろう．

## 5．脊髄損傷者の歩行機能再獲得に向けて

再生誘導などの方法を用いて脊髄損傷により途絶されていた神経をつなげることができたとしても，無数ある，異なる特性をもった神経線維がもとのように整然とつながれることは困難である．損傷部周辺の解剖学的再建がもたらす結果は，随意指令，感覚情報の伝達といったプラスの側面だけではなく，痛みやしびれなどの感覚，交感神経系の過剰反応などが発現する可能性も孕んでいる．神経再生そのものの実現可能性に焦点が当てられている現時点では，合併症やリスクについての検証（とりわけ動物実験で検証不可能な，ヒト対象の実証研究）にまで十分な視点が注がれておらず，侵襲的治療介入によって得られる効果とリスクについての倫理的側面の検討もいまだ十分ではないといえる．これらの点は今後，再生医療の実現を念頭に置いた取り組みを進めて行くうえで解決すべき課題であろう．

本稿で概説したように，再生医療研究の成果によって anatomical plasticity が実現された後に，繰り返しの神経入力によって use-dependent plasticity（機能回復）を目指す神経リハビリテーションの取り組みが呼応することで，脊髄損傷者の歩行機能回復を実現できる可能性が高まりつつある．多くの患者さんが歩行機能の再獲得に高い願望をもっていることからうかがい知れるように，歩行能力の低下・喪失がもたらす身体的，社会的，心理的影響はきわめて大きい．それだけに，患者さん方の多くがこれまで以上に再生医療に対する期待をもつことは必然であろうし，それとともに社会全体の要請に変わっていくだろう．現状，再生医療が現実的な可能性をどの程度もっているのかということ自体，医療従事者であっても正確に判断するための情報が不足している．したがって，これまで得られている情報の集約的な整理，各分野が向かうべき指針を明確化し，anatomical plasticity を目指す立場と，use-dependent plasticity を目指す立場の双方が相互不可分な取り組みによって，患者さんの機能回復に向かって足並みをそろえることが求められる．再生医療というと兎角，次世代のものというように捉えられがちであるが，臨床現場で行われている機能回復のためのリハビリテーションは，とりもなおさず use-dependent plasticity を理論的背景としており，また，再生誘導後の機能回復の可能性を広げる意味では，合併症や二次障害を最小限に抑止するという現行のリハビリテーションアプローチそのものが，これまで以上に重要な意義をもつことが予想される．したがって，リハビリテーション現場においても，再生医療の可能性を模索しつつ，現在の治療介入，方法のもとで，機能回復が最大限にどの程度見込むことができるのかを問うような試みが必要と思われる．

再生医療による解剖学的な再構築は，現行のリハビリテーションの効果を底上げする位置づけにあり，これまで機能回復訓練の対象とならなかった患者さんを，その対象に含ませる方向に導くものとも捉えられる．したがって，再生医療が今後，現実的に歩を進めていくとすれば，リハビリテーション領域にもこれに呼応したパラダイムシフトが訪れるだろう．

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RESEARCH ARTICLE

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

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**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):

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

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 $\times$ 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 $\chi^2$ 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).

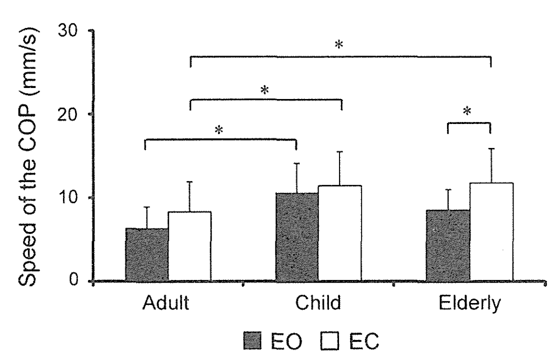


**Fig. 1** Mean and standard deviation of the speed of the A/P COP displacement among adult, child, and elderly groups in the EO and EC conditions. *Asterisk* significant difference ($P < 0.05$)

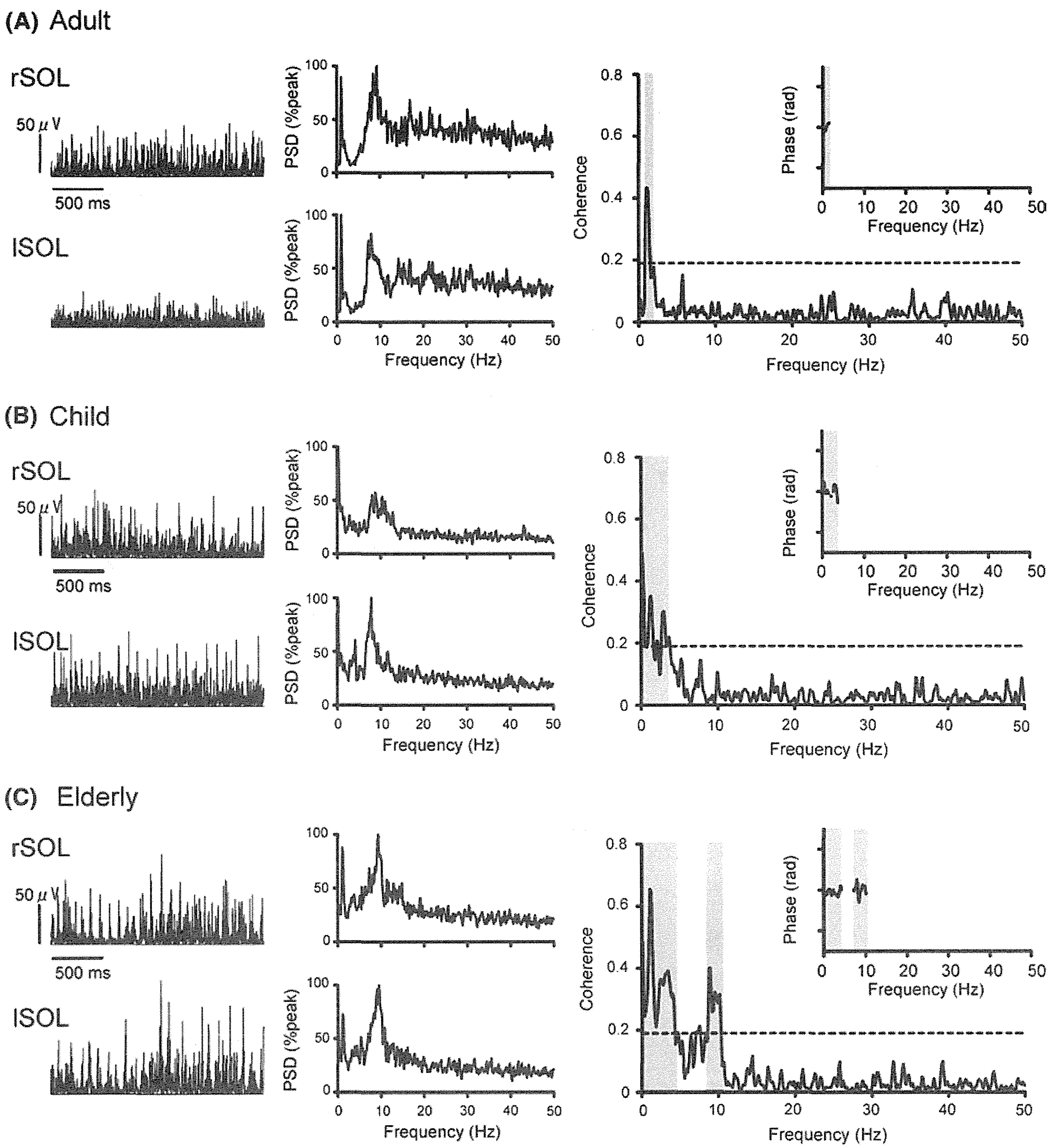


**Fig. 2** Typical examples of rectified surface EMGs (*right*), autospectral density functions (*middle*) in the *right* (*upper part*) and *left* (*lower part*) SOL, and their coherence function with phase function as an inset (*right*) in the EO condition for an adult (**a**), a child (**b**), and 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

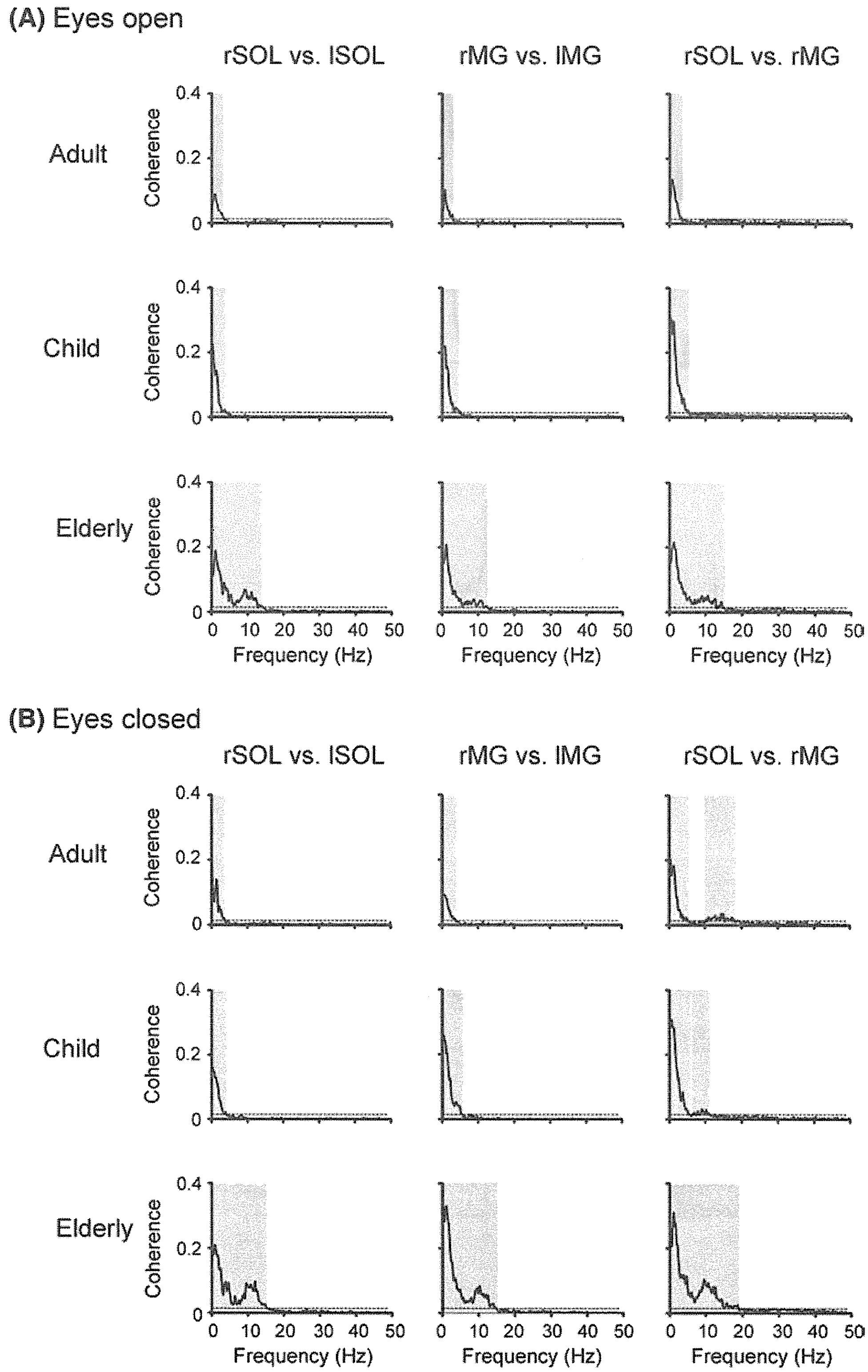


**Fig. 3** Pooled coherence plot for three age groups in all muscle pairs (i.e., rSOL–lSOL, rMG–lMG, and rSOL–rMG) in the EO (**a**) and EC (**b**) conditions. The 99 % confidence level is presented with *horizontal lines*. The frequency region where the corresponding coherence was significant is shown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

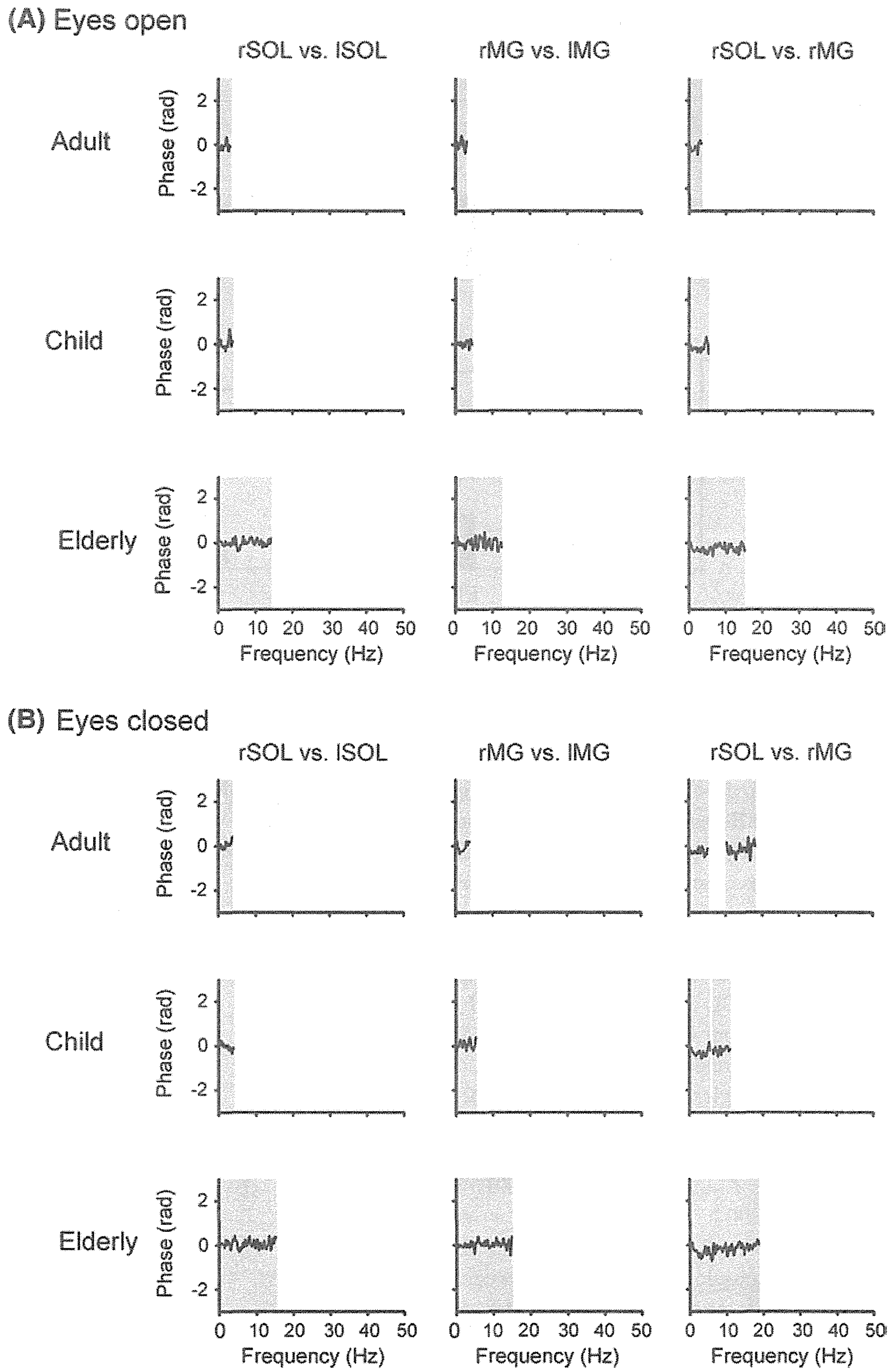


**Fig. 4** Pooled phase plot for three age groups in all muscle pairs (i.e., rSOL–lSOL, rMG–lMG, and rSOL–rMG) in the EO (**a**) and EC (**b**) conditions. The *phase plot* is shown for the frequency region where the corresponding pooled coherence was significant

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 ($P < 0.001$).

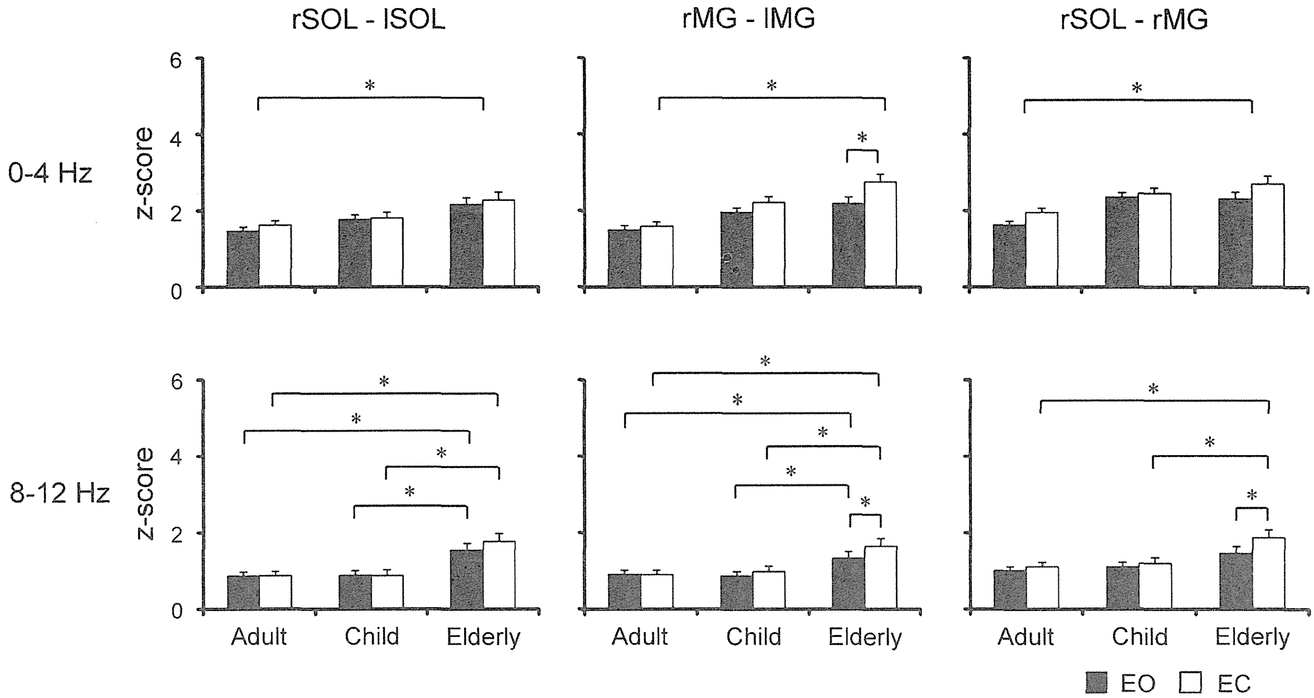


**Fig. 5** Comparisons of the mean coherence $z$-scores among three age groups in the 0- to 4-Hz and 8- to 12-Hz frequency regions in each muscle pair in the EO and EC conditions. *Asterisk* significant difference ($P < 0.05$)

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 $\times$ 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 $\times$ 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 $\times$ 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

**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 ($P < 0.05$)

region (Table 1a), the $\chi^2$ 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 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 $\chi^2$ 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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# 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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**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

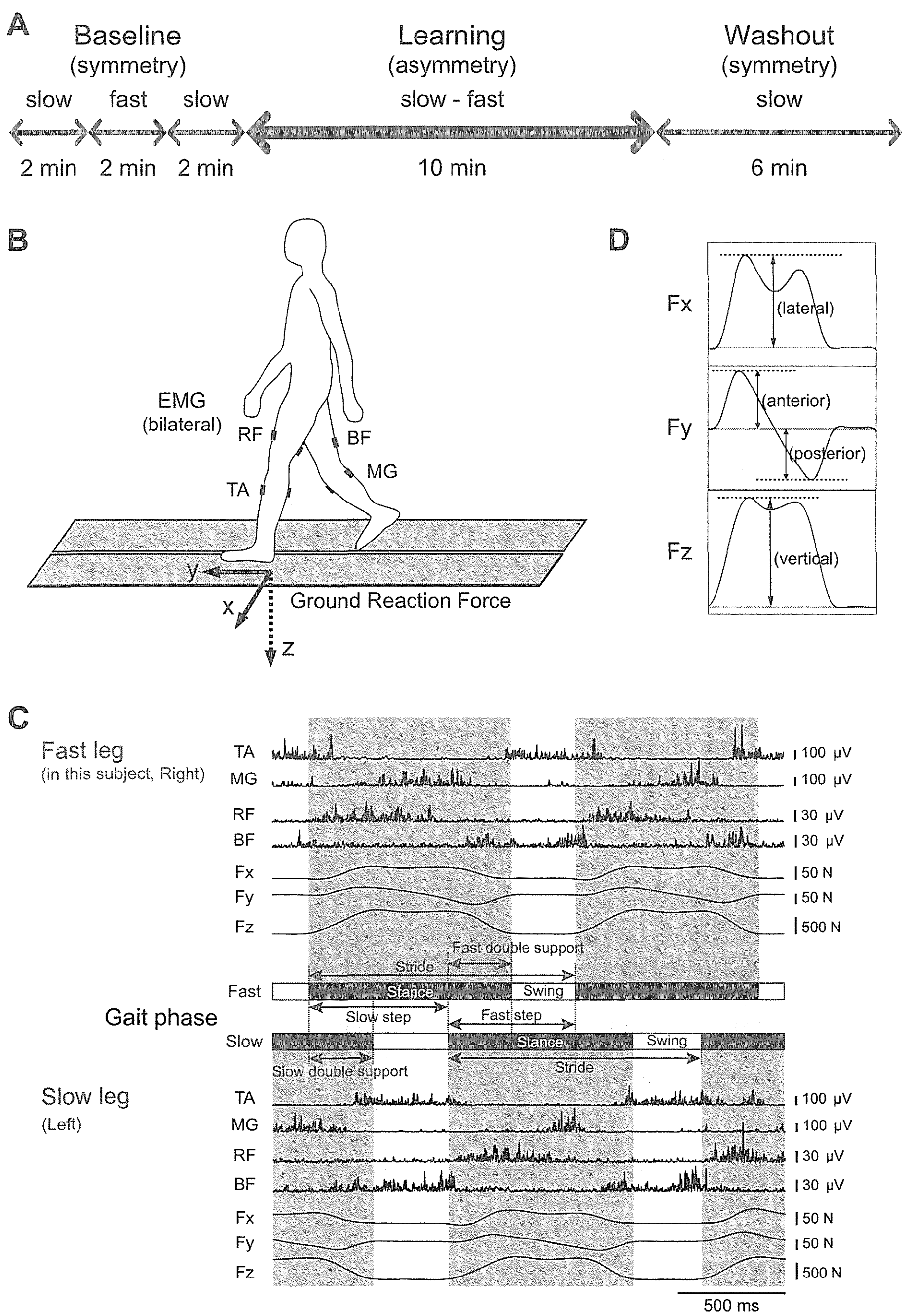


Fig. 1. *A*: time course of the experimental protocol. *B*: schematic of the experimental setup. The EMG activities in 4 muscles [medial head of the gastrocnemius (MG), tibialis anterior (TA), rectus femoris (RF); and biceps femoris (BF)] and the mediolateral (Fx), anteroposterior (Fy), and vertical (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