which may be associated with temporal correlations in COM acceleration.

1. Introduction

Much research has been devoted to the control mechanisms of standing and walking, which are fundamental behaviors in daily life. Studies of these activities are motivated by scientific interest and the need to find solutions to the problem of motor disabilities that develop as a result of disease and aging. One possible approach to finding a solution is to analyze the characteristics of body fluctuations in standing and walking. The control systems of standing and walking consist of various sensory-motor integrations at multiple levels of the nervous system, and the dynamic interaction between the nervous system and the musculo-skeletal system. Therefore, the study of changes in movement, such as body sway, can be useful in the detection of characteristics of the underlying system.

Many studies have focused on center of pressure (COP) fluctuations during quiet standing, in order to investigate upright postural control. The COP is proportional to the resultant ankle torque, which primarily controls the center of body mass (COM) during quiet standing and is partly regulated by the neural system (Loram, Maganaris, & Lakie, 2005a, 2005b; Masani, Popovic, Nakazawa, Kouzaki, & Nozaki, 2003; Masani, Vette, & Popovic, 2006; Peterka, 2000, 2002). Thus, by investigating COP dynamics, one may gain insight into the neural control of balance. Previous studies have reported that COP fluctuations are not random in time, but have temporal correlations (Collins & De Luca, 1993, 1994, 1995; Collins, De Luca, Burrows, & Lipsitz, 1995; Duarte & Zatsiorsky, 2000, 2001). Collins and colleagues (Collins & De Luca, 1993, 1994, 1995; Collins et al., 1995) believe that such temporal correlations reflect open-loop control in the short-time scale (within one second) and closed-loop control in the long time scale (over one second). Peterka (2000) suggested that this characteristic could be produced by appropriate selection of control parameters in a very simple feedback model that represents body dynamics as an inverted pendulum. Although these studies suggest different mechanisms for the emergence of temporal correlations, the common understanding between these studies is that the neural controller that maintains the COM over the base of support can modulate the temporal correlation. In fact, the degree of the correlation is influenced by aging and disease, which degrade the neural system for balance control (Collins et al., 1995; Laughton et al., 2003; Maurer, Mergner, & Peterka, 2004; Priplata, Niemi, Harry, Lipsitz, & Collins, 2003; Priplata et al., 2006).

Inter-stride fluctuations during walking have been used to investigate the control system of walking, with particular focus on falling in the elderly (Gabell & Nayak, 1984; Hausdorff, Rios, & Edelberg, 2001; Maki, 1997; Masani, Kouzaki, & Fukunaga, 2002; Pailhouse & Bonnard, 1992; Yamasaki, Sasaki, & Torii, 1991). Hausdorff and colleagues (Hausdorff, Peng, Ladin, Wei, & Goldberger, 1995; Hausdorff et al., 1996) demonstrated that the fluctuation of stride intervals shows temporal correlations, and that such time dependent dynamics are influenced by aging and disease (Hausdorff et al., 1997). There are some debates about the emerging process of the temporal correlation in stride intervals; Hausdorff et al. (1995) showed that the central pattern generator (CPG) model with memory function could generate a persistent temporal structure across stride intervals. West and Scafetta (2003) developed the super CPG (SCPG) model to explain the changes in stride interval temporal correlations in fast and slow walking speeds, as well as walking paced by a metronome. While these researchers focused on the neural mechanism that generates a given rhythm, Gates, Su, and Dingwell (2007) demonstrated that interaction among simple neural controllers, the musculo-skeletal system, and noise input could generate temporal correlations. It is unknown, however, if balance control in walking relates to the emergence of the temporal correlation observed in stride interval fluctuation. Furthermore, it has not been determined if the body fluctuations during walking show the temporal correlations that have been reported in body fluctuations while standing.

As a logical development, the next question would be whether body fluctuations in walking have temporal correlations similar to those in standing, and if so, how the structure in the body fluctuations during standing and walking are related. While the COM dynamics and CNS control strategies used in walking are generally considered to be different from that of standing (Winter, 1995), the control of posture and gait share the same neural (Mori, 1987, 1989; Mori, Nakajima, Mori, & Matsuyama, 2004; Morton & Bastian, 2003, 2004) and musculo-skeletal systems. In addition, both tasks have a common goal; the COM position must be controlled to prevent falling. We hypothesize that the temporal correlations in body fluctuations during standing and walking could be similar and correlate with each other among a group of people, i.e., those who have a strong correlation in walking would have a similarly strong correlation in standing.

A few studies have compared the stability between standing and walking. Shimada et al. (2003) investigated the response to a perturbation applied to the body during standing and walking, and demonstrated that the responses between the motor tasks were unrelated. Kang and Dingwell (2006) investigated the trunk motion during standing and walking, and analyzed its stability using local dynamic stability analysis. They measured the trajectory of the trunk in state space in standing and walking. They then estimated the rate of the divergence of the trajectory to the neighboring one, which describes local dynamic stability, i.e., faster divergence indicates greater instability. They found that the parameters of the divergence curves between standing and walking had no correlation, suggesting that the mechanisms governing standing and walking stability are different. Since temporal correlations during standing and walking may be affected by the stability of the control system of each task, their results could provide evidence against the above-mentioned hypothesis. However, as far as we know, no study has directly compared temporal correlations of body fluctuations among strides during walking with body fluctuations during standing.

In order to directly compare temporal correlations in body sway during standing and walking, we used "COM acceleration" (ACC) as a measure of body fluctuation since ACC is one of the representative and commonly measurable parameters of body behavior during the motor tasks. Therefore, the purposes of this study were to (1) investigate the temporal correlations for ACC in standing and walking, and to (2) test the hypothesis that the degree of temporal correlation in ACC time-series during standing and walking are related. A preliminary account of the results was published in abstract form (Abe, Nakazawa, Masani, & Akai, 2004).

2. Methods

2.1. Participants

Seventeen healthy subjects (9 males and 8 females), aged 21–34 years, participated in this study. The mean (±standard deviation: *SD*) height and weight of all participants was 1.72 ± 0.07 m and 64.5 ± 8.4 kg, respectively. None of the participants had a history of motor disorder. Informed consent was obtained from all participants prior to their participation in this study. The experimental procedure used was approved by the local ethics committee.

2.2. Apparatus

To obtain ACC during standing and walking, we recorded ground reaction forces (GRF) using a treadmill equipped with two force platforms (ADAL3D, Techmachine, Andrézieux-Bouthéon, France). GRF data in mediolateral (ML), anteroposterior (AP), and vertical (VL) directions from each force platform were recorded. The natural frequency of this apparatus was over 120 Hz and the linearity was ensured by the manufacturer to range from 0 to 3000 N for the vertical components and 500 N for the horizontal components. Belli, Bui, Berger, Geyssant, and Lacour (2001) examined the same type of treadmill in detail and concluded that the treadmill would be accurate for analyzing human gait behavior.

2.3. Protocol

Participants performed two tasks: a standing task and a walking task. In the standing task, participants were asked to stand still without moving their arms or feet for 10 min on the treadmill. The heel-to-heel distance between feet was about 6 cm. In the walking task, the participants were asked to walk for 12 min on the treadmill with the belt speed set at 1.1 m/s. All participants reported that the speed was natural, and that they performed the task easily without feeling excessive effort and fatigue. Before the recording session, participants performed a five-minute practice session. There were five-minute breaks between the pre-training and the experimental trials in walking tasks, and 10-min breaks between the standing and walking tasks. The length of each break was decided based on the participants' objective comments. They were able to execute the next task comfortably after the break.

2.4. Data analysis

The GRF data was recorded at 100 Hz using a 16-bit AD converter (WE7000, Yokogawa, Tokyo, Japan) and stored on a personal computer. All data were digitally low-pass filtered with a zero-phase-lag 10th order FIR filter with a Blackman window at a cut-off frequency of 20 Hz. This filtering removed noise artifacts during push-off, and enabled the moment of heel contact to be accurately identified. For the walking task, the last 10 min of data (out of 12 min) were used in the subsequent analysis. The standing and walking data in the AP and ML directions for 10 min were used to calculate COM acceleration in AP (A_{AP}) and ML (A_{ML}) directions as follows:

$$\begin{aligned} A_{AP}(t) &= F_{AP}(t)/m \\ A_{ML}(t) &= F_{ML}(t)/m \end{aligned} \tag{1}$$

where m is the mass of the body, and F_{AP} and F_{ML} are GRF data in AP and ML directions, respectively. Note that we only focused on balance control in horizontal plane and therefore did not analyze the vertical force in the present study, since vertical movement during standing is not prominent. The ACC absolute value in each direction (ACC_{AP} and ACC_{ML} for AP and ML directions, respectively) and the magnitude of the two-dimensional ACC vector (ACC_{2D}) were calculated for each trial as follows:

$$\begin{aligned} ACC_{AP}(t) &= \sqrt{A_{AP}(t)^2} \\ ACC_{ML}(t) &= \sqrt{A_{ML}(t)^2} \\ ACC_{2D}(t) &= \sqrt{A_{AP}(t)^2 + A_{ML}(t)^2} \end{aligned} \tag{2}$$

First, we assessed stride-to-stride fluctuations in the walking data by partitioning the time-series into individual strides. The stride interval was defined as the moment from one heel contact to the next ipsilateral heel contact. Heel contact was identified as the time when the vertical GRF reached 10% of participants' body mass. For all participants, the stride interval was about 1 s (1.09 ± 0.04 s, mean ± *SD*) and contained roughly 500–600 data points. For each stride interval, the average magnitudes of ACC_{AP}, ACC_{ML}, and ACC_{2D} were calculated as in Eq. (2). This created a new time-series for each variable that consisted of these average ACC magnitudes, in which the number of data points was equal to the number of stride intervals. Then based on these stride intervals, the entire sequence of ACCs in the standing task was divided into bins in which the data length was defined by the average stride interval for each participant. Fig. 1 represents typical examples of the ACC series for standing and walking. The number of data points was equal in the standing and walking tasks. Table 1 shows a summary of average and standard deviations for the ACC time-series.

To investigate temporal correlations in ACC, we used Detrended Fluctuation Analysis (DFA) (Peng, Havlin, Stanley, & Goldberger, 1995; Peng et al., 1993). DFA evaluates degree of correlation in a time-series by a parameter referred to as the scaling index (α). The scaling index is quantified by calculating the slope of the line relating log $F(n)$ to log n, where n and $F(n)$ represent the window size and the variance of the time-series within each window (of size n), respectively (Fig. 2). In DFA, the data

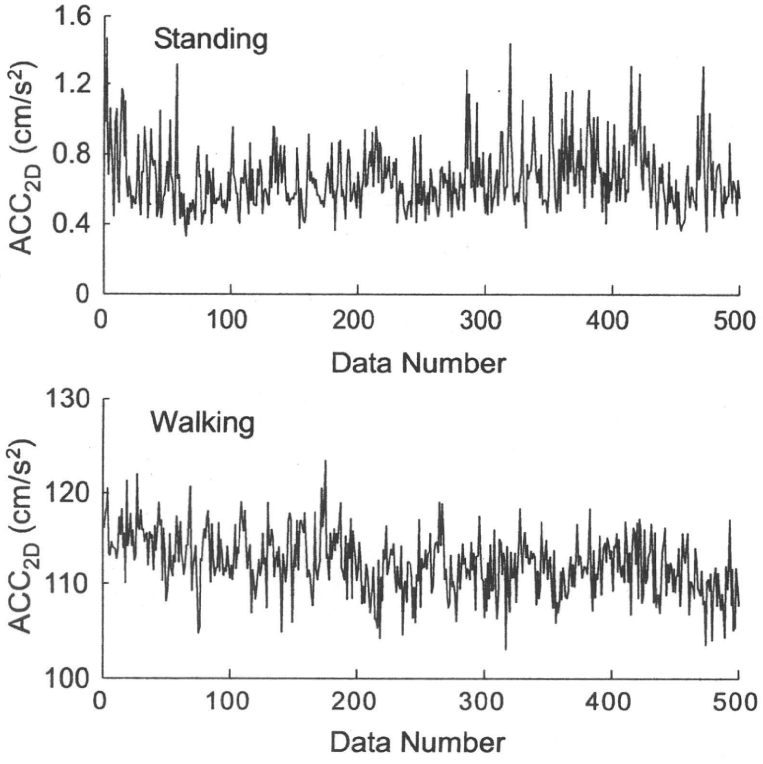

Fig. 1. Typical examples of the fluctuations of ACC_{2D} in standing (top) and walking (bottom).

Table 1
Mean and standard deviation of ACC.

	Mean (cm/s²)		Standard deviation (cm/s²)	
	Standing	Walking	Standing	Walking
ACC_{AP}	0.576 ± 0.126	75.7 ± 9.6	0.235 ± 0.070	4.09 ± 0.67
ACC_{ML}	0.330 ± 0.077	58.0 ± 7.7	0.161 ± 0.048	2.87 ± 0.58
ACC_{2D}	0.752 ± 0.136	99.7 ± 10.1	0.261 ± 0.071	3.51 ± 0.59

was normalized with mean = 0 and $SD = 50$, and integrated for the calculation of slope. If the scaling index (α) is less than 1, the time-series is categorized as a stationary signal (Eke, Herman, Kocsis, & Kozak, 2002). In addition, if there are no correlations between past and future fluctuations in the time-series, as in *white noise*, the scaling index will be $\alpha = 0.5$. When the signal is temporally correlated, the scaling index ranges from 0.5 to 1.0 (Eke et al., 2002). Note that $\alpha > 0.5$ in DFA does not necessarily indicate "long-range" correlations, as time-series having short-range correlations also can show $\alpha > 0.5$ in DFA (Maraun, Rust, & Timmer, 2004; Wagenmakers, Farrell, & Ratcliff, 2004, 2005). In this study, we used the scaling index simply as an estimation of the degree of time correlation. In stationary signals ($0.5 < \alpha < 1.0$), the scaling index is statistically equivalent to the degree of the decay of autocorrelation and power spectrum. Peng et al. (1993) demonstrated that the measurement of scaling index could dramatically reduce the influence of artifact noise compared to the other analyses.

The range of the slope calculation was from the 8th step to the 28th step ($8 < n < 28$) in which the slopes were straight. To validate our method for calculating the scaling index, we created twenty time-series with $\alpha = 0.5, 0.6, 0.7, 0.8, 0.9, 1.0$ (data length of 512) by using a previously validated method (Peng et al., 1993), and calculated the scaling indices using the above-mentioned method. The mean of the scaling indices for the simulated time-series was within 5% of the theoretical value as a result.

Although we recorded 10 min of data in standing and walking in order to compare their scaling index by the same time scale and same data number, these tasks might be affected by boredom

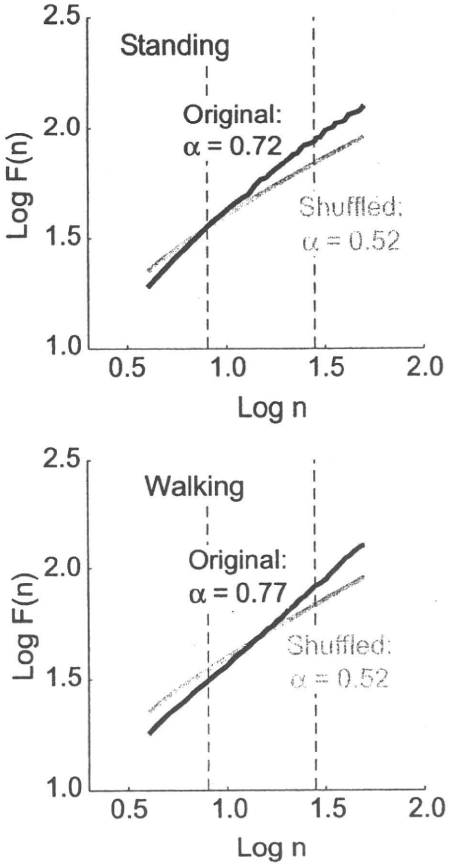

Fig. 2. Ensemble plots of detrended fluctuation analysis for ACC_{2D}. Black lines show the results of original data and gray lines show the results of shuffled surrogate data. The dotted lines represent the range for the slope calculation. The slopes, i.e., the scaling indices (α) are shown for each plot.

and fatigue. In particular, the standing task might be unnaturally long compared to standing in daily life. To check the influence of time effects over the scaling indices, the 10 min of data were divided into two bins (2 × 5 min) and scaling indices for these bins were compared in each direction by using a paired *t*-test. The test showed no significant difference between scaling indices in the two time bins for both tasks in three directions ($p > .05$ in all cases), suggesting that the effect of physical/mental fatigue on the scaling index of body fluctuation in standing and walking was not particularly critical in this study. Thus, we used the ACC series for 10 min in the subsequent analysis.

We performed a "shuffled" surrogate test (Scheinkman & LeBaron, 1989) for the scaling indices. While this test cannot distinguish white noise from linear-filtered white noise, we used it in order to confirm that the scaling index was generated from the temporal structure of the ACC series and not merely from the amplitude distribution (Theiler, Eubank, Longtin, Galdrikian, & Farmer, 1992). Twenty shuffled data sets from each of the ACC data were made by randomly shuffling the temporal order of the original data, and the averaged scaling index for the shuffled data set was compared with that of the original data by a paired *t*-test at each task and direction.

A comparison of the scaling indices of ACC in each condition was done by repeated measures two-way (Direction × Task) ANOVA with a Bonferroni post hoc test. The cross correlation between the scaling indices in standing and walking tasks in each direction was tested using Pearson's correlation coefficient. The significant levels of all statistical tests including the above analyses were set to $p < .05$.

3. Results

Fig. 2 shows the averaged DFA results for the original ACC_{2D} data and the shuffled data in standing and walking tasks for all participants. As shown in this figure, the scaling index of the original data was

much larger than 0.5 in both the standing and walking tasks, while the shuffled data set showed the scaling indices close to 0.5. Table 2 summarizes the results of the scaling indices of each ACC component for the standing and walking tasks. The scaling indices for the standing and walking tasks ranged from 0.524 to 0.915 and from 0.602 to 1.006, respectively. The ANOVA showed a significant interaction between conditions, $F(2, 32) = 5.267$, $p = .011$. The post hoc test for each direction showed a significant difference in the scaling indices for ACC_{ML} between standing and walking tasks ($p = .037$). There were no significant differences for ACC_{AP} and ACC_{2D} between the tasks ($p > .05$). Table 2 also shows the scaling indices for shuffled data. Paired t-tests between scaling indices in the original and shuffled data showed that the scaling indices of the original data were significantly larger than that of shuffled data for both tasks in all directions ($p < .05$).

Fig. 3 shows the relationships of the scaling indices for each ACC parameter between the standing and walking tasks across all participants. In all figures, the horizontal axis represents the scaling indices of the standing task and the vertical axis represents the scaling index of the walking task. There were strongly significant correlations between the scaling indices from the standing and walking tasks for ACC_{AP} ($r = .593$, $p = .012$) and ACC_{2D} ($r = .612$, $p = .009$). For ACC_{ML}, there was no significant correlation between the scaling indices during standing and walking ($r = -.081$, $p = .758$).

Previous studies for walking focused on the long-time correlation of the stride interval. Thus, we also compared scaling indices of ACC in walking with scaling indices of stride interval in walking. The averaged scaling index of the stride interval was 0.780 ± 0.112. There were no significant correlations between the scaling indices for stride interval and for ACC during the walking task in each direction ($r = .358$, $p = .159$ in ACC_{AP}, $r = -.128$, $p = .624$ in ACC_{ML}, and $r = .335$, $p = .189$ in ACC_{2D}).

4. Discussion

4.1. Temporal correlations in ACC fluctuations during standing and walking

The scaling indices of ACC for each direction ranged from 0.60 to 1.01 for walking and 0.52 to 0.92 for standing (Table 2 and Fig. 3). Except for one scaling index for ACC_{ML} in walking, these values were less than one, meaning that the fluctuations of these signals were stationary (Eke et al., 2002). This suggests that participants in this study controlled the center of body mass in both standing and walking so that the amplitude of the acceleration was maintained at a certain level. In addition, all parameters of ACC_{AP}, ACC_{ML}, and ACC_{2D} were significantly larger from the values of the surrogate data, i.e., ≈0.5, which indicates that the ACC signals were temporally correlated. The results of the surrogate testing indicate that the time correlations were due to the temporal ordering of the ACC fluctuations, and were not related to the amplitude distribution.

Temporal correlations in the body fluctuation during standing have been analyzed using COP (Collins & De Luca, 1993, 1994, 1995; Collins et al., 1995; Duarte & Zatsiorsky, 2000, 2001) and body displacement (Priplata et al., 2003, 2006). Duarte and Zatsiorsky (2001) examined COP using DFA and found that the scaling index of COP fluctuation during standing was $\alpha = 0.98 \pm 0.17$ and $\alpha = 1.01 \pm 0.03$ in AP and ML directions, respectively. Since their measurements were different from ACC, it is impossible to compare the values in their research directly to the results in the present study. It is true, however, that temporal correlations are commonly observed in body fluctuations measured using ACC as well as COP.

Table 2
Scaling indices of ACC in standing and walking for all participants. The right column "Mean (shuffled)" shows the result of shuffled surrogate test.

	Maximum–minimum		Mean		Mean (shuffled)	
	Standing	Walking	Standing	Walking	Standing	Walking
ACC_{AP}	0.87–0.52	0.80–0.60	0.67 ± 0.09	0.69 ± 0.05	0.51 ± 0.01	0.52 ± 0.01
ACC_{ML}	0.90–0.62	1.01–0.74	0.74 ± 0.08	0.84 ± 0.07	0.52 ± 0.01	0.52 ± 0.01
ACC_{2D}	0.92–0.52	0.89–0.69	0.72 ± 0.10	0.77 ± 0.05	0.52 ± 0.01	0.52 ± 0.01

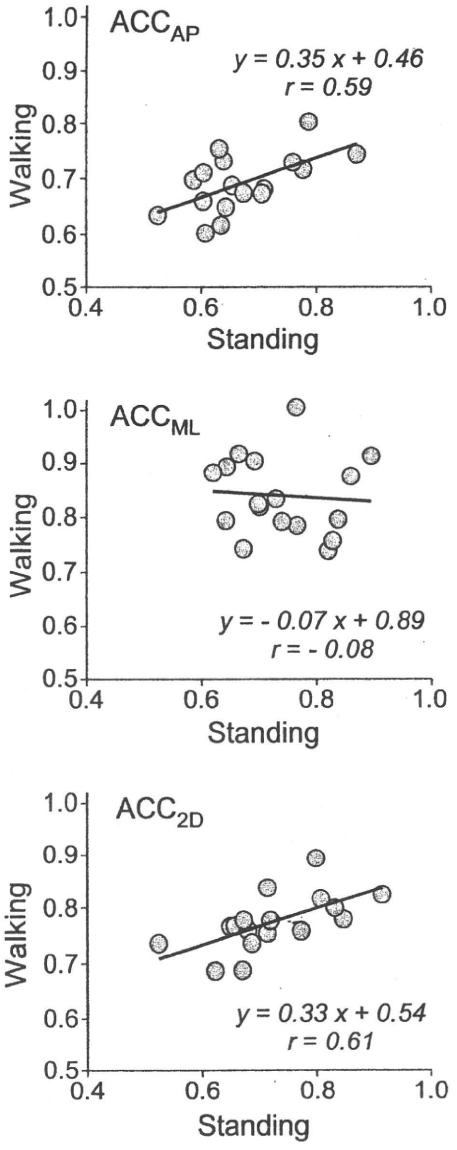

Fig. 3. Relations between scaling indices of ACC in standing (horizontal axis) and walking (vertical axis). The top, middle, and bottom figures show the results for ACC_{AP}, ACC_{ML}, and ACC_{2D}, respectively.

Temporal correlations in body sway during walking have been shown using the stride time interval of gait (Hausdorff, Ashkenazy et al., 2001; Hausdorff et al., 1997, 1995, 1996; Hausdorff, Zemany, Peng, & Goldberger, 1999). Hausdorff et al. (1995) reported the scaling exponent as $\alpha = 0.76 \pm 0.11$ for young participants. This value is close to the value for ACC in this study. In fact, the scaling index for the stride interval in this study also showed a similar value (0.78 ± 0.11). The scaling indices of both ACC and stride interval during walking, however, were not significantly correlated across participants. This suggests that temporal correlations of ACCs during walking were not simply a by-product of fluctuations in stride intervals.

Two possible causes of the temporal correlations are considered: neural effects related to balance control and mechanical effects of the musculo-skeletal system. The temporal correlations can reflect neural processes for balance control in which the equilibrium of the body during standing and walking is maintained by referring to past states of the body. In this context, the degree of temporal correlation reflects the underlying neural mechanism for maintaining postural stability. On the other hand, the temporal correlations may be caused by the filtering properties of the musculo-skeletal system during standing and walking (Gates et al., 2007; Peterka, 2000). Even if motor commands generated by the

neural system have no temporal correlations, these outputs can be low-pass filtered by the musculo-skeletal system, based on its visco-elastic and inertial properties. Such neuro-mechanical influences, and the interaction between them, can affect the degree of correlation in ACC, although this study cannot identify the relative contributions.

Temporal correlations in ACC fluctuations during walking might be influenced by the use of a treadmill. While the treadmill with twin force platforms afforded us precise and stable recordings of ACC in walking, the constant belt speed might decrease variability compared to overground walking (Dingwell, Cusumano, Cavanagh, & Sternad, 2001). Although the scaling indices for stride interval in walking, as described above, showed similar levels with those of previous studies that recorded overground walking, further tests would be needed to determine the relationship between ACCs in treadmill and overground walking.

4.2. Comparison of the degree of temporal correlation between standing and walking

While scaling indices of ACC in standing and walking showed inter-subject variability, they were correlated for ACC_{AP} and ACC_{2D} measures (Fig. 3). This result indicates that an individual, who shows strong temporal correlations when standing, also shows strong temporal correlations when walking, and *vice versa*. This result is interesting because, in general, balance control and body segmental dynamics in standing and walking are considered different (Winter, 1995). The positive relationship between the temporal correlations in standing and walking has two potential explanations. First, the temporal characteristics of balance control in standing and walking might be similar across participants. Second, the intrinsic properties of the participants' musculo-skeletal systems may have similar effects on the temporal correlations of ACC during standing and walking.

Previous studies suggested that there is little relation between balance controls in standing and walking (Kang & Dingwell, 2006; Shimada et al., 2003). The difference between previous investigations and this study might be due to the adopted methods. In the present study, periodic components of walking data were removed by using the averaged data at each stride, and the temporal correlations among strides was compared with that of standing data in the same time scale. Focusing on the body fluctuations among strides in walking allowed a direct comparison between time-dependent characteristics of standing and walking in the same time scales.

Unlike ACC_{AP} and ACC_{2D}, the scaling index for ACC_{ML} in walking was significantly larger than that in standing. In addition, there was no significant correlation between the scaling indices in standing and walking for ML direction. Compared to the AP direction, ACC in the ML direction may be more strongly determined by properties of the musculo-skeletal system. Lateral dynamics in walking is more unstable than in standing, as it takes more time to recover after a lateral perturbation. This could induce large temporal correlations in ACC during walking. The relatively larger difference between standing and walking in this direction might hide the similarity seen in AP and 2D direction. In fact, previous studies demonstrated that the body fluctuations in the ML direction during standing are not sensitive enough to reflect changes induced by aging (Collins & De Luca, 1995; Prieto, Myklebust, Hoffmann, Lovett, & Myklebust, 1996), although the body fluctuations in the ML direction during walking are more sensitive (Dean, Alexander, & Kuo, 2007; Owings & Garabiner, 2004).

5. Conclusions

In summary, we demonstrated that the fluctuations of COM acceleration during standing and walking have a similar degree of temporal correlation ($0.5 < \alpha < 1.0$). There was a positive relationship between the standing and walking ACC temporal correlations in the anteroposterior direction and also in the horizontal plane, but not in the mediolateral direction. This suggests common characteristics in the balance control system in standing and walking, which may be related to the fluctuations in COM acceleration. While neural effects related to balance control and the mechanics of the musculo-skeletal system are presumed to be the causes of the temporal correlation, further studies are needed to identify the relative contribution of the neural and mechanical components in the AP and ML directions.

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ORIGINAL ARTICLE

Positive effect of balance training with visual feedback on standing balance abilities in people with incomplete spinal cord injury

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Objectives: (1) To evaluate the learning potential and performance improvements during standing balance training with visual feedback (VBT) in individuals with incomplete spinal cord injury (SCI) and (2) to determine whether standing static and dynamic stability during training-irrelevant tasks can be improved after the VBT.
Setting: National Rehabilitation Center for Persons with Disabilities, Tokorozawa, Japan.
Methods: Six participants with chronic motor and sensory incomplete SCI who were able to stand for at least 5 min without any form of assistive device performed the VBT, 3 days per week, for a total of 12 sessions. During the training, participants stood on a force platform and were instructed to shift their center of pressure in the indicated directions as represented by a cursor on a monitor. The performance and the rate of learning were monitored throughout the training period. Before and after the program, static and dynamic stability was assessed.
Results: All participants showed substantial improvements in the scores, which varied between 236 ± 94 and 130 ± 14% of the initial values for different exercises. The balance performance during training-irrelevant tasks was significantly improved: for example, the area inside the stability zone after the training reached 221 ± 86% of the pre-training values.
Conclusion: Postural control can be enhanced in individuals with incomplete SCI using VBT. All participants showed substantial improvements during standing in both game performance and training-irrelevant tasks after the VBT.
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Keywords: spinal cord injury; balance training; biofeedback; motor learning; plasticity

Introduction

The ultimate aim of individuals with spinal cord injury (SCI) is to maximize their independence in all aspects of life, given the limitations imposed by their injury.[1–3] Recovery of balance ability during standing is, therefore, one of the primary and essential aims of rehabilitative programs in individuals with incomplete SCI. These patients are obliged to develop and re-establish compensatory strategies to maintain balance, including activation of appropriate trunk, neck, and upper limbs muscles in response to internal and external postural disturbances. Conventional therapy in this population focuses on muscle strengthening and improving task-specific balance reactions.[4] In addition, the importance of learning to use visual cues and sensory inputs from neurologically intact parts of the body has been emphasized to help maintain safe balance.[4,5]

Recent advances in technology have resulted in the availability of visual feedback for the retraining of balance function in individuals with neurological disorders, including stroke,[6,7] cerebellar ataxia,[7] cerebral palsy,[8] and Parkinson's disease.[7] Although further studies are needed to investigate a potential association between positive results obtained from laboratory force plate measures and clinical and functional outcomes,[6,9] it has been shown that the main positive effect of such training on postural control can be attributed to sensorimotor integration[5,10–13] as well as the coordination improvement because of the task specificity of training.[14,15] In the SCI population, benefits of game-based exercises[16] and virtual reality[3] have been suggested for dynamic *sitting* balance. These studies have shown their potential for substantial improvements in sitting balance

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through the inclusion of functional approaches in the training.[3,16] However, the effect of balance training with visual feedback during *standing* in the SCI population has not been reported well. It has been suggested that the standing posture has a number of therapeutic and functional benefits[17] aimed at overcoming physiological problems, such as bladder infections,[17] spasticity,[18] blood pressure homeostasis,[19] and bone demineralization.[20] We believe that regaining functionality during self-governed standing will decrease secondary complications and increase independence, and consequently, improve the quality of life of individuals with SCI.

We hypothesized that balance training with visual feedback during standing can improve postural control in individuals with incomplete SCI. The purposes of our study were the following: (1) to evaluate the learning potential and performance improvements during the balance training and determine whether voluntary postural control during different tasks can be improved in individuals with incomplete SCI; (2) to determine whether static and dynamic stability during training-irrelevant tasks can be improved after the balance training; and (3) to suggest mechanisms that may be responsible for a potential improvement in postural control in individuals with incomplete SCI.

Materials and methods

Participants

Six ambulatory participants with motor and sensory incomplete SCI participated in this study (Table 1). Information about each participant's characteristics was based on a self-reported American spinal injury association impairment scale classification, the neurological level of the injury, observed assistive device requirements, and the mobility status at the time when baseline measurements were recorded. The inclusion criteria were the following: (1) at least 12 months post-injury to ensure stability of the participants' neurological condition; (2) ability to stand for at least 5 min without any form of assistive device; and (3) ability to walk 10 m or more with or without the help of parallel sidebars. During the study, the participants did not participate in other rehabilitation or research interventions that might have influenced the outcomes of this study. Each participant gave written informed consent to the experimental procedure, which was approved by the local ethics committee in accordance with the declaration of Helsinki on the use of human subjects in experiments.

Experimental setup and procedure

The training and the data collection were performed with the force plate analysis system 'Stabilan-01' (Rhythm, Taganrog, Russia). The Biodex Unweighing System (Biodex, Shirley, New York, USA) was used in combination with a harness to prevent falls during standing. During the training, participants stood on the force plate and were instructed to look at the monitor, placed at eye level, approximately 1.5 m in front of the force plate. The center of pressure (COP) position signal was used as an input to game-based exercises.

The training was performed 3 days per week for a total of 12 sessions. If a participant was not able to attend a

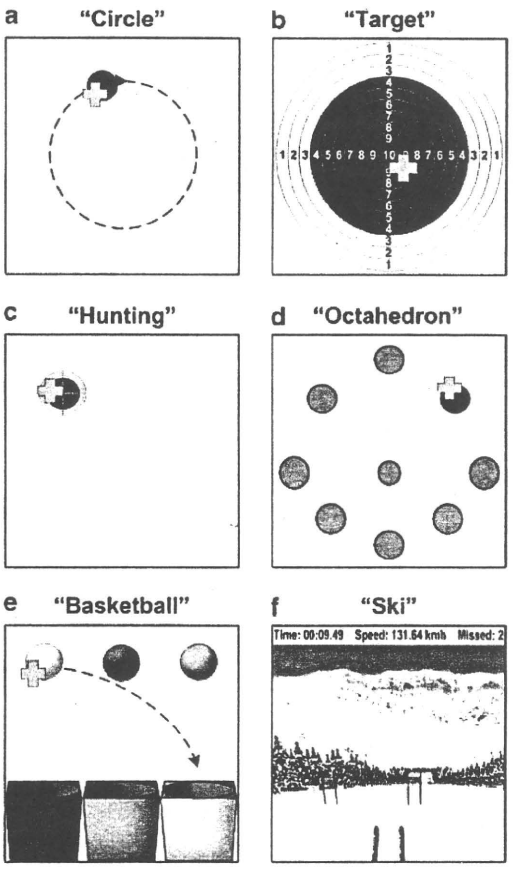

Figure 1 Interface examples of the game-based exercises: (**a**) 'circle,' (**b**) 'target,' (**c**) 'hunting,' (**d**) 'octahedron,' (**e**) 'basketball,' and (**f**) 'ski.' Arrows depict directions for the COP indicator translation (were not shown during the exercises).

Table 1 Characteristics of SCI participants

Participant	*Age (years)*	*Sex*	*Height (cm)*	*Weight (kg)*	*Duration of injury (years)*	*Level*	*AIS*	*Assistive device*
1	62	Male	173	65	3	C4	D	Walker
2	50	Male	175	68	4	C4	D	Walker
3	30	Male	180	77	11	T10	C	Wheelchair[a]
4	42	Female	164	62	23	T10	C	Wheelchair[a]
5	27	Male	179	78	6	T11	C	Wheelchair[a]
6	35	Male	178	75	8	T12	C	Wheelchair[a]

Abbreviations: AIS, American spinal injury association (ASIA) impairment scale; SCI, spinal cord injury.
[a]Participants used ankle foot orthoses and canes for walking.

scheduled session, the participant was asked to come to a replacement session. Each session lasted up to 60 min with a total standing time of at least 30 min.

Training protocols

In the 'circle' exercise (Figure 1a), a target moved around the center of the screen. The participant was instructed to track the target and hold the COP indicator over it. In the 'target' exercise (Figure 1b), the participant was asked to keep the COP indicator in the center of a target as still as possible. In the 'hunting' exercise (Figure 1c), a target appeared on the screen in random locations. Once the COP indicator was held 'still' within the boundaries of the target for 3 s, the target would reappear in a different location. In the 'octahedron' exercise (Figure 1d), eight targets were presented at 45-degree angles from one another around the center. The participant was asked to move the COP indicator to each target, and hold the position for 5 s. In the 'basketball' exercise (Figure 1e), three targets (balls) of different color appeared on the top of the screen. The participant was asked to 'capture' the target, and 'drag' it into the basket of the matching color. In the 'ski' exercise (Figure 1f), the participant was asked to simulate downhill skiing.

The duration of each exercise varied from 1 to 2 min. The score was calculated based on the accumulated time that the COP indicator was over the targets or/and based on the number of successful trials. The exercises were presented in random order. Once a consistent score in each exercise was attained by the participants, the difficulty level of the exercise was increased. The initial difficulty of the exercises was adjusted to each participant based on their performance during the familiarization session. During each training session, an equal number of rounds of each exercise was presented to the participant.

Exercise performance

During the training period, the level of the performance and the rate of learning were monitored. The performance for each exercise was expressed as a percentage of the initial score on the first session. A one-way ANOVA with repeated measures ($\alpha = 0.05$) and a subsequent Dunnet's test were applied to the pooled data. We estimated the rate of learning for different exercises by performing a regression analysis

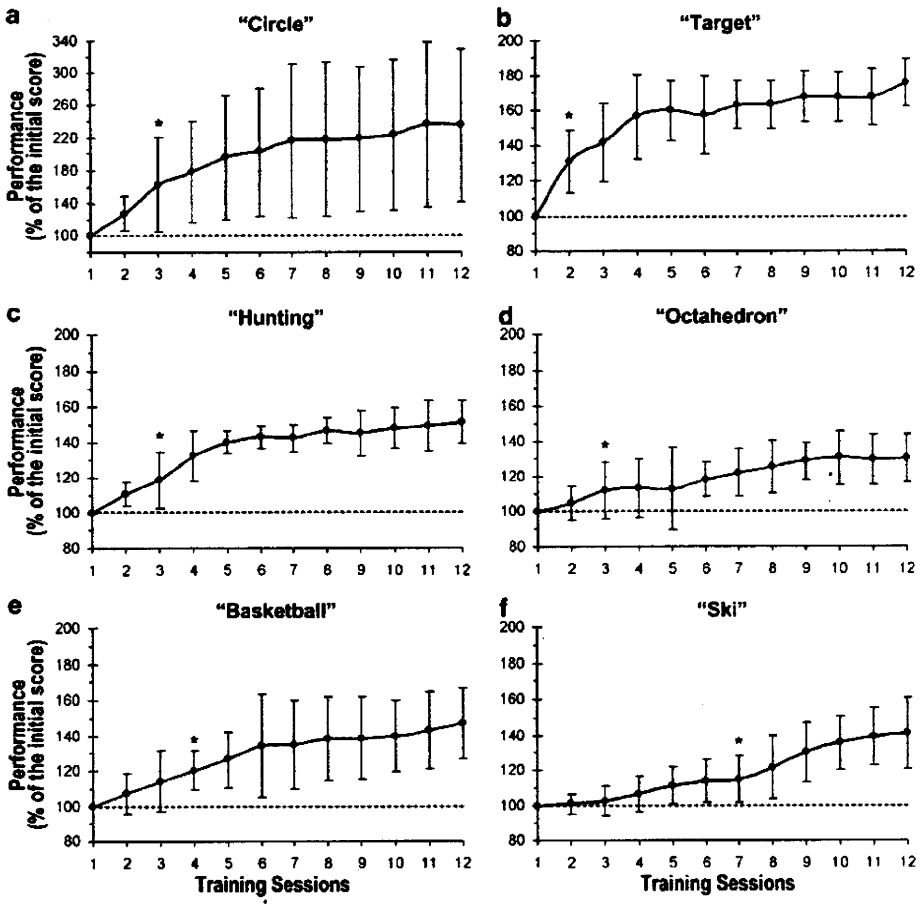

Figure 2 Pooled data showing the performance throughout the training period for all six exercises: (a) 'circle,' (b) 'target,' (c) 'hunting,' (d) 'octahedron,' (e) 'basketball,' and (f) 'ski.' Shown are the percentages of the initial score values obtained in the first session of the training (mean ± s.d.). Asterisks indicate the first session of the training for which the performance was significantly different from the performance during the initial session of the training ($P < 0.05$).

using a logarithmic model in which the rate of learning was proportional to the logarithm of the learning time. The model was described using the following equation:[7]

$$y = a + b \times \log_{10} d, \quad (1)$$

where y is the expected performance on the day of the training d, and a and b are the regression coefficients, describing the initial level of performance and slope, respectively. To compare the rate of learning across exercises, confidence intervals (CIs) of the slopes were computed using the following equation:

$$\mathrm{CI} = S \pm Z_{\alpha/2} \times (\mathrm{s.e.}/n^{1/2}), \quad (2)$$

where S is a value of the slope, α is a significance level, Z is a z-score for a two-tailed distribution equal to 1.96, s.e. is the standard error of the measure, and n is the number of the training session. The desired width of the CI was 95%.

Postural stability assessment

Before and after the training period, two different aspects of balance were evaluated: *static* and *dynamic stability*.

During the static stability test, the participant was instructed to stand on the force plate as still as possible for 60 s with the eyes open. After 2 min of rest, the task was repeated with the eyes closed. The fluctuations of the COP were analyzed with root mean square distance (RDIST), the 95% confidence ellipse area (AREA-CE), and the mean velocity (MVELO).[21–23]

During the dynamic stability test, the ability to voluntarily displace the COP to a maximum distance without losing balance was assessed.[24] Eight targets were presented on the screen at 45-degree angles from one another around the center. The participant was instructed to shift the COP indicator as far as possible toward a target, which changed its color, hold this position, and then return the COP indicator to the center. The target was active for 7 s. The average amplitudes of the COP displacements were defined for each direction for the time interval from 3 to 6 s, and were then used as vertices of an octagon. The area of this octagon was defined as the stability zone (AREA-SZ) and was calculated using the following formula:

$$S = \frac{1}{2} \sum_{i=0}^{n-1} (x_i y_{i+1} - x_{i+1} y_i) \quad (3)$$

where x is the anterior–posterior position of COP and y is the medial–lateral position of COP.

For each measure, comparisons between values before and after the training were performed using a paired t-test. The level of significance was set at $\alpha = 0.05$ for all analyses. The results for the pooled data are presented as mean values and s.d.

Results

Exercise performance

Figure 2 shows the pooled data of the participants' performance throughout the training period in all exercises as a percentage of the initial scores values obtained on the first day of the training. The most prominent performance was revealed in the exercises 'circle' (Figure 2a) and 'target' (Figure 2b): at the end of the training period, the average score reached 236 ± 94, and 176 ± 14% of the initial values, respectively. Somewhat similar yet lower performance was observed in the exercise 'hunting' (Figure 2c): the score on the 12th session reached 151 ± 12% of the initial value. A lower level of performance improvement occurred in exercises 'octahedron,' 'basketball,' and 'ski' (Figures 2d–f): the score on the 12th training session increased in comparison with the initial values, reaching 130 ± 14, 147 ± 20, and 141 ± 20%, respectively.

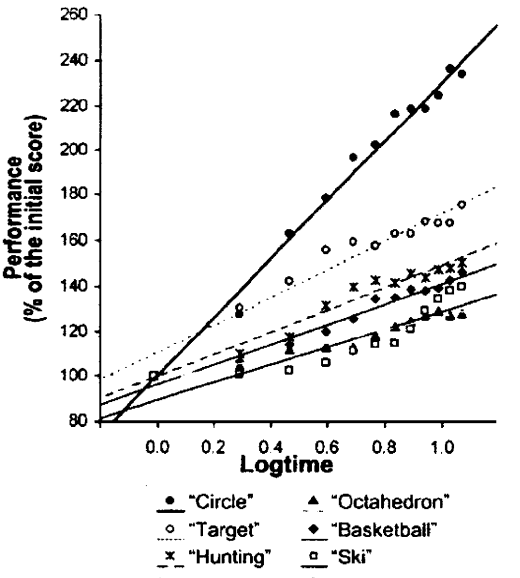

Figure 3 Regression curves representing the pool-average rate of learning for different exercises during the training period (logarithmic model). The abscissa indicates the log10 of the number of training session.

The results of the regression analysis (Figure 3) revealed that the most significant changes in the learning rate occurred in the exercises 'circle' and 'target': the slope of the regression curves in the logarithmic model reached 56.9 (CI from 30.3 to 83.5) and 26.9 (CI from 23.0 to 30.8), respectively. Lower learning rates occurred in the exercises 'hunting,' 'basketball' and 'ski,' where the slope of the regression curve reached 21.5 (CI from 17.2 to 25.9), 19.6 (CI from 13.1 to 26.1), and 17.2 (CI from 12.5 to 21.9), respectively. Finally, the slowest learning rate took place in the exercise 'octahedron,' where the slope of the regression curve reached 12.7 (CI from 10.1 to 15.2).

Postural stability

In Figure 4, the pooled data of RDIST (Figure 4a), MVELO (Figure 4b), and AREA-CE (Figure 4c) are depicted for the performance before and after the balance training. The results show that all measures except MVELO of the medial–lateral COP fluctuation were significantly decreased after the balance training (Table 2).

During the test of dynamic stability, AREA-SZ was significantly increased after the training period, reaching 221 ± 86% of the pre-training values (Figure 5; Table 2).

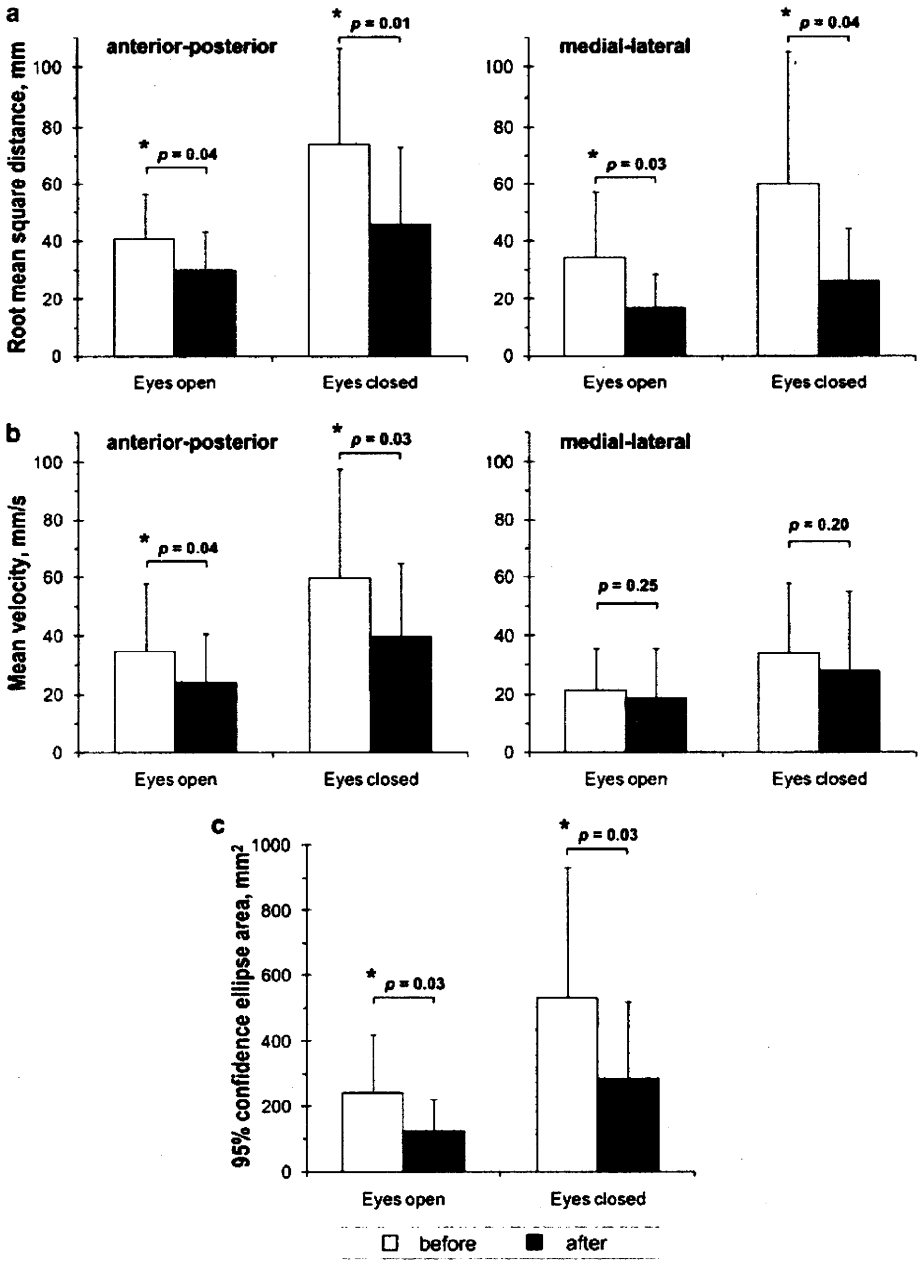

Figure 4 Test of static stability. Pooled data showing (a) the root mean square distance (RDIST), (b) the mean velocity (MVELO), and (c) the 95% confidence ellipse area (AREA-CE) of the COP fluctuation during standing with eyes open and eyes closed before (white columns) and after (black columns) the balance training (mean ± s.d.). RDIST (a) and MVELO (b) during anterior–posterior and medial–lateral fluctuations of the COP are shown on the left and right panels, respectively. Asterisks indicate statistically significant differences between the values before and after the training ($P<0.05$).

Discussion

In this study, two main results were found. First, after the balance training with visual feedback, all participants showed substantial improvement in the scores of each exercise, though the achieved performance and rate of learning varied across different exercises. Second, the balance performance during both static and dynamic assessment was significantly improved after the training.

Improved balance function

Two types of supervised learning conditions were implemented during the balance training.[7] For the first type ('circle' and 'target'), a given stereotyped pattern of movement had to be generated, requiring a high precision of movement performance. For the second type ('basketball' and 'ski'), the participants apparently applied a general strategy of voluntary postural control that included attention, decision making, and performance of the task with

Table 2 Average values of the RDIST, MVELO, AREA-CE, and AREA-SZ after the balance training (mean ± s.d.)

Measure	*Condition*	*Anterior–posterior (% of initial values)*	*Medial–lateral (% of initial values)*
RDIST	EO	75 ± 17	61 ± 35
	EC	60 ± 25	38 ± 30
MVELO	EO	73 ± 20	85 ± 30
	EC	66 ± 25	79 ± 34
AREA-CE	EO	52 ± 32	
	EC	46 ± 25	
AREA-SZ	EO	221 ± 86	

Abbreviations: AREA-CE, 95% confidence ellipse area; AREA-SZ, area inside the stability zone; MVELO, mean velocity; RDIST, root mean square distance.

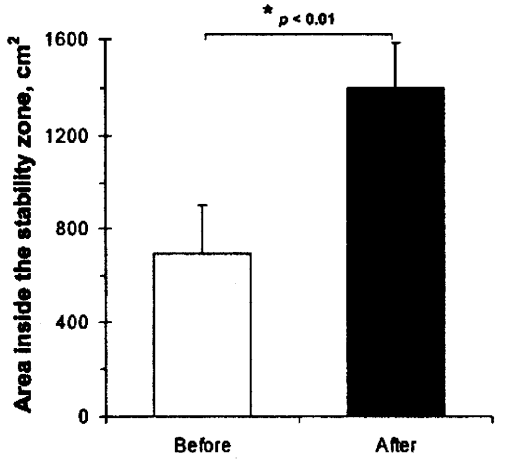

Figure 5 Test of dynamic stability. Average values of the area inside the stability zone before (white column) and after (black column) the balance training (mean ± s.d.). Asterisks indicate statistically significant difference between the value before and after the training ($P<0.05$).

different movement patterns. In addition, mixed conditions ('hunting' and 'octahedron') were used during the training. Our analysis revealed that the most successful improvement was achieved in exercises of the first type that presented the same movement pattern again and again, whereas less progress was obtained in exercises with different movement patterns. The lowest performance and learning rate during the exercise 'octahedron' might be explained by a greater muscle activity during this exercise; thus, the improvement of muscle performance occurred with a lower increment than enhancement in postural synergies and strategies.

Evidence from human studies has shown that goal-oriented and task-specific training improves impaired function after central and peripheral nervous system disorders or lesions.[14–16] Presumably, an increase in cortical control of muscles after incomplete SCI might allow functional recovery through the development of alternative movement strategies.[25] As a result, the motor programs for balance control strategies, provided by *task-specific* training, seemed to be effective and could affect the final outcome of the participants in our study.

At the same time, both static and dynamic stability tests did not correspond directly to the motor tasks engaged throughout the training period. Nonetheless, both static and dynamic stability tests (including eyes-closed condition during the static test) revealed a significant improvement of postural control after the training period in all participants. It has been earlier shown that during static postural stability test, RDIST and AREA-CE can be related to the effectiveness of, or the stability achieved by, the postural control system; and MVELO has been related to the amount of regulatory activity associated with this level of stability.[21–23] The increased AREA-SZ on the other hand has been related to an enhancement of muscle strength.[24] Consequently, we can also assume a *non-specific* effect of the training on the postural control mechanisms after our balance training program.

Potential mechanisms

The central nervous system of individuals with incomplete SCI is susceptible to substantial reorganization as cortical, subcortical, and much of the local spinal cord circuitry remain largely intact and still partially interconnected by unlesioned fibers.[25] Although any of the adaptive reorganizations might contribute to the exhibited improvement, we turn our attention toward the main function of supraspinal reorganization (plasticity) as the mechanism most likely associated with cognitive processes—namely, the formation of internal models and learning of limits.

It has been suggested in studies with stroke survivors that by giving the participants additional visual information, they became more aware of the body's displacements and orientation in space,[13] were able to integrate somatosensory and visual information in relation to stance and movements,[26] recalibrate deficient proprioceptive information,[13,27] and compensate the sensorimotor deficit.[10] We hypothesize that in individuals with SCI, mechanisms of balance improvement because of altered sensorimotor integration and more extensive processing of residual proprioceptive and cutaneous sensory information also seem feasible.[25,28–30]

Our training program provided a progressive challenge and overload to the postural control system throughout the training period.[31] We assume that such activity *per se* could improve the strength and endurance of muscles participating in control of posture, especially in participants with minimal function before the training.[24,32,33] Furthermore, our balance training program included exercises that closely mimicked reaching in standing tasks, thereby providing muscle activation associated with functional challenge of maintaining balance.[24,34–36] We, therefore, suggest that the improved function during dynamic tasks might be at least partially attributed to enhancements of the muscle properties.

Study limitations and future directions

Further studies in a larger group of individuals with SCI are required to confirm our observations. Ideally, these studies would include a control group and clinical information

(for example lower extremity motor score) as well as measures of activity limitation and participation restriction to determine the clinical impact and functional consequences of balance training with visual feedback. In addition, muscle strength and aerobic capacity have to be measured in important postural muscles.

Conclusion

As the first report in this field, we showed that individuals with chronic incomplete SCI show improvements in upright static and dynamic postural control after balance training with visual feedback during standing. Although our observations have to be confirmed in further studies, we assume that balance training with visual feedback opens up a possibility to supplement routine rehabilitative interventions in individuals with incomplete SCI. The main positive effect of the balance training on postural control may be associated with the improvement of existing and the development of new motor strategies, sensorimotor integration, and a direct effect of the training on the muscles' functional properties.

Conflict of interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Hyperphosphorylated neurofilament NF-H as a biomarker of the efficacy of minocycline therapy for spinal cord injury

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Study design: An *in vivo* study in a rat model of acute spinal cord contusion.
Objectives: To assess the efficacy of novel therapies for acute spinal cord injury (SCI), methods to evaluate accurately the effects of these therapies should be developed. Although neurological examination is commonly used for this purpose, unstable clinical conditions and the spontaneous recovery of neurological function in the acute and subacute phases after injury make this measurement unreliable. Recent studies have reported that the phosphorylated form of the high-molecular-weight neurofilament subunit NF-H (pNF-H), a new biomarker for axonal degeneration, can be measured in serum samples in experimental SCI animals. Therefore, we aimed to investigate the use of plasma pNF-H as an indicator of the efficacy of minocycline, a neuroprotective drug, for treating SCI.
Setting: This study was carried out at Saitama, Japan.
Methods: Spinal cord injured rats received either minocycline or saline intraperitoneally. The plasma pNF-H levels and functional hind limb score were determined after the injury.
Results: Minocycline treatment reduced plasma pNF-H levels at 3 and 4 days post-injury (dpi). Rats with lower plasma pNF-H levels at 3 dpi had higher hind limb motor score at 28 dpi.
Conclusions: pNF-H levels may serve as a biomarker for evaluating the efficacy of therapies for SCI.
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Keywords: biomarker; pNF-H; minocycline; spinal cord injury

Introduction

The sensorimotor dysfunction that occurs after spinal cord injury (SCI) results from both the primary mechanical insult and secondary damage, which includes multiple components such as inflammatory reaction, delayed neuronal and glial cell death, and axonal degeneration.[1,2] These biological processes continue for several days, and can therefore be targeted in therapeutic intervention. Various therapeutic strategies have been developed to ameliorate tissue loss arising due to secondary damage.[3]

Appropriate assessment methods are required to determine the efficacy of novel neuroprotective therapies. The American Spinal Injury Association assessment scale is a standardized tool that is used widely to assess neurological state (grade A–E) and motor score in SCI patients. However, the spontaneous neurological recovery in acute and subacute SCI patients may limit the reliability of assessments of the initial state.[4] Further, as the degree of spontaneous recovery varies among patients in clinical trials of SCI therapies, it is unclear whether the neurological improvement is because of the therapeutic intervention or spontaneous recovery. Therefore, a novel technique that is independent of neurological status is required for monitoring progressive tissue damage; this development will facilitate further clinical trials of SCI therapies.

The severity or stage of a disease is usually determined by measuring the levels of certain biomarkers in blood or cerebrospinal fluid. In the clinical field of traumatic brain injury, several proteins that are synthesized in neurons and glial cells, such as S100B, neuron-specific enolase, myelin basic protein and glial fibrillary acid protein, have been proposed as surrogate markers that can be used in clinical trials.[5,6] However, there are only a few reports on biomarkers in SCI patients.[7,8]

Recently, studies in experimental SCI animals and aneurismal subarachnoid hemorrhage patients revealed an association between the level of the phosphorylated form of the high-molecular-weight neurofilament subunit NF-H (pNF-H) in blood and prognosis.[9,10] Because NF-H is one of the

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major structural complexes in axons, increased levels of the phosphorylated form of the protein, which is resistant to proteases, indicate increased axonal damage. In contrast to the other neural-cell-derived biomarkers such as serum S100B and neuron-specific enolase, whose levels peak within 24 h after injury, serum pNF-H levels peak 3 days after SCI.[9,11] This temporal pattern may reflect progressive axonal loss due to secondary damage. A previous study in experimental SCI rats reported a relation between the serum pNF-H level and the intensity of the initial impact (primary insults) delivered by the SCI device.[9] However, whether pNF-H can be used as a marker to evaluate the efficacy of therapeutic interventions against secondary damage in SCI remains unknown. In this study, we measured the plasma pNF-H levels in SCI rats treated with minocycline, a neuroprotective drug.[3,12,13]

Materials and methods

Surgical procedures

All surgical procedures were approved by the ethical committee of Research Institute, National Rehabilitation Center. Experimental SCIs were induced in adult 10- to 12-week-old Sprague–Dawley rats (body weight, 280–320 g). Animals were anesthetized by intraperitoneal injection of barbiturate. Thereafter, the lower thoracic lamina was exposed, and the lamina was removed at the level of Th10. Contusion injuries were then induced by using the Infinite Horizon SCI device (Precision Systems and Instrumentation, Lexington, KY, USA). The intensity of the device was set to 1.5 N (150 kdyn), which induces moderate contusion injury. After the surgical procedure, the rats were allowed to recover on a warm blanket. From the day after the surgery, urination was assisted manually until voluntary urination was restored.

Minocycline treatment

Rats were randomly assigned into two groups ($N=4$ per group) and were administered an intraperitoneal injection of either control saline (control group) or minocycline (15 mg ml^{-1} in saline; treated group) (Sigma, St Louis, MO, USA). The injured rats received an initial dose of 90 mg kg^{-1} body weight minocycline immediately after the injury, followed 9 h later by a second dose of 45 mg kg^{-1} body weight. From the following day, either control saline or 45 mg kg^{-1} body weight minocycline was administered twice a day up to 3 days post injury (dpi).[12,14]

To evaluate the motor recovery, animals were observed by one individual masked to the treatments on 1, 3, 7, 14, 21 and 28 dpi. Lower limb functions were assessed by the Basso, Beattie and Bresnahan scale.[15]

Measurement of blood pNF-H levels

Blood samples were taken from the tail vein of the injured rats on 1, 2, 3, and 4 dpi. The blood samples were anticoagulated using ethylenediamine tetraacetic acid and centrifuged at 3000 r.p.m. for 10 min to obtain plasma. The plasma samples were frozen and stored until the pNF-H assay was performed. The pNF-H assay was carried out using a commercially available enzyme-linked immunosorbent assay kit (ELISA-pNF-H; EnCor Biotechnology, Gainesville, FL, USA). The frozen plasma samples were allowed to thaw, and then diluted 1/5 with a dilution buffer. The samples were then loaded onto an enzyme-linked immunosorbent assay plate. The assay was performed according to the manufacturer's protocol. To standardize the pNF-H value, we divided the absolute pNF-H concentration by the total protein concentration of each sample.

Statistical analysis

The hind limb function score was analyzed by the Mann–Whitney *U*-test. Quantitative plasma pNF-H values between the two groups were analyzed by repeated-measure analysis of variance. The relation between plasma pNF-H levels and hind limb function score was assessed by determining the Spearman's rank correlation coefficient. Error bars indicate the standard error, and differences with a *P*-value of <0.05 were considered statistically significant.

We certify that all applicable institutional and governmental regulations concerning the ethical use of animals were followed during the course of this research.

Results

Minocycline improves hind limb motor function after incomplete spinal cord injury

To determine whether plasma pNF-H levels can be used as a marker for evaluating the efficacy of neuroprotective therapies for SCI, we analyzed the plasma pNF-H levels in experimental SCI rats treated with minocycline, a drug with proven neuroprotective effects.[3,12–14] As minocycline is known to prevent secondary damage in neural tissue by inhibiting microglial activation,[3,12] we assumed that the administration of this drug may also reduce biomarkers of tissue damage.

First, we confirmed the efficacy of minocycline treatment. Behavioral assessments at 28 dpi (Figure 1) revealed that minocycline-treated rats had better hind limb motor function than did the control rats (mean Basso, Beattie and Bresnahan score ± standard error of the mean (s.e.m.): treated group, 14.5 ± 0.6 vs control group, 12.4 ± 0.4; $P<0.05$). The better hind limb function observed in the treated rats suggests that minocycline exerted neuroprotective effects after SCI in this rat model.

Minocycline treatment modulates plasma pNF-H levels

Because minocycline reduces axonal damage in the injured spinal cord by preventing secondary damage, we assumed that the plasma pNF-H level in the treated group would be lower than that in the control group. The plasma pNF-H level and pNF-H/total protein ratio were determined from the blood samples (Figure 2). In both the groups, pNF-H was detected from 1 dpi and its levels peaked at 3 dpi; however, the pNF-H level at 3 dpi was lower in the treated group than in the control group (treated group, 0.088 ± 0.018 μg g^{-1}; control group, 0.112 ± 0.011 μg g^{-1}). Although this difference