Table 1
Group comparisons of the characteristics of participants, MTST performance, gaze behavior, and other clinical tests.

	HR older ($n=11$)		LR older ($n=26$)		Younger ($n=20$)		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	p value	
Participant details								
Age	80.8	3.6	77.1	7.7	21.1	1.4	<0.001*	b,c
Height, cm	155.1	8.8	153.8	10.2	164.4	9.7	<0.001*	b,c
Weight, kg	48.8	5.8	55.5	10.1	56.3	9.0	<0.001*	b
Gender (male=0, female=1), %	63.6		61.5		50.0			
Rapid Dementia Screening Test, point	8.91	1.13	9.27	1.60	12.00	0.00	<0.001*	b,c
Vision acuity score, decimal	0.75	0.39	0.77	0.30	0.73	0.33	0.885	
MTST performance								
Stepping failure (yes=1, no=0), %	72.7		7.6		0.0			a,b
Number of stepping failure, times	0.7	0.5	0.1	0.3	0.0	0.0	<0.001*	a,b
Avoidance failure (yes=1, no=0), %	100.0		15.3		0.0			a,b
Number of avoidance failure, times	3.7	2.9	0.5	1.6	0.0	0.0	<0.001*	a,b
Performance time, s	36.2	4.0	29.8	8.9	18.7	6.2	<0.001*	b,c
Stepping interval time, s	2.8	0.4	2.5	1.4	1.2	0.4	<0.001*	b,c
Spin (yes=1, no=0), %	63.6		15.3		50.0			a,c
Gaze toward target								
Gaze duration, s	0.85	0.38	0.78	0.63	0.62	0.24	0.402	
Gaze initiation, s (before stepping)	1.36	0.26	1.94	1.09	3.54	1.56	<0.001*	b,c
Gaze termination, s (before stepping)	0.52	0.42	1.17	0.97	2.91	1.60	<0.001*	a,b,c
Initiation/interval	0.50	0.09	0.89	0.53	2.94	1.21	<0.001*	a,b,c
Termination/interval	0.19	0.16	0.61	0.56	2.41	1.27	<0.001*	a,b,c
Other clinical tests							t-Test	
10 m walking time, s	16.1	2.7	11.5	3.7			0.001*	
Timed Up and Go, s	19.8	4.3	13.1	4.4			<0.001*	
One leg stand, s	1.2	1.5	9.3	12.7			0.005*	
Functional reach, cm	18.3	3.9	24.1	4.7			0.006*	
5 chair stand, s	19.7	11.2	13.3	3.5			0.020	

ANOVA: Bonferroni correction $p=0.016$ (0.05/3).
Post hoc test: $p<0.016$.
[a] Post hoc test: HR vs LR.
[b] Post hoc test: HR vs young.
[c] Post hoc test: LR vs young.

about the protocol of the MTST has been given in an earlier study (Yamada et al., 2011).

2.3. Data analyses of the MTST

All dependent measures were obtained only from the first main trial (Yamada et al., 2011). This was because, as other clinical standard tests used for identifying HR older individuals, the MTST had been developed so that participants could complete the task in a short time. The earlier study demonstrated that analyzing stepping performance in a single trial was effective to identify HR older individuals (Yamada et al., 2011). The stepping performance obtained from the second main trial was used only to calculate test–retest reliability.

The main dependent measures were two types of failure indicating less accurate stepping performance: a stepping failure

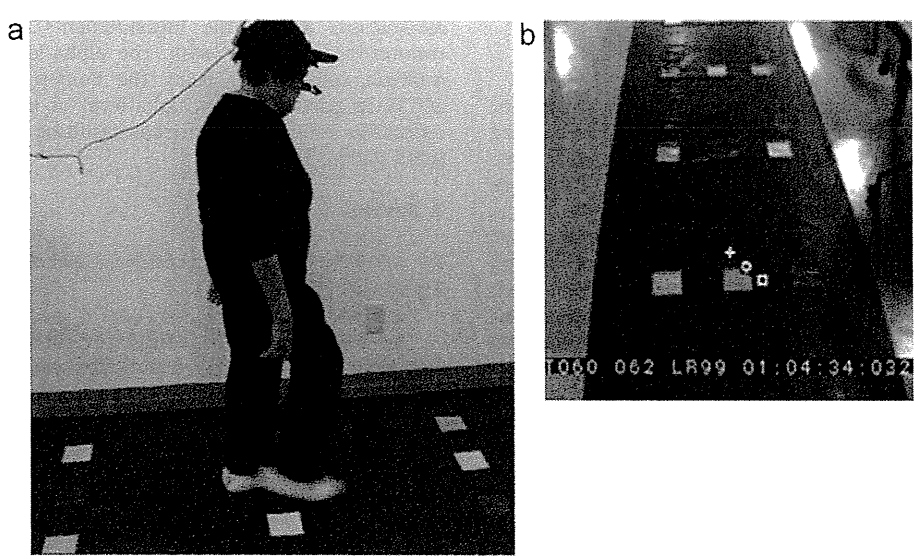

Fig. 1. (a) An older participant performing the MTST. Each square in each line was made of red, blue, or yellow tape. The participant intended to walk at a self-selected pace while stepping on a target square of an assigned color while avoiding to step on other squares. (b) A video-based image of the visual field while performing the MTST. The location of fixation, indicated by a circle mark, was calculated with the information obtained from the left (a plus mark) and right (a square mark) eyes.

(i.e., failure to step on the footfall target) and an avoidance failure (i.e., failure to avoid distracters). Even a step on the edge of the target was regarded as successful. These measures were analyzed statistically from two perspectives. First, the participants who experienced each type of failure at least once were totaled for both the HR and LR groups. For each failure, the numbers, expressed as the frequency of failure occurring in the group (%), were compared statistically among the groups with a Chi-square analysis. Secondly, the number of failures for each participant was statistically compared among the groups with a one-way analysis of variance (ANOVA). To investigate the test–retest reliability for the two types of the stepping failure, Kappa coefficients (k-values) between the two trials were calculated. A k-value of 0.61–0.80 was regarded as good agreement (Naessens et al., 2010).

The time (s) taken to perform the MTST, referred to as the MTST performance time, was measured with a stopwatch. The time of the interval between each step was also measured with the accelerometers attached to each heels. The timing of each step was defined as the time when peak acceleration occurred in the vertical direction. Each MTST performance time and stepping interval was compared statistically among the groups with a one-way ANOVA. To investigate the test–retest reliability for the MTST performance time, the inter-trial correlation coefficient (ICC 1.1) between the two trials was calculated.

Regarding the frequency of the maladaptive turning behavior (spin turn), the participants who experienced crossover steps at least once in a trial were totaled for each of the three groups. The frequencies of failure occurring in the group (%) were compared statistically among the groups with a Chi-square analysis. To investigate the test–retest reliability for the frequency of the spin turn, a k-value between the two trials was calculated.

Frame-by-frame video-based analyses were performed to identify where fixations were located. Stabilization of the gaze at one location for a minimum of 100 ms (three video frames) was defined as a fixation. The locations of fixations were classified into one of four categories: target, distracter, path, or other. The durations of each fixation were quantified and statistically compared among the groups using a one-way ANOVA. To statistically test the fixation patterns, each participant's average fixation time, as a percentage of total fixations, in each fixation-location was compared among the groups using a one-way ANOVA.

2.4. Data collection and analyses of gaze behavior

For the purpose of examining how far ahead the participants' fixations were located, the time to initiate (referred to as gaze initiation) and terminate (gaze termination) gazing at a given target before stepping on it was measured. The data of the gaze initiation (termination) were calculated by subtracting the time to initiate (terminate) fixation toward the imminent footfall target from the time to step on the target, which was obtained through the three-dimensional accelerometers attached to each heel. Dividing these timing data by the duration of the stepping interval (referred to as initiation/interval and termination/interval) expressed the degree to which the participants directed their fixation toward a future target. For instance, when the value of initiation/interval was 1.0 (i.e., the duration between the initiation of fixation toward a certain target and stepping on that target was equal to the duration of the stepping interval), a participant began to fixate a next footfall target just when stepping on the imminent footfall target. A value smaller than 1.0, therefore, meant that a fixation was directed toward the imminent target, whereas a value larger than 1.0 meant that a fixation was directed toward a future footfall target. A one-way ANOVA was used to compare these measurements statistically among the groups.

2.5. Data collection and analyses of other clinical tests

Other clinical tests that have been used to identify high-risk elderly adults in many studies, i.e., the TUG (Podsiadlo and Richardson, 1991), the functional reach test (FR) (Duncan et al., 1992), the one-leg standing test (OLS) (Vellas et al., 1997), the 10 m walking test (10 m walking) (Lopopolo et al., 2006), and the 5-chair stand (5CS) test (Guralnik et al., 1994), were measured prior to performing the MTST on the first measurement day. All tests except the 5CS were used in the earlier study (Yamada et al., 2011). In the 5CS, participants were asked to stand up and sit down five times as quickly as possible. A 5CS score was defined as the average of two trials regarding the time in seconds for the completion of this task. The order in which these tests were performed was randomized. The participants performed each task for two trials. A t-test analysis was examined for each clinical test to statistically compare the scores between the HR and LR groups.

2.6. Associations among the measurements

To quantitatively describe the associations between the stepping accuracy in the MTST and other measurements, the 37 older participants were divided into two groups according to whether they experienced both stepping and avoidance failures or not. Each of all measurements regarding gaze behavior and the clinical tests was compared statistically between the two groups with a t-test. To examine whether a spin turn was likely to occur when a participant's fixations were directed closer to an imminent footfall target, the participants were also divided into two groups according to whether they experienced a spin turn. Each of all measurements regarding gaze behavior was compared statistically between the two groups with a t-test. Furthermore, whether the experience of a spin turn was associated with the scores of the clinical tests was also analyzed. A comparison with a t-test was performed between the two groups.

2.7. Adjustment of a significance level for multiple statistical comparisons

In the present study, three different analyses were undertaken with the same data set (i.e., a comparison among the HR, LR older and young groups, and two two-group comparisons for testing associations among the measurements). To avoid a risk of committing a Type 1 error, the alpha-level was adjusted for multiple comparisons using the Bonferroni correction (Feise, 2002). In particular, the alpha-level of 0.05 was corrected to reflect five different comparisons, resulting in an adjusted alpha of 0.016 (0.05/3).

3. Results

3.1. MTST performance, gaze behavior, and clinical tests (Table 1 and Fig. 2)

The HR older participants experienced significantly higher frequency of both stepping and avoidance failures than the LR older and younger participants. The average number of each failure occurring in each group was greater for the HR older participants than for the LR older and younger participants. Both the MTST performance time and the stepping interval were significantly shorter for the younger participants than the HR and LR older participants. The HR older and younger participants experienced significantly higher frequency of the spin turns than the LR participants. The investigation of the test–retest reliability indicated that the k-value was 0.724 for the stepping failure, 0.746 for the avoidance failure, and 0.877 for the spin turn. The

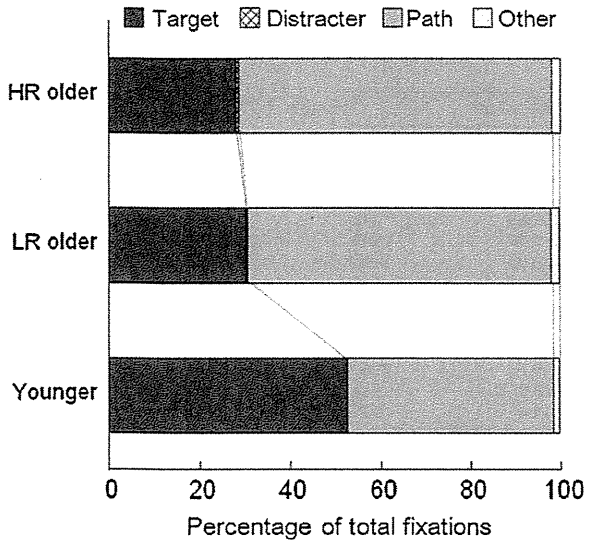

Fig. 2. Frequency of fixation directed toward each location in each group. The location-category of the distracter is not included because none of the participants fixated toward the distracters.

correlation between the first- and second-time measurements of the MTST performance time was very high (ICC = 0.969 (95%CI: 0.954–0.979)).

The group differences in the gaze duration were not statistically significant. The timing of gaze initiation was significantly earlier for the younger participants than the HR and LR older participants. The difference in this measurement was not significant between the HR and LR participants. The differences in the gaze termination, initiation/interval, and termination/interval were all significant for each pair in the three groups. The average percentages of total fixation durations (Fig. 2) showed that the fixation was directed toward the target more frequently for the younger participants than for the HR and LR older participants ($p < 0.016$). Participants rarely directed their fixation toward the distracters (0.4, 0.2, and 0% for the HR, LR, and younger groups, respectively). The younger participants directed their fixation toward the path less frequently than the HR and LR participants ($p < 0.016$).

Comparison of the performances in other clinical tests between the HR and LR participants showed that the HR older participants showed a significantly lower score than the LR older participants in all clinical tests except the 5CS.

3.2. Associations among the measurements (Tables 2 and 3)

Eight older participants experienced both stepping and avoidance failures (other two participants experienced only stepping failures, whereas seven experienced only avoidance failures). Regarding the association of stepping accuracy with gaze behavior and clinical tests (Table 2), the participants who experienced both failures initiated and terminated fixation toward an imminent target significantly later than those who did not. The mean values of initiation/interval and termination/interval were significantly greater for the participants who experienced both types of failures than for those who did not. The participants who experienced both failures showed significantly lower scores for the TUG, OLS, and FR than the participants who did not. No significant differences in all measurements on gaze behavior and on the clinical tests were identified between the participants who experienced a spin turn and those who did not (Table 3).

4. Discussion

The purpose of the present study was to examine whether maladaptive turning and gaze behavior existed while HR older individuals were performing the MTST. Before discussing this issue it is important to address that the present findings successfully replicated earlier ones (Yamada et al., 2011) regarding the fact that the HR older participants showed less stepping accuracy in the MTST. The HR older participants showed a significantly higher rate of stepping and avoidance failures than the LR older and younger participants. It is noteworthy that avoidance failure always occurred as a result of an accidental step in the way the participants were walking from target to target but not as a result of the wrong selection of a target from the three squares in the line that they intended to step on. Avoidance failure, therefore, resulted mainly from incorrect planning of the walking path from target to target and not from the wrong selection of a target from the three squares in a line due to impaired contrast sensitivity. The test–retest examination showed that these measurements were statistically reliable. These findings supported the conclusion of the earlier study (Yamada et al., 2011) that measuring the stepping accuracy while performing the MTST is potentially an important factor in the identification of HR older individuals.

Analysis of the frequency of the spin turn supported the hypothesis that impaired stepping performance in HR older individuals was accompanied with more frequent spin turns. Seven out of 11 HR older participants (63.6%) made a spin turn at least once to change their walking direction. In contrast, many of the LR older participants (22 out of 26 participants) did not select a

Table 2
Associations of the experience of stepping and avoidance failures with gaze behavior and clinical tests.

	Failure				*p* value	E/S
	Yes ($n=8$)		No ($n=29$)			
	Mean	SD	Mean	SD		
Gaze toward target						
Gaze duration, s	0.87	0.40	0.78	0.61	0.61	0.24
Gaze initiation, s (before stepping)	1.28	0.26	1.97	1.06	0.01*	2.63
Gaze termination, s (before stepping)	0.41	0.35	1.13	0.93	0.00*	2.05
Initiation/interval	0.50	0.11	0.85	0.51	0.00*	3.10
Termination/interval	0.17	0.17	0.57	0.54	0.00*	2.36
Other clinical tests						
10 m walking time, s	14.92	1.77	12.23	4.23	0.02	1.52
Timed Up and Go, s	17.67	1.75	14.41	5.75	0.01*	1.86
One leg stand, s	0.76	1.18	9.06	12.52	0.00*	7.05
Functional reach, cm	19.67	1.37	23.52	5.42	0.00*	2.82
5 chair stand, s	17.25	10.10	14.17	5.41	0.30	0.30

Bonferroni correction $p = 0.016$ (0.05/3).

Table 3
Associations of the experience of spin turns with gaze behavior and clinical tests.

	Spin turn				p value	E/S
	Yes (n=11)		No (n=26)			
	Mean	SD	Mean	SD		
Gaze toward target						
Gaze duration, s	0.80	0.36	0.79	0.64	0.959	0.020
Gaze initiation, s (before stepping)	1.49	0.47	1.89	1.09	0.127	0.850
Gaze termination, s (before stepping)	0.69	0.68	1.10	0.95	0.152	0.600
Initiation/interval	0.65	0.34	0.83	0.52	0.242	0.510
Termination/interval	0.34	0.39	0.55	0.55	0.201	0.530
Other clinical tests						
10 m walking time, s	12.6	3.3	12.8	4.4	0.917	0.040
Timed Up and Go, s	15.3	3.9	15.0	5.9	0.860	0.080
One leg stand, s	4.1	5.8	9.1	13.5	0.161	0.860
Functional reach, cm	21.3	2.9	23.5	5.9	0.193	0.750
5 chair stand, s	15.5	8.2	14.4	5.7	0.701	0.140

Bonferroni correction p=0.016 (0.05/3).

spin turn. This suggests that the LR older individuals successfully avoided the risk of destabilization while performing the MTST. The existence of such a clear difference in turning strategy between the HR and LR older participants is likely to contribute to enhancing the predictive power of the MTST to identify HR older individuals.

Interestingly, the younger participants also showed a higher rate of spin turns. A similar finding was reported in a previous study (Moraes et al., 2004), which demonstrated that their young participants preferred stepping medially (i.e., making a spin turn) rather than stepping laterally (i.e., making a step turn) to avoid a planar obstacle. The authors argued that modification of foot placement in response to an obstacle involves minimum displacement of the foot from its normal landing spot; stepping medially could be more suitable to satisfy this goal than stepping laterally. According to these previous findings, the younger participants in the present study may have not hesitated to select a spin turn because they had the ability to take pro-active action to bias the location of COM to ensure that it did not fall outside the BOS.

Analysis of gaze behavior supported another hypothesis that fixation in older individuals should be directed closer toward the imminent footfall target. The measurements of the initiation/interval and termination/interval revealed that the HR and LR older participants directed their gaze toward the imminent footfall target. Such a tendency was significantly higher for the HR older participants than the LR older ones. In contrast, the younger participants directed their gaze toward approximately 3 targets ahead. These findings clearly supported previous findings that, whereas younger individuals use visual information regarding the location of an imminent footfall target in a feedforward manner, older individuals appear to use it in an online, feedback manner (Patla and Vickers, 2003; Chapman and Hollands, 2006a).

Analyses of the association of stepping accuracy with gaze behavior demonstrated that the observed fixation patterns in the HR older participants were related to the stepping and avoidance failures (Table 2). The participants who experienced both the stepping and avoidance failures initiated and terminated fixation toward an imminent target significantly later than those who did not. From these findings, we suggest that one of the reasons for the higher rate of stepping and avoidance failures in the HR older individuals could be attributed to their tendency to fixate on/around the imminent footfall target, which prevented them from considering the locations of future footfall targets.

The HR older participants showed a higher rate of failure of stepping on the footfall targets in spite of the fact that they concentrated on fixation toward the imminent footfall target. The measurements of gaze termination showed that, on average, the HR older participants terminated fixation on the imminent footfall target approximately 0.5 s before stepping on that target. This indicated that they did not fixate on the imminent footfall target until they stepped on it; that is, the imminent footfall target was captured through peripheral vision or out of sight. The present findings suggest that the observed spatiotemporal patterns of fixation toward the imminent footfall target in the HR older participants may not have led to accurate foot control for stepping on a footfall target. Similarly, the average percentages of total fixation durations (Fig. 2) demonstrated that the participants rarely fixated toward the distracters (only 0.4% of total fixation times for the HR older, 0.2% for the LR older, and 0% for the younger participants). This suggests that the information regarding the locations of the distracters was obtained through peripheral vision (Patla and Vickers, 1997; Zietz and Hollands, 2009; Miyasike-daSilva et al., 2011). The failure to avoid the distractors may have resulted from their impaired ability to control their foot placement based on peripheral vision (Di Fabio et al., 2005).

The duration of fixation was not significantly different among the groups. This was inconsistent with previous findings demonstrating that HR individuals looked at footfall targets longer (Chapman and Hollands, 2006b, 2007). The contradictory findings between the previous and present studies may have been attributed to the difference in the spatial demand for stepping between these studies. In other words, a longer target fixation of the target would have been necessary when the spatial demand for stepping on the target was relatively strict, as in previous studies. Alternatively, given that the fixation was directed toward the path more frequently for the HR and LR older participants (Fig. 2), fixation on the place of each step, rather than on the target alone, may have been necessary while the HR older participants were performing the MTST. As a result, they may not have directed their fixation toward the target for a particularly longer time.

Theoretically, a spin turn could occur more frequently as fixation was located closer toward the imminent footfall target and, as a result, the locations of future footfall targets were not considered. However, we failed to demonstrate a significant association between the frequency of the spin turn and the pattern of fixations (Table 3). In fact, the experience of a spin turn was not significantly associated with any measurements about gaze behavior and other clinical tests. The precise mechanism for causing maladaptive turning behavior remains unclear. A future study should address this issue.

Analyses of the association of stepping accuracy with other clinical measurements demonstrated that the participants who experienced both stepping and avoidance failures showed lower scores for the TUG, OLS, and FR (Table 2). This was generally consistent with the findings in our earlier study (Yamada et al.,

2011), which demonstrated that the number of avoidance failures showed mild negative correlation with the performance of the TUG and OLS. These findings suggest that impaired stepping performance in the MTST was likely to be associated with the impairment of general balance abilities, lower extremity function, and mobility.

In conclusion, the present study demonstrated impaired stepping performance of the HR older individuals in the MTST was accompanied with their maladaptive turning and gaze behavior. One of the most important findings was that the HR older individuals fixated closer toward the imminent footfall target. This suggests that they have difficulty in using visual information regarding the location of an imminent footfall target in a feedforward manner. Such a pattern of fixations would prevent them from considering the locations of future footfall targets and, therefore, can cause a maladaptive strategy to step in a different direction. In fact, the stepping performance in HR older individuals was accompanied with more frequent spin turns. Due to the lack of a significant association of the spin turn with the patterns of fixations, future studies should identify a precise mechanism for selecting the maladaptive turning behavior.

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None.

Conflict of interest statement

None.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Faster decline of physical performance in older adults with higher levels of baseline locomotive function

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Aim: The purpose of this longitudinal study was to determine whether the rate of decline in community-dwelling older adults varies according to baseline locomotive function levels.

Methods: This longitudinal study was conducted in community-dwelling older adults in Kyoto, Japan. In addition to information about falls, physical performance was assessed using a series of tests, including 10-m walking time, timed up and go (TUG) test, functional reach, one-leg stand test, and five chair stand test. The outcomes for each patient were measured once in 2009 and then followed up 1 year later. The change in physical performance was then determined. We divided the participants into tertiles (T1, T2, and T3) according to timed up and go test results, and the differences among the three groups were compared.

Results: Of the 252 individuals who were enrolled in the study, 231 (91.6%) completed the 12-month follow-up: 77 in the T1 group; 78 in the T2 group; and 76 in the T3 group. The T1 group showed a significantly larger decrease than the T2 and T3 groups in the 10-m walking time and TUG tests ($P < 0.05$). However, there were no significant differences in functional reach, one-leg standing test, or five chair stand test among the three groups. In the T1 group, the number of falls and elderly who had developed fear of falling increased during the study period.

Conclusions: This study demonstrated that elderly with the highest baseline performances were more likely to show a greater decline in locomotive performance than the other groups. Further study is required to elucidate the mechanism of faster physical functional decline in robust elderly. **Geriatr Gerontol Int 2012; 12: 238–246.**

Keywords: level of frailty, locomotive function, longitudinal study, robust elderly.

Introduction

Maintenance of physical performance in later life is an important component of healthy aging.[1] Walking speed has been identified as one of the most influential physical performances associated with deterioration in activity of daily living among older adults.[2] The timed up and go test (TUG) is a simple tool developed to screen basal mobility performance, which has been shown to be significantly associated with activity of daily living in frail older adults.[3] Thus, evaluating walking speed and TUG is important for predicting the risk of functional decline.

Several cross-sectional studies have shown that a gradual decline in physical performance is significantly

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associated with age.[4,5] Several longitudinal studies have also found a time-dependent decline in the physical performance of community-dwelling older adults.[6,7] However, few studies have addressed the factors involved in longitudinal change in physical performance. Therefore, we conducted several studies to demonstrate that the differential factors are related to daily activities and depend on community-dwelling older adults' level of frailty.[8] Our data suggests that a resistance training program is effective for improving physical performance in frail elderly, but not in non-frail elderly,[9] indicating a difference in the effect of physical training on elderly persons with varying levels of physical fitness. Therefore, it is important to examine longitudinal changes in the physical performance of elderly persons with varying levels of physical fitness.

The purpose of this longitudinal study was to determine whether the rate of decline in older adults differs according to baseline locomotive function levels.

Methods

Participants

Study participants were recruited through ads in the local press requesting healthy community-dwelling volunteers. A total of 252 Japanese participants, 65 years and older living in Kyoto city, were included in the baseline survey in October 2009. One year later in October 2010, the second survey was conducted. We screened 332 people, and 252 who agreed to participate were enrolled. Of the 252 individuals, 231 (91.7%) completed the 12-month follow-up (Fig. 1).

The screening process was used to exclude participants based on the following criteria: severe cardiac, pulmonary, or musculoskeletal disorders; comorbidities associated with an increased risk of falling such as Parkinson's disease and stroke; and use of psychotropic drugs. Written informed consent was obtained from each participant for the trial in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Helsinki, 1996.

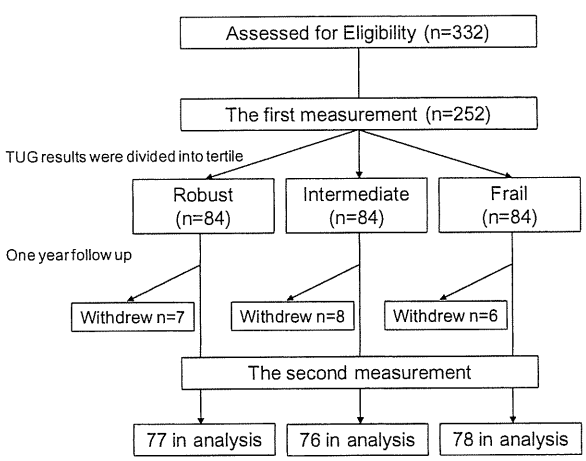

Figure 1 A flow chart showing the distribution of participants.

Outcome measures

All participants underwent five tests for measurements: 10-m walking time,[10] TUG test,[3] functional reach (FR),[11] one-leg standing (OLS) test,[12] and five chair stand (5CS) test.[13] Outcome measures were conducted in October 2009 and October 2010. No exercise program was prescribed to participants during the interim period. Before the study started, all researchers were trained by one of the authors (MY) on correct protocols for administering the assessment measures. If a participant normally used a walking aid, this aid was used during the 10-m walking time and TUG tests.

In the 10-m walking time test, participants walked 15 m at a comfortable pace, as determined by the individual. A stopwatch was used to record the time required to reach the 10-m point that was marked in the middle of the path. The test-retest reliability using the intertrial correlation coefficient (ICC; 1.1) was 0.943. The better performance of the two trials was used as the walking time score in the analysis. In the TUG test, participants were asked to stand up from a standard chair with a seat height of 40 cm, walk a distance of 3 m at a maximum pace, turn, walk back to the chair, and sit down. The test-retest reliability using the ICC (1.1) was 0.929. The TUG score was defined as the better performance of the two trials. In the FR test, each participant was positioned next to a wall with one arm raised at 90° and fingers extended. A meterstick was mounted on the wall at shoulder height. The distance that a participant could reach while extending forward from an initial upright posture to the maximal anterior leaning posture, without moving or lifting the feet, was measured in centimeters according to the position of the tip of the third finger against the mounted meterstick. The distances measured in the two trials were averaged to obtain the FR score. The test-retest reliability using the ICC (1.1) was 0.915. In the OLS test, participants were instructed to start from a standing position with a comfortable base as support with their eyes open and arms at their sides. They were then instructed to stand unassisted on either leg. OLS was measured in seconds from the time one foot was lifted from the floor to when it touched the ground or the standing leg. The test-retest reliability using the ICC (1.1) was 0.905. The participants stopped the OLS if the time exceeded 60 s. In 5CS, participants were asked to stand up and sit down five times as quickly as possible. They were timed from the initial sitting position to the final standing position

at the end of the fifth stand. The test-retest reliability using the ICC (1.1) was 0.954. The 5CS score was defined as the better performance of the two trials. The percent change for physical performance was calculated as follows:

Percent change (%) = 100 × (2010 measurement − 2009 measurement)/2009 measurement

Falls and the fear of falling

Participants were interviewed about falling during the past year and their fear of falling in 2009 and 2010. Falls were defined as all situations in which a participant suddenly and involuntarily came to rest upon the ground or a surface lower than their original station.[14] Falls resulting from extraordinary environmental factors (e.g. traffic accidents or falls while riding a bicycle) were excluded.

We assessed participants' fear of falling by asking a single yes-or-no question with a high test-retest reliability, "Are you afraid of falling?"[15] This question was asked during the interviews in 2009 and 2010. The test-retest reliability using the kappa coefficient was 0.960.

Statistical analysis

We divided the participants into tertiles (T1, T2, and T3) according to TUG test results. TUG was chosen for several reasons. First, it is a simple measure of physical function that involves lower extremity strength, dynamic balance, gait, and agility. Second, TUG has been shown to identify physical function limitations in geriatric patients in a clinical setting.[16,17]

We analyzed the outcome measurements using a two-way ANOVA. Tukey tests were used for post-hoc analysis. Differences in the physical variables between elderly who had or had not fallen and between those with or without a fear of falling were analyzed by two-way ANOVA. Data were analyzed using SPSS v. 18.0 for Windows (Chicago, IL, USA). A *P*-value of <0.05 was considered statistically significant for all analyses.

Results

Of the 252 individuals, 231 (91.7%) completed the 12-month follow-up: 77 in T1 group (91.7%), 78 in T2 group (92.9%) and 76 in T3 group (90.5%) (Fig. 1). There were no significant differences in all performance measurements and age between men and women.

Baseline characteristics

There were significant differences in age (T1, 73.9 ± 6.6; T2, 79.1 ± 7.0; T3, 82.0 ± 6.9; F = 25.2, $P < 0.001$), walking time (T1, 7.4 ± 1.4 sec; T2, 9.7 ± 2.8 sec; T3, 12.7 ± 2.6 sec; $P < 0.05$), TUG (T1, 6.9 ± 0.9 sec; T2, 9.2 ± 0.9 sec; T3, 12.7 ± 1.3 sec; $P < 0.05$), FR (T1, 29.0 ± 7.0 cm; T2, 26.5 ± 6.7 cm; T3 21.3 ± 7.1 cm; $P < 0.05$), OLS (T1, 19.5 ± 13.6 sec; T2, 10.0 ± 10.7 sec; T3, 5.4 ± 5.5 sec; $P < 0.05$), and 5CS (T1, 8.5 ± 2.4 sec; T2, 10.4 ± 2.1 sec; T3, 13.5 ± 3.8 sec; F = 28.0, $P < 0.001$). There were no significant differences in height or weight (Table 1).

Follow-up measures

There were significant differences in walking time (T1, 8.0 ± 1.9 sec; T2, 9.3 ± 2.0 sec; T3, 12.3 ± 2.7 sec; $P < 0.001$), TUG (T1, 7.5 ± 1.5 sec; T2, 9.3 ± 1.8 sec; T3, 13.0 ± 3.2 sec; $P < 0.001$), FR (T1, 30.2 ± 8.8 cm; T2, 27.6 ± 8.4 cm; T3, 21.0 ± 6.5 cm; $P < 0.001$), OLS (T1, 19.0 ± 12.8 sec; T2, 8.7 ± 9.4 sec; T3, 4.3 ± 3.8 sec; $P < 0.001$), and 5CS (T1, 7.4 ± 2.0 sec; T2, 9.5 ± 3.2 sec; T3, 13.6 ± 5.5 sec; $P < 0.001$) (Table 1, Fig. 2).

Group-time interactions are summarized in Table 1. A statistically significant group-time interaction was observed for walking time and TUG ($P < 0.05$).

Falls and fear of falling

In the T1 group, the number of falls and elderly who had developed a fear of falling increased between baseline and follow-up (falls, 19.5% to 27.2%; fear of falling, 13.0% to 26.0%). There were no significant differences in FR, OLS, or 5CS. In T2 and T3 groups, the number of falls and elderly who had developed fear of falling did not change between baseline and follow-up (Table 1).

Characteristics of elderly with or without falls

Group-time interactions are summarized in Tables 2, 3, and 4. In T1 group, a statistically significant group-time interaction was observed for TUG and 5CS ($P < 0.05$). However, we did not find any significant differences in T2 and T3 groups (Tables 2, 3 and 4).

Characteristics of elderly with or without fear of falling

Group-time interactions are summarized in Tables 2, 3, and 4. In T1 group, a statistically significant group-time interaction was observed for TUG ($P < 0.05$) (Table 2). In T2 group, a statistically significant group- time interaction was observed for TUG and 5CS ($P < 0.05$) (Table 3). In T3 group, there were no significant differences (Table 4).

Discussion

In the current study, we have shown that elderly with the highest baseline performances are more likely to show a decline in locomotive performance than the

Table 1 Comparison of outcome measurements among the three groups

	T1 (≤8.2) (n = 77)	T2 (8.3–10.9) (n = 76)	T3 (≥11.0) (n = 78)	F-value	*P*-value	*Post-hoc*
Age	73.9 ± 6.6	79.1 ± 7.0	82.0 ± 6.9	25.2	<0.001	†‡§
Height (cm)	157.1 ± 9.0	155.0 ± 8.1	155.8 ± 10.9	0.5	0.620	–
Weight (kg)	57.7 ± 9.8	56.5 ± 8.3	54.5 ± 10.1	0.7	0.492	–
Gender, female	57 (74.0)	60 (78.9)	60 (76.9)			–
Falls, n (%)						
2009	15 (19.5)	20 (26.3)	26 (33.3)			
2010	21 (27.2)	22 (28.9)	28 (35.9)			
Fear of falling, n (%)						
2009	10 (13.0)	29 (38.2)	36 (46.2)			
2010	20 (26.0)	30 (39.5)	37 (47.4)			
Walking time (sec)						
2009	7.4 ± 1.4	9.7 ± 2.8	12.7 ± 2.6	9.227	<0.001	†‡§
2010	8.0 ± 1.9	9.3 ± 2.0	12.3 ± 2.7			†‡§
Change (%)	5.3 ± 17.6	–5.1 ± 25.2	–3.4 ± 20.1			†‡
Timed up and go (sec)						
2009	6.9 ± 0.9	9.2 ± 0.9	12.7 ± 1.3	3.361	0.037	†‡§
2010	7.5 ± 1.5	9.3 ± 1.8	13.0 ± 3.2			†‡§
Change (%)	5.8 ± 14.1	2.4 ± 16.2	2.6 ± 22.6			†‡
Functional reach (cm)						
2009	29.0 ± 7.0	26.5 ± 6.7	21.3 ± 7.1	1.254	0.291	
2010	30.2 ± 8.8	27.6 ± 8.4	21.0 ± 6.5			
Change (%)	5.5 ± 28.0	5.8 ± 28.1	–3.3 ± 37.9			
One-leg standing (sec)						
2009	19.5 ± 13.6	10.0 ± 10.7	5.4 ± 5.5	0.906	0.439	
2010	19.0 ± 12.8	8.7 ± 9.4	4.3 ± 3.8			
Change (%)	–5.3 ± 41.4	–2.9 ± 31.2	–6.7 ± 32.8			
Five chair stand (sec)						
2009	8.5 ± 2.4	10.4 ± 2.1	13.5 ± 3.8	0.217	0.885	
2010	7.4 ± 2.0	9.5 ± 3.2	13.6 ± 5.5			
Change (%)	–10.0 ± 24.5	–6.4 ± 33.3	1.0 ± 31.7			

†T1 *versus* T2. ‡T1 *versus* T3. §T2 *versus* T3.

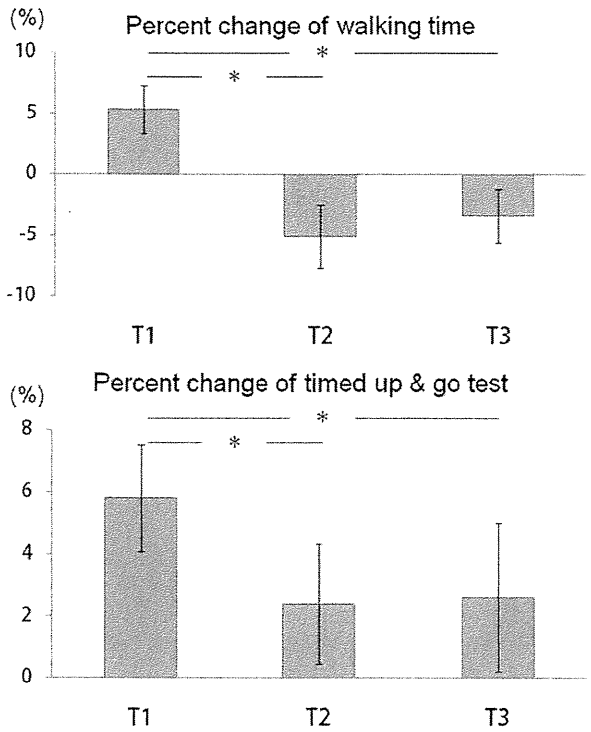

Figure 2 Percent change in the walking time and timed up and go tests among the three groups. The means ± SEM in T1, T2, and T3 groups are shown. $*P < 0.05$.

others. These results are quite unexpected. However, Koster *et al.* compared the leg strength of octogenarians and septuagenarians, and found more rapid decline in leg strength in septuagenarians.[18] Moreover, it has been reported that active community-dwelling elderly men and women respectively lose 0.8% and 0.7% of lean leg mass per year on average.[18] These characteristics of the aging process might account for why the T1 group showed a greater decrease in locomotive functions. Yet, it is possible that a floor effect may account for this longitudinal maintenance of physical performance in the T2 and T3 groups. Previous cross-sectional studies have shown an age-dependent gradual decline in locomotive function,[4,5] while longitudinal studies have shown a time-dependent decline in locomotive function in community-dwelling older adults.[6,7] The subjects of these studies were community-dwelling older adults with a relatively high level of performance, presumably equivalent to our study's T1 or T2 groups. However, participants in our study had a wider range of physical performance levels. For example, the reference values for TUG were 8.1 s for persons aged 60 to 69 years old, 9.2 s for persons aged70 to 79 years, and 11.3 s for persons aged 80 to 99 years.[19] The reference values for the T1 group was 6.9 s, 9.2 s for the T2 group, and 12.7 s for the T3 group. Thus, the level of physical performance may have affected our results.

The T1 group showed a significantly larger decrease in 10-m walking time and TUG than the other groups. An earlier longitudinal study indicated that the age-related decline was accelerated in lower extremity performance.[7] Walking speed, in particular, is a good predictor for the onset of functional dependence in a Japanese community population.[2] In the same manner, TUG has been shown to be significantly associated with activities of daily living function in frail older adults.[3] Thus, physical training, such as resistance training, maintains level of activity of daily living in healthy elderly is very important.

The T1 group showed an increase in falls (19.5% to 27.2%) and fear of falling (13.0% to 26.0%) in 2010. In general, at least one-third of people aged 65 and older fall at least once annually.[20,21] In addition, the major risk factor for fear of falling is shown to be history of at least one fall.[22] In the T1 group, elderly with a fear of falling were more likely to show a decline in locomotive performance than elderly without a fear of falling. Several studies have indicated that people who are afraid of falling appear to enter a debilitating spiral of loss of confidence, restricted physical activities, physical frailty, lack of social participation, falls, and loss of independence.[23–28] Therefore, it is possible that the increased fear of falling is associated with decreased locomotive function in T1 group.

There were several limitations of this study that warrant mention. First, although we used TUG to define frailty, TUG may not be sufficient to define frailty. The Edmonton Frail Scale adopts eight other domains such as cognition, general health status, functional independence, social support, medication use, nutrition, mood, and continence other than TUG.[29] Further study is required to test the levels of these domains in this cohort. Second, the standard deviations for the percent change values are quite large, which shows major individual differences. These factors may have affected the current results. Third, the results of men and women were combined in this research because of the relatively small sample size. A larger sample size is required to analyze in each gender. Finally, participants were probably more motivated and showed greater interest in health than the general population of older adults.

This was a longitudinal study to demonstrate that the participants with the highest baseline levels of performance were more likely to show a greater decline in locomotive performance than the other groups. Further study is needed to explore the mechanism of a faster decline in physical performance in the robust elderly. Future work should also be done to determine whether the effects of a training program on physical performance differ according to the level of physical well-being.

Table 2 Characteristics of elderly who have or have not fallen and with or without a fear of falling in T1 group

	Falls (2010)				Fear of falling (2010)			
	Falls (2010) ($n = 21$)	No falls ($n = 56$)	F-value	*P*-value	Fear ($n = 20$)	No fear ($n = 57$)	F-value	*P*-value
Age	76.0 ± 6.6	73.1 ± 6.5		0.08†	74.1 ± 7.5	73.9 ± 6.3		0.90†
Height (cm)	155.5 ± 9.7	157.6 ± 8.8		0.49†	158.7 ± 9.7	156.1 ± 8.5		0.34†
Weight (kg)	61.0 ± 14.1	56.2 ± 7.2		0.26†	62.0 ± 10.5	55.0 ± 8.6		0.08†
Gender, female	15 (71.4%)	42 (75.0%)		0.48‡	13 (65.0%)	44 (77.2%)		0.22‡
Walking time (sec)								
2009	7.3 ± 1.5	7.4 ± 7.5	0.03	0.88	7.6 ± 1.6	7.4 ± 1.6	0.11	0.74
2010	8.4 ± 2.5	7.8 ± 1.2			8.9 ± 1.9	7.6 ± 1.8		
Change (%)	8.9 ± 18.6	3.8 ± 15.9			12.3 ± 17.5	2.4 ± 15.4		
Timed up and go (sec)								
2009	7.0 ± 0.9	6.8 ± 0.7	4.34	0.04	7.0 ± 1.1	6.9 ± 0.8	23.22	0.00
2010	7.9 ± 1.6	7.3 ± 1.2§			8.2 ± 1.1	7.1 ± 0.9§		
Change (%)	8.8 ± 15.1	4.6 ± 13.2			12.4 ± 16.9	3.5 ± 11.8		
Functional reach (cm)								
2009	27.7 ± 6.9	29.5 ± 7.0	0.80	0.37	27.9 ± 6.1	29.4 ± 7.3	0.65	0.42
2010	26.7 ± 7.6	30.5 ± 8.9			28.0 ± 7.4	31.0 ± 9.2		
Change (%)	−1.2 ± 24.5	8.2 ± 29.1			4.7 ± 32.8	5.8 ± 26.2		
One-leg standing (sec)								
2009	23.6 ± 32.4	20.5 ± 14.0	0.21	0.65	23.8 ± 14.1	20.7 ± 24.4	0.35	0.56
2010	15.0 ± 11.7	21.0 ± 12.9			22.7 ± 14.9	17.8 ± 11.7		
Change (%)	−11.2 ± −47.2	2.8 ± 39.3			−14.3 ± 27.9	−1.4 ± 46.1		
Five chair stand (sec)								
2009	8.2 ± 2.5	8.6 ± 2.3	6.33	0.02	8.6 ± 2.2	8.5 ± 2.5	0.44	0.51
2010	8.0 ± 2.4	7.1 ± 1.8§			7.5 ± 2.2	7.3 ± 1.9		
Change (%)	−6.1 ± −25.4	14.1 ± 16.4			−10.6 ± 22.1	−13.1 ± 17.2		

†Student's *t*-test. ‡χ^2 test. §As calculated by group comparison.

Table 3 Characteristics of elderly who have or have not fallen and with or without fear of falling in T2 group

	Falls (2010)				Fear of falling (2010)			
	Falls (2010) ($n = 22$)	No falls ($n = 54$)	F-value	P-value	Fear ($n = 30$)	No fear ($n = 46$)	F-value	*P*-value
Age	79.9 ± 6.6	78.8 ± 7.2		0.57†	79.5 ± 7.9	78.9 ± 6.5		0.72†
Height (cm)	155.0 ± 8.9	155.0 ± 8.0		0.99†	154.6 ± 7.1	155.2 ± 8.9		0.83†
Weight (kg)	58.0 ± 8.5	56.0 ± 8.4		0.62†	57.9 ± 6.8	55.7 ± 9.2		0.54†
Gender, female	17 (77.3%)	43 (79.6%)		0.52‡	22 (73.3%)	38 (82.6%)		0.25‡
Walking time (sec)								
2009	10.3 ± 1.8	9.5 ± 3.0	0.09	0.76	10.1 ± 2.0	9.6 ± 3.1	0.10	0.75
2010	9.8 ± 1.7	9.2 ± 1.9			10.0 ± 2.0	9.0 ± 1.6		
Change (%)	−6.4 ± 0.1	−4.5 ± 0.3			−1.8 ± 15.0	−7.2 ± 30.0		
Timed up and go (sec)								
2009	9.4 ± 0.7	9.3 ± 0.7	2.70	0.11	9.5 ± 0.7	9.3 ± 0.7	4.31	0.05
2010	9.9 ± 1.5	9.2 ± 1.9			10.1 ± 1.9	8.9 ± 1.6§		
Change (%)	3.1 ± 0.1	−4.8 ± 0.2			4.3 ± 14.2	−7.3 ± 16.7		
Functional reach (cm)								
2009	25.4 ± 6.4	26.9 ± 6.8	0.43	0.52	24.2 ± 5.7	28.0 ± 6.9	0.36	0.56
2010	24.2 ± 6.2	27.9 ± 8.9			24.7 ± 6.9	29.4 ± 8.9		
Change (%)	−4.9 ± 0.3	6.3 ± 0.3			6.3 ± 29.9	5.5 ± 27.1		
One-leg standing (sec)								
2009	7.7 ± 9.1	11.1 ± 14.4	0.00	0.99	11.1 ± 17.4	9.5 ± 9.7	0.01	0.93
2010	6.3 ± 4.9	10.1 ± 11.1			5.8 ± 5.3	11.0 ± 11.4		
Change (%)	−1.4 ± 0.4	−0.1 ± 0.3			−13.8 ± 30.8	7.7 ± 35.1		
Five chair stand (sec)								
2009	10.6 ± 3.1	10.3 ± 1.5	0.01	0.93	10.7 ± 1.5	10.2 ± 2.4	5.84	0.02
2010	10.4 ± 4.2	9.2 ± 2.8			11.3 ± 3.0	8.2 ± 2.7§		
Change (%)	−8.9 ± 0.1	−12.4 ± 0.2			2.6 ± 17.7	−22.0 ± 16.8		

†Student's *t*-test. ‡χ^2 test. §As calculated by group comparison.

Table 4 Characteristics of elderly who have or have not fallen and with or without fear of falling in T3 group

	Falls (2010)				Fear of falling (2010)			
	Falls (2010) ($n = 28$)	No falls ($n = 50$)	F-value	P-value	Fear ($n = 37$)	No fear ($n = 41$)	F-value	P-value
Age	82.0 ± 6.4	82.0 ± 7.3		0.99†	83.9 ± 7.6	80.1 ± 6.8		0.02†
Height (cm)	155.6 ± 9.8	155.9 ± 11.5		0.94†	153.2 ± 10.8	161.5 ± 8.0		0.07†
Weight (kg)	49.2 ± 5.4	56.3 ± 10.8		0.14†	52.0 ± 11.6	59.5 ± 8.4		0.09†
Gender, female	20 (71.4%)	40 (80.0%)		0.17‡	28 (75.7%)	32 (78.0%)		0.35‡
Walking time (sec)								
2009	11.87 ± 2.01	12.99 ± 2.94	3.53	0.07	12.6 ± 2.7	12.6 ± 2.7	0.14	0.71
2010	12.47 ± 2.89	12.27 ± 2.54			12.3 ± 2.2	12.4 ± 3.1		
Change (%)	2.91 ± 14.69	−7.09 ± 21.47			−3.6 ± 22.4	−3.4 ± 17.2		
Timed up and go (sec)								
2009	12.92 ± 1.08	12.73 ± 1.21	0.52	0.47	12.9 ± 1.2	12.7 ± 1.1	0.36	0.55
2010	12.91 ± 2.58	13.28 ± 4.03			13.3 ± 3.5	13.0 ± 3.7		
Change (%)	−3.17 ± 17.78	2.40 ± 26.53			2.0 ± 23.7	3.4 ± 23.8		
Functional reach (cm)								
2009	22.42 ± 7.11	20.69 ± 7.06	0.37	0.55	22.4 ± 7.5	20.3 ± 6.6	0.01	0.92
2010	22.92 ± 5.56	20.11 ± 6.72			21.6 ± 5.9	20.3 ± 7.0		
Change (%)	5.68 ± 25.46	−2.01 ± 43.44			−5.1 ± 37.1	1.4 ± 39.3		
One-leg standing, sec								
2009	4.47 ± 3.28	5.29 ± 5.80	0.16	0.69	4.7 ± 4.0	5.3 ± 6.0	0.49	0.49
2010	3.67 ± 2.92	4.29 ± 4.08			3.6 ± 3.2	4.6 ± 4.2		
Change (%)	−8.63 ± 38.58	−0.62 ± 45.06			−2.7 ± 41.0	−1.4 ± 45.9		
Five chair stand (sec)								
2009	14.89 ± 3.39	12.90 ± 3.94	0.41	0.53	13.1 ± 3.4	14.3 ± 4.6	1.79	0.19
2010	15.72 ± 6.70	12.57 ± 4.67			14.1 ± 6.3	12.7 ± 3.8		
Change (%)	3.44 ± 24.64	−4.73 ± 30.54			1.6 ± 30.8	−8.0 ± 24.5		

†Student's t-test. ‡χ^2 test.

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1

Introduction – Developmental Overview of the Human Embryo

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1. Introduction

In this chapter, we provide a historical background on human embryo collections and describe their significant contribution to the understanding of human ontogenesis. More particularly, an overview of human embryonic development is presented using computer-generated images obtained from embryonic specimens housed at the Kyoto Collection in Japan.

1.1 Human embryology and embryo collections

Historically, several human embryo collections have been created. The Carnegie Collection, the Blechschmidt Collection, the Hinrichsen Collection and the Kyoto Collection are reported as the four famous compendiums of human embryos in the world. The Carnegie Collection is the oldest and was established as early as 1887, while the Blechschmidt collection was created in 1948 by the Göttingen anatomist Erich Blechschmidt, well known for its contribution to the development of novel methods of reconstruction. In 1961, the Kyoto Collection of Human Embryos was instigated, followed by the Hinrichsen Collection in 1969. While the Blechschmidt and the Hinrichsen collections are described in Chapter 2, here, we focus on the Carnegie and the Kyoto Collections.

1.2 The carnegie human embryo collection

The basis of the Carnegie Human Embryo Collection was established by Franklin P. Mall. After earning his medical degree at the University of Michigan in 1883, Mall traveled to Germany to receive a clinical training and there he met Wilhelm His and other eminent biologists. Mall then became aware of the importance of studying human embryology, and initiated a collection of human embryos in 1887. When he returned to the United States and took on a position in the Anatomy department of the Johns Hopkins School of Medicine in Baltimore, Maryland, he already had in his possession several hundreds of specimens. In 1913, as a professor of Anatomy at the Johns Hopkins School of Medicine, Mall applied for a Carnegie grant to support his research on human embryos, was successful in his application and thus, in 1914, became the first director of the Department of Embryology at the Carnegie Institution of Washington, in Baltimore, MD. The collection grew up at a rate of about 400

specimens a year, and the number of samples attained over 8,000 by the early 1940s. The most difficult task, however, was to organize and catalogue the collection. Age or size proved to be a poor way to organize embryos, as embryos could shrink a full 50% in the preserving fluids. Mall devised a better way and based his staging scheme on morphological characteristics instead. To that end, Mall and his colleagues not only prepared and preserved serial sections of the embryos; they also made hundreds of three-dimensional models at different stages of growth. Over 700 wax-based reconstructions were created.

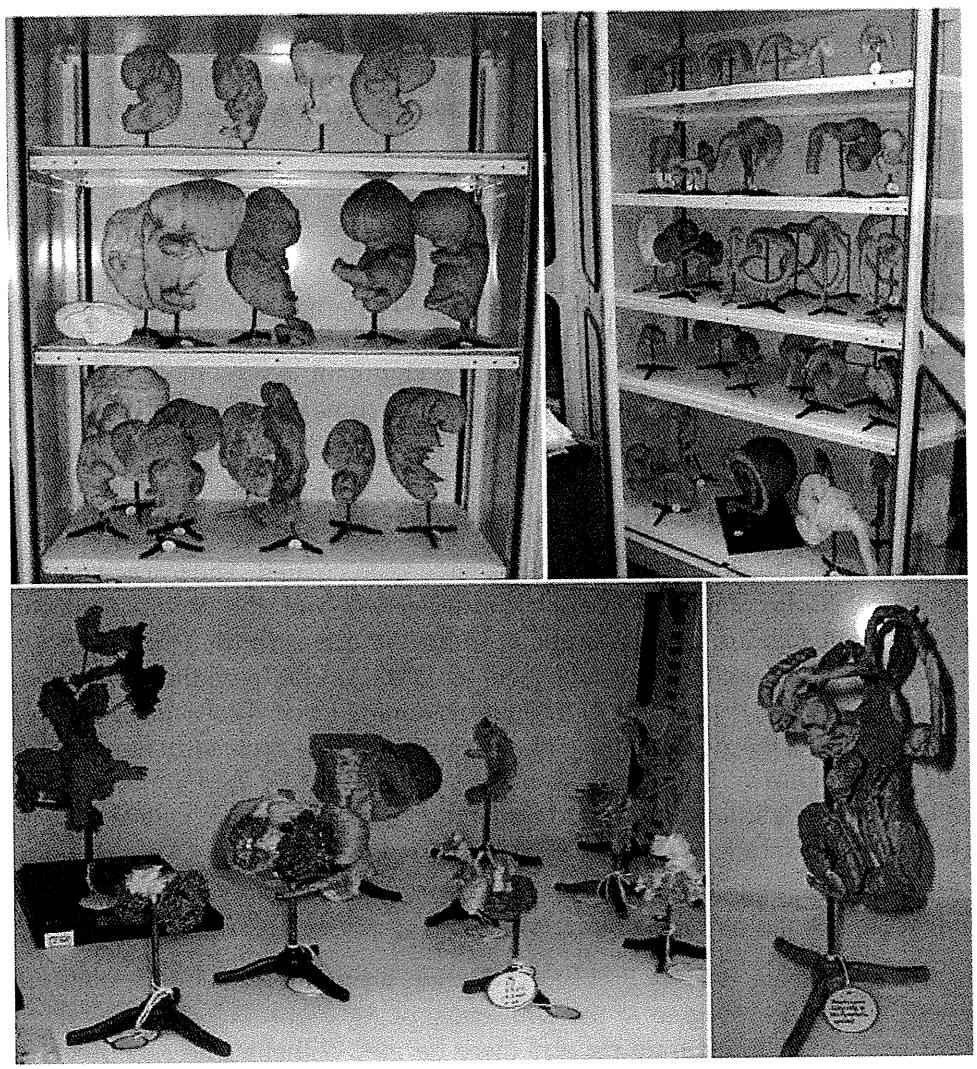

Fig. 1. Wax reconstruction models at the Carnegie Collection, housed at the National Museum of Health and Medicine, Washington, DC. Surface reconstruction of human whole embryos (top left), neural tubes and brains (top right), hearts and great vessels (bottom left), and membranous labyrinth and perilymphatic spaces (bottom right).

Throughout the Mall's era, several members of his department became renowned scientists. George L. Streeter and Franz J. Keibel were both former students of Wilhelm His; Osborne O. Heard worked as an embryo modeler; and James D. Didusch as a scientific

illustrator. Mall documented his research in a series of papers compiled in the *Contributions to Embryology of the Carnegie Institution of Washington*, published from 1915 to 1966. Today, these articles are still regarded as textual and visual standards for human embryologists. In 1917, Mall unexpectedly died, and Streeter became the second director of the Department of Embryology. Under his supervision, hundreds of specimens continued to join the collection every year. Notable were the rare, very young normal specimens. At the time, induced abortions were illegal in the United States and miscarriages usually result in abnormal embryos. Streeter was the first to define the 23 Carnegie Stages currently used to classify the developmental stages of the human embryo.

When Streeter retired in 1940, George W. Corner became the third director of the department. Corner was a former Johns Hopkins researcher who discovered the ovarian hormone progesterone. Under his direction, many advances in human reproductive physiology were made. Research in human embryology continued to be actively pursued, but came to an end in 1956 with the succeeding director. In 1973, the Collection was sent to the University of California at Davis Medical School, where the Carnegie Laboratories of Embryology, under the directorship of Ronan O'Rahilly, officially opened in 1976. In 1991, following O'Rahilly's retirement, the collection was donated to the National Museum of Health and Medicine, located at the Walter Reed Army Medical Center in Washington, D.C. The specimens remain available for use by researchers, and are in high demand. Adrianne Noe and colleagues have generated an online database system for easy information access to some 660 embryos from the collection. These embryos were selected to represent the full range of embryonic growth from single cells through to eight weeks of age. The Carnegie Collection forms the centerpiece of the Human Developmental Anatomy Center, and is used by hundreds of researchers every year. Further details of the embryo collection can be found in earlier publications (Brown, 1987, O'Rahilly, 1988) as well as on the web (http://nmhm.washingtondc.museum/ collections/hdac/carnegie_history.htm).

1.3 The Kyoto collection of human embryos

In 1961, Hideo Nishimura, Professor in the Department of Anatomy at Kyoto University School of Medicine, instigated a collection of human conceptuses. Induced abortions were then legal in Japan under the Maternity Protection Law of Japan, therefore, in a great majority of cases; pregnancies were terminated for social reasons during the first trimester. Fifteen years later, the number of specimens reached over 36,000 and the Congenital Anomaly Research Center was created in 1975. Today, the embryo collection comprises over 45,000 specimens, and represents the largest human embryo collection in the world. The specimens were primarily obtained from pregnancies interrupted by dilatation or curettage. Other specimens resulted from spontaneous or threatened abortions. When the aborted materials were brought to our laboratory, the embryos were measured, staged, and examined for gross external abnormalities and signs of intrauterine death under a dissecting microscope. The developmental stage of the embryos (Carnegie stage: CS) was determined according to the criteria proposed by O'Rahilly and Müller (1987). Since the attending obstetricians were not involved in examining the aborted materials, the collection of embryos was not biased by their outcome (e.g., normal or abnormal, live or dead), thus, the embryo collection is considered representative of the total intrauterine population in Japan (Nishimura, 1974, 1975). Using this representative embryo population, it was reported that

the incidence of malformations in embryos were more frequent than that in infants (Nishimura et al., 1968), and that embryos with severe malformations were prone to spontaneous abortion at high rates (Shiota, 1991). Of these embryonic malformations, holoprosencephaly (HPE) was observed at a high frequency in the Kyoto Collection. HPE is a group of malformation characterized by specific dysmorphia of the brain and the face. They are caused by an impaired or incomplete midline cleavage of the prosencephalon into cerebral hemispheres. Although HPE is a rather rare anomaly in newborns (1/10,000-20,000), it is encountered much more frequently (1/250 or more) in the unselected early human embryonic population (Matsunaga and Shiota, 1977). This estimation may be lower than the actual prevalence as milder forms of HPE also exist but are more difficult to diagnose (Yamada et al., 2004, Yamada, 2006). Well-preserved samples were stored and some of them were selected to be sectioned serially; a total of 500 normal embryos and 500 abnormal embryos were stored as complete serial sections, including HPE embryos.

Fig. 2. The Kyoto Collection of Human Embryos. Stock room (top left, top middle), and individual files containing epidemiological data (top right). Histological specimens (middle left, middle right). Digital slide scanners manufactured by Claro Inc. (http://www.claro-inc.com/); LINCE (bottom left) and TOCO (bottom right).

A unique feature of the Kyoto Collection is that maternal epidemiological data and detailed clinical information on the pregnancies were collected in association with every specimen. Based on these epidemiological data, statistical analyses are currently conducted to determine the existence of potential causative links between maternal factors and congenital anomalies (Kameda et al., 2012).

Recently, owing to advances in imaging technologies, embryos can be scanned and 3D digital models can be generated. Using magnetic resonance (MR) microscopes equipped with superconducting magnets ranging from 1.0T to 7.0T, embryos from the Kyoto Collections were imaged (Haishi et al., 2001, Matsuda et al., 2007, Matsuda et al., 2003, Yamada et al., 2010) and morphologically analyzed using 3D reconstruction (Hirose et al., 2011). Episcopic Fluorescence Image Capture (EFIC) and phase-contrast x-ray computed tomography have also been applied to human embryos of the Kyoto Collection (Yamada et al., 2010, Yoneyama et al., 2011). Further details on imaging techniques and reconstruction can be found in Chapter 7. Additionally, a project aiming at digitizing all histological sections comprised in the library is now ongoing. As mentioned earlier, the Kyoto Collection contains a register of 1,000 embryos sectioned serially; half of them are classified as normal and the other half with anomalies. The project is currently focusing on serial sections of normal embryos. Parts of the digitized serial sections are accessible from our website (http://atlas.cac.med.kyoto-u.ac.jp).

2. Human embryonic development

2.1 Developmental overview (Carnegie stages: CS)

Classification into developmental stages is necessary to accurately describe prenatal growth. Embryonic staging of animals was introduced at the end of the 19th century (Hopwood, 2007), and was first applied to human embryology by Mall (1914), as described earlier. At first, human embryos were classified based on their length on the basis of "3-mm stage", but the approach was quickly abandoned due to high inter-individual variations. Subsequently, Streeter (1942, 1945, 1948, 1951) developed a 23-stage developmental scheme of human embryos, commonly known as the Carnegie stages, a staging scheme which remains widely used today. Here below are illustrated all 23 stages using computer graphics either based on photographs acquired in multiple directions, with precise measurements (CS 1-12), or based on data acquired by magnetic resonance microscopy (Yamada et al., 2006, Matsuda et al., 2003).

Relation between the Carnegie stage and estimated age after fertilization (Table 1)

It is accepted that a wide range of normal variations can occur in actual human embryonic age for any given Carnegie stage. The standard criteria proposed by O'Rahilly and Müller (1987) are close to those suggested by Olivier and Pineau (1962). It is also important to point out that Streeter's human series included pathological specimens obtained from spontaneous abortion or ectopic implantation. In the present chapter, the CG models ranging from CS1 to CS11 were based on Carnegie criteria (O'Rahilly and Müller, 1987), while CS13 to CS23 were based on Kyoto Collection samples (Nishimura et al., 1968, Nishimura et al., 1974).

Carnegie stage (CS)	Ovulation age (days)					
	Streeter (1942, 1945, 1948, 1951)	Nishimura (1968, 1974)	Olivier and Pineau (1962)	Iffy et al. (1967)	Jirásek (1971)	O'Rahilly and Müller (1987)
11	24	27	24	-	23-26	23-25
12	26	30	26	-	26-30	25-27
13	28	32	28	28	28-32	28
14	29	34-35	32	32	31-35	32
15	31.5	36	33	34.5	35-38	33
16	33	38	37	37	37-42	37
17	35	40	41	40	42-44	41
18	37	42	44	43	44-48	44
19	39	44	47.5	45	48-51	47-48
20	41	46	50.5	47	51-53	50-51
21	43	48	52	48.5	53-54	52
22	45	50	54	50	54-56	54
23	47	52	56.5	52	56-60	56-57

Table 1. Estimated ovulation age (days) based on developmental stages (CS) of human embryos, according to various authors. Modified from Nishimura (1983).

Carnegie stage 1: Fertilized ovum
1 day after fertilization, 0.1 mm in diameter

The oocyte is 120-150 μm in diameter and is surrounded by the zona pellucida. The second maturation division of the oocyte completes as the sperm penetrates the egg (fertilization). The sperm head and the nucleus of the oocyte then swell to form the male and female pronuclei, respectively. Once they unite, the resultant diploid cell is called the zygote. The first mitotic division soon begins.

Carnegie stage 2: Cleavage
1.5-3 days after fertilization, 0.1-0.2 mm in diameter

The conceptus is composed of two to 16 cells but has no blastocystic cavity yet and the zona pellucida can still be easily recognized. The size of the embryo is 0.1-0.2 mm in diameter. The cell division at this stage is called cleavage since furrows (clefts) appear as the cytoplasm divides. The daughter cells are called blastomeres. An embryo with 16-32 cells is called a morula.

Carnegie stage 3: Free blastocyst
4 days after fertilization, 0.1-0.2 mm in diameter

The conceptus is a free (unattached) blastocyst. The blastocyst is a hollow mass of cells characterized by the blastocystic cavity. The blastocystic cavity begins by the coalescence of intercellular spaces when the embryo has acquired about 32 cells. The blastomeres segregate into an internally situated inner cell mass and an outer trophoblast. The trophoblast cells form an epithelial arrangement with tight junctions.