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IS THERE A RELATIONSHIP BETWEEN FATIGUE QUESTIONNAIRES AND GAIT MECHANICS IN PERSONS WITH MULTIPLE SCLEROSIS?

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Abstract

Objective: To evaluate the reported fatigue levels and gait deficits in Multiple Sclerosis (MS) patients to determine the relationships that may exist between fatigue in MS patients and alterations in gait mechanics.

Design: Cross-sectional

Setting: Biomechanics laboratory

Participants: Subjects with MS (n = 32) and age- and sex-matched controls (n = 30).

Interventions: None

Main Outcome Measures: Fatigue Severity Scale (FSS), Modified Fatigue Index Scale (MFIS), and shortform SF-36 to assess fatigue and general health. Biomechanical gait analysis was performed to measure peak joint torques and powers in the sagittal plane at the ankle, knee, and hip. Correlations were performed between fatigue measures and degree of deficit within each MS patient for each joint torque and power measure.

Results: FSS was significantly correlated with deficits in ankle power generation at late stance and walking velocity. MFIS was significantly correlated with deficits in peak knee extensor torque and in knee power absorption at early stance. SF-36 subscales were correlated with several of the joint torque and power variables.

Conclusions: subjective fatigue rating scales alone should not be used as an indicator of motor disability or of disease progression as it affects the walking performance of the MS patients

Key words: joint torque, joint power, general health, neurological disease

*Manuscript without author identifiers

Introduction

Fatigue is one of the most common symptoms of multiple sclerosis (MS). It is reported by up to 90% of patients and is described as an increased weakness with exercise or as the day progresses, as an abnormal constant and persistent sense of tiredness, or as fatigable weakness exacerbated by activity or heat [1, 23]. Measurement of fatigue in MS patients is based primarily on the patient's own reports, and as a result, the measures are inherently subjective. Fatigue ratings in MS patients may be affected by the individual's performance self efficacy and altered sensory input during activity. Also, ratings may be affected if an observer rates the fatigue based on reports of decreased effort due to impaired motor control capabilities[4].

Because fatigue is a subjectively reported symptom, there are currently no tests or objective signs allowing the clinician to quantify its severity outside of fatigue related questionnaires [5]. Studies to investigate relationships between fatigue scores have reported weak correlations and noted that fatigue is a multi-factorial symptom which may not be fully explained by one fatigue scale or another[1, 2]. Additionally, changes in fatigue ratings do not correlate with changes in walking performance which led researchers to suggest monitoring reports of fatigue with more objective measures[6]. Lack of correlation between fatigue ratings and walking performance may exist because self-reported fatigue scales rely on subjective reporting by patients and therefore cannot differentiate an inability to generate or maintain voluntary force from an unwillingness to do so[4].

MS fatigue symptoms are likely due to 'central fatigue' which indicates a problem with the neural drive to sustain muscle force[4]. Neural drive is also required to facilitate walking and thus is feasible to expect fatigue to be reflected as alterations in walking mechanics when MS patients are compared to healthy controls. This association between specific reports of fatigue and the gait mechanics of patients with MS has not previously been investigated.

The purpose of this study was to evaluate both the reported fatigue levels in MS patients and these patients' deficits in gait mechanics to determine whether relationships exist between fatigue in MS patients and alterations in gait mechanics. It was hypothesized that since both fatigue in MS patients and neural control of gait are mediated by supraspinal and spinal inputs [4, 7-9], there would be a significant relationship between reported fatigue levels and the alterations in gait mechanics of MS patients. Additionally, alterations in walking mechanics could lead to increased metabolic cost and overall greater energy expenditure during walking [10, 11]. Thus, persons with MS who have greater alterations in walking mechanics could have greater fatigue levels. In addition to fatigue measures, general health measures were also investigated and compared to gait measures to determine whether general health perceptions of MS patients are related to gait mechanics. Because general health perceptions are likely influenced by fatigue levels, it was hypothesized that general health perceptions are also related to deficits in gait mechanics.

Methods

Multiple Sclerosis patients. The study comprised of 32 MS patients and 30 age, weight, gender and height matched healthy controls. All participants were recruited by our clinicians at the University's Medical Center Department of Neurology and through advertisements placed with the local chapter of the National Multiple Sclerosis Society. They provided informed consent in accordance with procedures approved by the University's Medical Center Institutional Review Board.

Inclusion criteria for patients with MS included cognitive competency to give informed consent as determined by our MS clinician (coauthor MF), age ranging from 19 years to 65 years, an Expanded Disability Status Scale (EDSS) score 1 – 6.0 [12]. There was no requirement for MS disease type for inclusion in the study. Healthy controls were age 19 to 65 years and free of any neurological, orthopaedic, or other co-morbid condition which could affect walking mechanics. Exclusion criteria for both patient with MS and healthy controls for the study included: inability to give informed consent, pregnancy or breastfeeding or within 3 months post partum at the initiation of the study, any other neurological or vestibular disorder, and any other co-morbid conditions which would affect gait mechanics. Controls were recruited from family members of MS subjects and through the community to match the overall MS group characteristics but were not matched to individual subjects.

Data Collection Protocol

In order to evaluate gait mechanics, joint torques and powers from the lower extremities were used to evaluate the overall joint muscular contributions and their responses during locomotion. Joint torques and powers have been used successfully to classify gait mechanics in the elderly and in patients with osteoarthritis, total joint replacement, and anterior cruciate ligament deficiency [13-16] to make surgical decisions [17], and to evaluate treatment outcomes in pathological populations [18, 19]. For all data collections, the subjects (patients and controls) arrived at the laboratory where informed consent was obtained. Next, anthropometric data of the lower extremities was measured and reflective markers were placed according to anatomical location [20]. Figure 1 shows the marker set-up from the frontal plane only. Subjects walked through 10 meter walk-way equipped with an embedded force platform (Kistler 9281B, Kistler Instrumentation Corporation, Amhurst, NY) and surrounded with an 8 camera Motion Analysis system (Eagle system, Motion Analysis Corp., Santa Rosa, CA). Figure 2 shows a subject walking with a foot striking the force platform. The subject walked through the walkway from the determined starting position while

INSERT FIGURE 1 AND FIGURE 2

real-time marker position (60 Hz) and force platform (600 Hz) data was collected simultaneously. Once the trial was completed, the MS patient rested for at least one minute. The same process was then repeated at least four more times to obtain five good trials with the subject's footfall landing completely within the force plate without altering the stride. After five successful trials, the other leg was collected using the same process. Participants typically needed to complete a total of 15 walking trials in order to obtain 5 good trials on each side. Finally, the MS patients completed two fatigue specific questionnaires and a general health survey, the SF-36 questionnaire. These are described below.

Qualitative measures

Fatigue Severity Scale. The FSS is a method of evaluating fatigue in MS patients and in other conditions including chronic fatigue immune dysfunction syndrome and systemic lupus erythmatosis. The FSS is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. The FSS questionnaire is comprised of nine statements related to the patients' subjective perception of fatigue and its consequences on everyday activities. Patients are asked to rate their level of agreement (toward seven) or disagreement (toward zero) with the nine statements. The FSS has been validated for use with MS patients where the scale demonstrated high internal consistency with a Cronbach's alpha of 0.81 [21].

Modified Fatigue Impact Scale. The MFIS is a modified form of the Fatigue Impact Scale based on items derived from interviews with MS patients. The scale assesses the effect of fatigue in terms of physical, cognitive, and psychosocial functioning with a 21-item questionnaire. The MFIS has been validated for use with MS patients by Kos et al [22] who found the overall Cronbach's alpha was 0.9223, 0.8813 for the physical, 0.9219 for the cognitive and 0.6496 for the psychosocial subscale.

Short form SF-36. Eight health domains are assessed with the SF-36: Physical Function, limitation due to Physical Health, limitation due to Emotional Problems, Energy, Mental Health, Bodily Pain, General Health, and Social Function. The SF-36 has been used extensively to evaluate and differentiate between groups of varying health status [23, 24] and has previously been used with MS patients [25, 26].

Quantitative Measures

Joint Torques & Powers. During post processing, a low-pass second order Butterworth digital filter with a 7 Hz cutoff frequency was used to smooth the marker trajectories. Subsequently, the joint angles were calculated for the sagittal plane during the stance phase of walking based on the methods of Vaughan et al [27] and Nigg et al [28]. Joint torques were then calculated from the joint angles of the lower limb segments and the simultaneous ground reaction forces produced based on inverse dynamics [29]. Joint powers were calculated based on the resultant joint torques and the angular velocities of the limb segments. Calculation of joint torques and powers was accomplished using custom made laboratory software generated in Matlab (The MathWorks, Inc., Natick, MA).

The peak values for joint extensor and flexor torque, and joint power absorption and generation (Figures 3 and 4) were identified for the ankle, knee and hip joints during the stance phase according to other gait studies on joint kinetics [13, 30-32]. To identify the difference between MS patients and controls for the joint torques and powers, the value for each peak joint torque and peak joint power variable (average from 5 trials) for each MS patient was subtracted from the corresponding average value of the same variable from the healthy control group (Table 3). For example, for each MS subject, the differenced joint torque and joint power variables were calculated as:

$$d\_APT = APT_{control\ mean} – APT_{MS\ subject}$$

Because control subjects were recruited as a group and not matched to individual MS subjects, this methodology allowed for identification of the differences between MS patients and the entire control group rather than single control subjects.

INSERT FIGURE 3 HERE

INSERT FIGURE 4 HERE

Statistical Analysis

A sample of 30 MS patients and 30 matched controls yielded 80% power to detect an effect size of 0.9 for differences in gait variables between the two groups. Independent t-tests were used to compare demographic data for patients with MS to healthy controls. Pearson correlations were performed between the scores for the FSS, MFIS, each of the eight SF-36 domains and each of the differenced joint torque and power parameters. All data was assessed for normality (Q-Q plots) and found to be normally distributed. Analyses were performed using SPSS 16.0 statistical software (SPSS Inc, Chicago, IL) with alpha equal with 0.05. Due to the exploratory nature of this study, no adjustments were made for multiple comparisons.

Results

A total of 32 patients with MS and 30 healthy controls were included. The MS group and healthy controls did not significantly differ in terms of age and mass. None of patients with MS experienced a relapse of symptoms within 3 months of participating in the gait analysis. All of the MS subjects were on disease modifying, but not on symptom modifying therapies. The mean EDSS score for the MS group was 2.6 ± 0.7 which indicates a relatively mild level of motor disability.

INSERT TABLE 1 HERE

The mean scores for the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS) and for each subscale of the SF-36 are listed in Table 2.

INSERT TABLE 2 HERE

The FSS showed a significant relationship only with walking velocity (Table 3) and peak ankle power generation (A2) (Table 4). The MFIS showed a significant relationship only with peak knee extensor torque (Table 3) and the peak knee power absorption (K1) (Table 4). The SF-36 Physical Function subscale revealed a significant relationship with several parameters from the joint torques (4 out of 6; Table 3) and joint powers (6 out of 8; Table 4). The Limitation due to Emotional Problems and Social Function subscales each showed a significant relationship with one joint torque (Table 3) and one joint power parameter (Table 4). The Limitation due to Physical Function subscale showed a significant relationship with walking velocity (Table 3) and with one joint power parameter (Table 4). The Energy subscale showed a significant relationship with one joint power parameter (Table 4). The Bodily Pain subscale showed a significant relationship with walking velocity (Table 3), two joint torque parameters (2 out of 6; Table 3) and three joint power parameters (3 out of 8; Table 4).

INSERT TABLES 3 & 4 HERE

Importantly, all the significant relationships between the quantitative gait measures (joint torques and powers) and the fatigue scales (FSS and MFIS) were small or medium (0.1 to 0.3 and 0.3 to 0.5, respectively) [33]. In contrast, the SF-36 physical function subscale revealed large correlations (0.5 to 1.0) with walking velocity and with the joint torque and joint power parameters (Table 3 and 4).

Discussion

This study outlines the relationship between reported fatigue levels and the deficits in joint torques and powers during overground walking in MS patients. The FSS, which specifically evaluates fatigue levels independent of depression, showed only two significant relationships out of 15 (13.3%), indicating a limited relationship with the changes that occur in the gait mechanics of patients with MS. The MFIS, which is an MS patient specific fatigue measure, showed similar results with only two significant relationships out of 15 (13.3%). It was hypothesized that fatigue and gait mechanics would reveal significant relationships because both fatigue in MS patients and gait control. Because both gait and fatigue are affected by central neural drive[4, 7, 9], it is expected that any alterations in gait mechanics would likely contribute to fatigue. This hypothesis was shown to be only partially true with respect to the utilized fatigue scales. With respect to SF-36, the Physical Function subscale and the Bodily Pain subscale both showed relationships with the gait mechanics of patients with MS with 11 out of 15 (73.3%) and 6 out of 15 (40.0%) correlations, respectively, being significant. The larger number of significant relationships with gait mechanics and the SF-36 subscales is partially in agreement with the original hypothesis that general health perceptions would be related to gait deficit measures.

The lack of correlations between fatigue questionnaires (FSS and MFIS) and measures of gait mechanics indicate that the use of fatigue questionnaires to infer information regarding MS patient’s functional capability may be inappropriate. The SF-36 subscales focus more on specific function areas and show stronger relationship with gait mechanics. Thus, we believe that it may be possible to better represent the relationship between fatigue in MS patients and their gait mechanics by expanding the fatigue questionnaires to incorporate the effects of fatigue on specific areas of physical function as the SF-36 does.

The FSS was significantly and positively related with walking velocity (Table 3) and with the joint power measure A2 (Table 4). Overall, the FSS focuses on the perception of fatigue and its consequences on everyday activities, so the results indicate that the worse the MS patient's perception of fatigue was, the larger the differences in walking velocity and in power generation at the ankle (A2) during late stance between the patients and the healthy controls. The decrements in power generation at the ankle (A2) during late stance indicate that the MS patients have difficulty propelling the trunk and the leg into the swing phase and indicate that the ankle plantarflexors (soleus and gastrocnemius) are not providing sufficient power to accelerate the trunk which would result in slower walking velocity [34]. The significant relationship between FSS and walking velocity decrements in MS patients indicate that FSS is related primarily with the mechanisms related to forward progression during walking. Decreased walking velocity and decreased capability to maintain forward progression during walking could result in increased energy expenditure during walking [35] and would likely affect performance on everyday activities [34, 36], causing increased overall fatigue, thus demonstrating a relationship between A2 and FSS score.

The MFIS, which outlines the effect of fatigue in terms of physical, cognitive, and psychosocial functioning, was correlated decreased power absorption at the knee (K1) and extensor torque at the knee (KET) during early stance phase. The decreased power absorption at the knee (K1) and extensor torque at the knee (KET) indicate that MS patients have difficulty during weight acceptance in single stance and are not able to generate the necessary extensor activity to eccentrically absorb power at the knee (negative muscle) during early stance[35]. Loss of the high efficiency negative work at the knee could result in increased metabolic energy expenditure during gait[35] and a larger metabolic cost of walking for patients with MS. Because

MFIS shows a significant relationship with the amount of negative work being performed at the knee during early stance, we can speculate that the MFIS is related mostly with the overall energy expenditure of patients with MS during walking.

MS patients may be likely to perceive fatigue levels as higher since their ability to maintain forward progression is diminished and overall metabolic cost is likely increased during walking. To maintain forward progression an increase in the frequency of muscle firing would be necessary, but this could be difficult to maintain for an MS patient due to demyelination of nerve fiber and conduction block seen in structurally intact axons [37]. This conduction block is proposed as the primary causation of fatigue in MS patients seen during voluntary effort [4]. The correlations between FSS, MFIS, and the specified joint power measures may be a reflection of the theorized primary causation of fatigue in MS patients.

Finally, the SF-36 subscales for Physical Function and Bodily Pain, which measure overall perceptions of general health, both had negative correlations with joint parameters which indicate that as differences in the gait measures between MS patients and healthy controls increased, the perception of physical function capability decreased in MS patients and the perceptions of bodily pain increased in MS patients. These results are not surprising since Motl et al [38]reported that worsening MS symptoms have a direct negative relationship with self-efficacy and physical activity; hence any changes in actual physical capability levels (reflected here by joint torques and powers) would also be related to perception of physical function. The same investigators also reported that with worsening of symptoms, including an increase in bodily pain, there is a significant decrease in levels of physical activity and physical function[39]. Because these scales are significantly related with several of the gait measures, it is fair to report that the SF-36 subscales are relatively successful in reflecting the motor disability level of MS patients.

Because alterations in joint torques and powers would likely cause changes in energy expenditure during walking, it is likely that there is a relationship between gait measures and fatigue in persons with MS. However, this study showed limited correlations between the FSS and MFIS with gait measures. The SF-36 subscales showed more relationships with gait measures which may indicate that the SF-36 is a better measure of overall functional status in MS patients, however, a larger follow-up study would be needed to confirm these findings. The idea that fatigue specific questionnaires may not be the best tool to reflect physical disability level has also been reported by others [6, 40, 41]. These previously published findings combined with the findings of the current study indicate that subjective fatigue rating scales alone should not be used as an indicator of motor disability or of disease progression as it affects the walking performance of the MS patients. Instead, more quantitative measures, such as gait analysis should be used to indicate the relationship between gait problems and fatigue in MS patients and to support clinical decision making.

Limitations

Several limitations exist in this study. First, it should be noted that we included only MS patients who were ambulatory in the study. Thus, the findings of this study, in terms of usefulness of fatigue scales to indicate functional status and disability, are generalizable only to MS patients who are ambulatory without bilateral aid (EDSS < 6.0). Second, the causes of gait dysfunction in patients with MS are likely multi-factorial and this study did not attempt to differentiate which disease mechanisms, i.e. spasticity, neuropathy, muscle weakness, were specifically related to measures of fatigue and general health. Finally, reported fatigue in MS patient is also multi-factorial. Specific medication, sleep patterns, and overall lifestyle influences may affect reports of fatigue. By utilizing fatigue rating scales that are well established for use with patients who have MS, this study did not seek to specify the sources of reported fatigue but only the relative MS fatigue rating and whether those ratings were related to objective and reliable measures of walking performance.

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Figure Legends

Figure 1: Marker set from the frontal plane

Figure 2: A subject walking with one foot striking the force platform

Figure 3: Joint Torque figures which identify the gait variables used

Figure 4: Joint Power figures which identify the gait variables used

Tables

Table 1: Demographic information of study participants. P-value is indicated for independent t-test between groups.

	MS Patients (n = 32)	Healthy Controls (n = 30)	
Sex	5 male, 27 female	8 male; 22 female	
Age	46.3 ± 10.8 yrs	41.4 ± 12.2 yrs	$p = 0.097$
EDSS	2.6 ± 0.7	-	
Height (cm)	165.0 ± 6.7	170.6 ± 11.2	$p = 0.021$
Mass (kg)	79.9 ± 18.5	76.9 ± 18.5	$p = 0.535$

Table 2: Averaged scores for each fatigue scale and for each component of the Medical Outcomes Short Form 36 Health Survey (SF-36) for MS patients.

Questionnaire Scale	*MS patient score* mean ± SD
Fatigue Severity Scale	4.6 ± 1.5
Modified Fatigue Impact Scale	42.3 ± 15.4
SF-36	
Physical function	57.8 ± 23.6
Limitation due to Physical Function	43.0 ± 36.1
Limitation due to Emotional Problems	46.8 ± 43.0
Energy	46.4 ± 22.5
Mental Health	65.0 ± 22.0
Social Function	61.9 ± 27.3
Bodily Pain	65.4 ± 22.9
General Health	50.3 ± 20.6

Table 3: Correlation matrix between quantitative parameters of gait mechanics (joint torques) and the qualitative self-perceived measures of fatigue (Fatigue Severity Scale, Modified Fatigue Impact Scale) and functional status (SF-36) of MS patients. Pearson correlation values are reported.

Qualitative Measure	*Quantitative Measure*						
	d_Velocity	**d_ADT**	**d_APT**	**d_KET**	**d_KFT**	**d_HET**	**d_HFT**
FSS	***0.35 (.049)**	0.22	0.31	0.30	0.09	0.26	0.02
MFIS	0.34	0.20	0.14	***0.37 (.038)**	-0.03	0.16	-0.09
SF-36							
Physical function	***-0.70 (.000)**	***-0.54 (.002)**	***-0.51 (.003)**	***-0.69 (.000)**	-0.15	-0.22	***-0.39 (.029)**
Limitation due to Physical Function	***-0.35 (.050)**	-0.09	-0.09	-0.26	0.21	-0.070	-0.02
Limitation due to Emotional Problems	-0.11	0.04	-0.22	***-0.36 (.041)**	0.32	-0.12	-0.16
Energy	0.05	0.06	0.18	-0.13	0.23	-0.12	0.16
Mental Health	0.13	0.04	0.12	-0.23	0.32	-0.06	0.31
Social Function	-0.15	-0.08	-0.08	***-0.37 (.038)**	0.10	-0.01	0.05
Bodily Pain	***-0.46 (.008)**	***-0.37 (.037)**	-0.26	***-0.45 (.011)**	-0.15	-0.03	-0.13
General Health	-0.11	-0.100	-0.08	-0.13	0.07	-0.10	0.16

SF-36: Medical Outcomes Survey Short Form 36 Health Survey.

*Significant correlations (*p* -value).

d_Velocity – difference in walking velocity; d_ADT - difference in Peak ankle dorsiflexion moment during early stance; d_APT - difference in Peak ankle plantarflexion moment during late stance; d_KFT - difference in Peak knee flexion moment during stance; d_KET - difference in Peak knee extension moment during stance; d_HFT - difference in Peak hip flexion moment during late stance; d_HET - difference in Peak hip extension moment during early stance.

Table 4: Correlation matrix between quantitative parameters of gait mechanics (joint powers) and the qualitative self-perceived measures of fatigue (Fatigue Severity Scale, Modified Fatigue Impact Scale) and functional status (SF-36) of MS patients. Pearson correlation values are reported.

Qualitative Measure	*Quantitative Measure*							
	d_A1	***d_A2***	***d_K1***	***d_K2***	***d_K3***	***d_H1***	***d_H2***	***d_H3***
FSS	0.25	**0.42 (.010)**	0.28	0.27	0.31	0.31	0.07	0.00
MFIS	0.31	0.32	**0.35 (.048)**	0.33	0.11	0.21	0.07	0.10
SF-36								
Physical function	**-0.38(.033)**	**-0.69 (.000)**	**-0.62 (.000)**	**-0.42 (.017)**	**-0.43 (.015)**	-0.11	**-0.56(.001)**	0.09
Limitation due to Physical Function	-0.10	-0.23	-0.24	**-0.37 (.035)**	-0.29	-0.17	-0.10	-0.17
Limitation due to Emotional Problems	-0.11	-0.28	-0.29	**-0.45 (.009)**	-0.19	-0.04	-0.28	-0.22
Energy	-0.09	-0.01	-0.08	**-0.37 (.037)**	-0.15	-0.03	0.06	-0.24
Mental Health	-0.06	0.01	-0.11	-0.22	-0.02	-0.10	0.05	-0.04
Social Function	-0.18	-0.22	-0.34	**-0.38 (.030)**	-0.24	-0.09	-0.12	-0.32
Bodily Pain	-0.32	**-0.48 (.005)**	**-0.50 (.003)**	**-0.39 (.026)**	-0.14	-0.13	-0.27	0.14
General Health	-0.01	-0.20	-0.11	-0.04	-0.06	-0.15	-0.05	0.04

SF-36: Medical Outcomes Survey Short Form 36 Health Survey.

*Significant correlations (*p* -value).

d_A1 - difference in Peak ankle power absorption in early stance; d_A2 - difference in Peak ankle power generation in late stance; d_K1 - difference in Peak knee power absorption in early stance; d_K2 - difference in Peak knee power generation in mid-stance; d_K3 - difference in Peak knee power absorption in late stance; d_H1 - difference in Peak hip power generation in early stance; d_H2 - difference in Peak hip power absorption in late mid-stance; d_H3 - difference in Peak hip power generation in late stance.

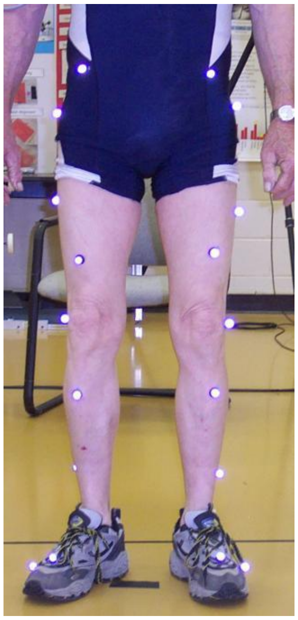

Figure 1: Marker set from the frontal plane

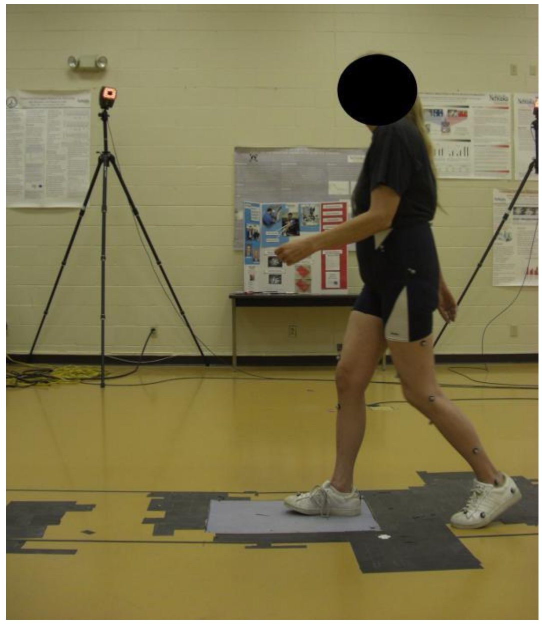

Figure 2: A subject walking with one foot striking the force platform

Figure

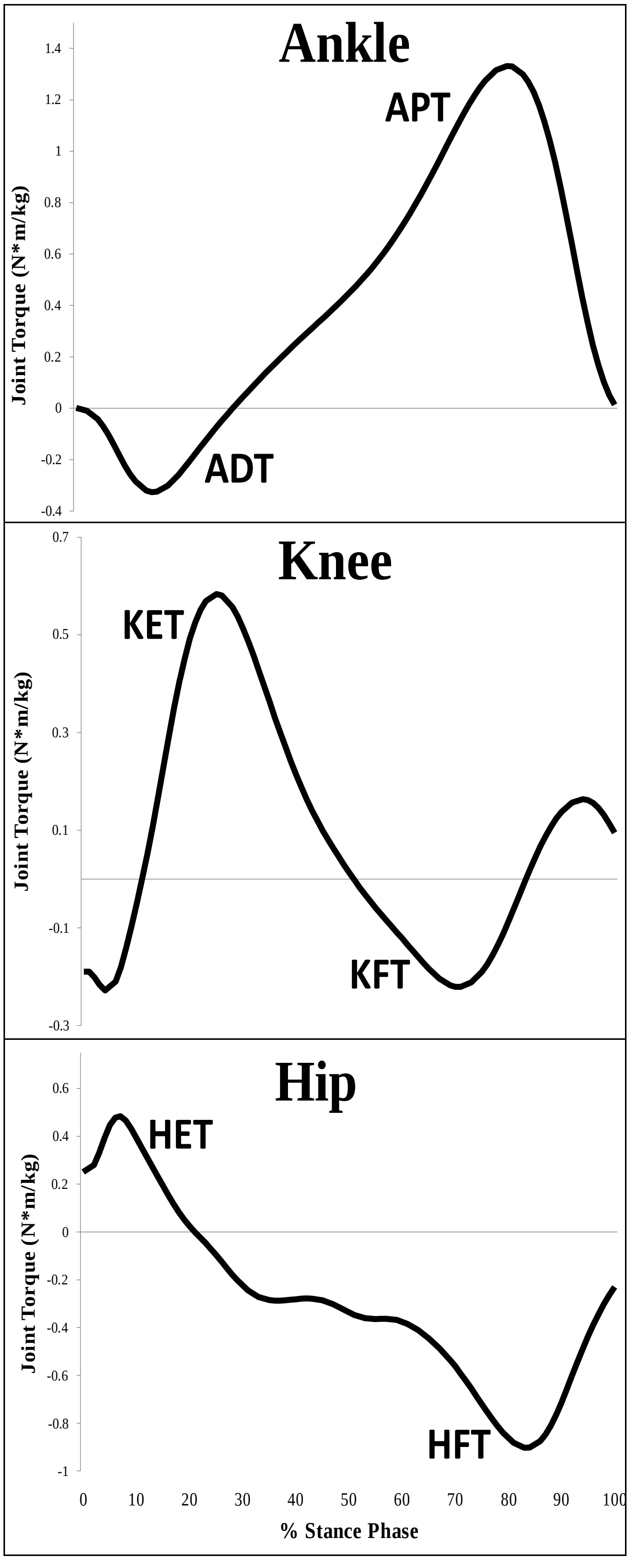

Figure 3: Joint Torque figures which identify the gait variables used

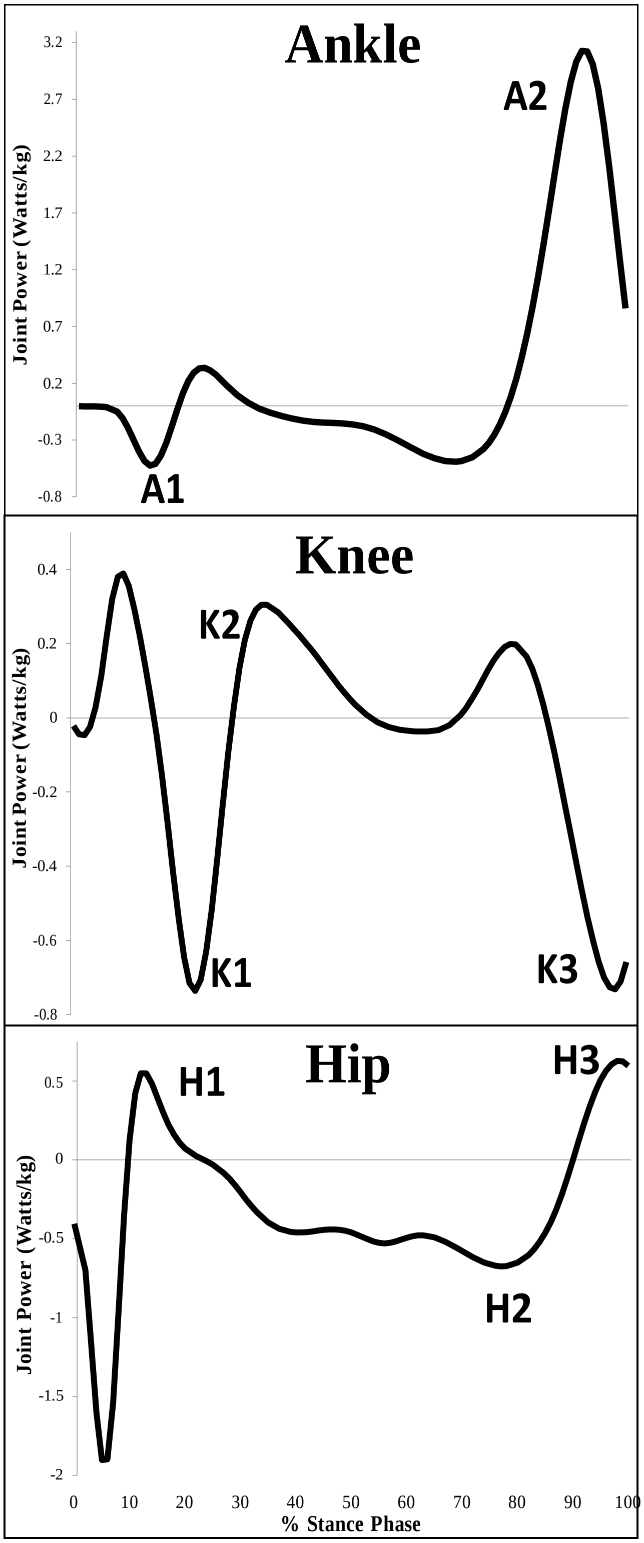

Figure 4: Joint Power figures which identify the gait variables used