Published in final edited form as:

Arch Phys Med Rehabil. 2018 October ; 99(10): 2030–2037. doi:10.1016/j.apmr.2017.11.010.

Dynamic balance is related to physiological impairments in persons with multiple sclerosis

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Abstract

Objectives—To compare physiological impairments between persons with multiple sclerosis (MS) with a history of falls and persons with MS without a history of falls and to investigate the association between physiological impairments and dynamic balance.

Design—Cross-sectional study.

Setting—University motion analysis laboratory.

Participants—Fifty-five persons with MS (27 recurrent fallers and 28 non-fallers). Participants were classified as fallers if they self-reported 2 or more falls in the previous six months.

Interventions—None.

Main Outcome Measures—Physiological impairment was assessed with sensorimotor delays, spasticity, plantar cutaneous sensation, and the sensory, cerebellar, and pyramidal Expanded Disability Status Scale (EDSS) subscales. Dynamic balance was assessed using the average and variability of margin of stability and variability of trunk accelerations.

Results—Compared to non-fallers, fallers had lower plantar sensation, longer sensorimotor delays, more spasticity, and more impairment in the pyramidal and cerebellar EDSS subscales.

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Additionally, these impairments were all moderately to strongly correlated with worse dynamic balance.

Conclusions—The present study highlights the multifactorial nature of instability in persons with MS. A better understanding of the physiological mechanisms of dynamic instability in persons with MS can be used to improve methods of monitoring disease progression, identifying which impairments to target through interventions, and appropriately evaluating intervention efficacy.

Keywords

Walking; Balance; Falls; Neurological disorder

Approximately 2.1 million worldwide have multiple sclerosis (MS),¹ which results in a wide variety of physiological impairments, such as slowed neural conduction speed, sensory loss, muscle weakness, and spasticity.² Balance impairment is a major issue of persons with MS (PwMS) since over half of PwMS fall in a six month period³ which can result in injury,³ high health care costs,¹ fear of falling,⁴ and activity curtailment.⁴ Extensive research has examined the contributions of physiological impairments to static balance,⁵⁻⁸ but falls most frequently occur during dynamic activities, such as walking.⁹ Static and dynamic balance are controlled through different mechanisms and are often unrelated.^{10, 11} Understanding the mechanisms of balance dysfunction during walking in PwMS could help design specific intervention programs to reduce fall risk, allow for a better understanding of how to evaluate intervention efficacy, and further our understanding of which physiological impairments are important to monitor through disease progression.

Gait is a complex whole-body task which requires the integration of sensory information to regulate and control many muscle groups in order to maintain forward progression and upright posture.¹² Maintaining stable gait requires active control of balance, where sensory feedback is integrated to sense the position and velocity of the center of mass (CoM) and an appropriate step placement is chosen to stabilize and redirect the CoM.^{13, 14} The distance between the extrapolated (velocity-adjusted) CoM and the base of support (step placement) is the margin of stability (MoS).¹⁵ PwMS walk with slower, shorter, and wider steps than healthy controls,¹⁶ tending to increase their MoS at heel strike.¹⁷ These gait adaptations have been speculated to be a cautious gait strategy to allow for more response time to external perturbations,¹⁷ to account for excessive and irregular trunk motions,^{17, 18} or to compensate for less precise control of step placement.¹⁹ While these adaptations may represent a cautious gait, fallers with MS walk with slower²⁰ and wider²¹ steps than non-fallers and MoS is positively correlated with number of falls,¹⁷ showing that this cautious gait strategy may actually cause instability. It has been hypothesized that maintaining a constant MoS during gait is advantageous²² and that stride-to-stride variability of MoS reflects dynamic balance better than average MoS.²³ In PwMS, variability of both anterior-posterior (AP) and mediolateral (ML) MoS is higher in recurrent fallers compared to non-fallers and healthy controls, but similar between non-fallers and to healthy controls.²⁴ While MoS evaluates the interaction between the CoM and base of support, investigating the kinematic irregularities of the trunk alone is also a valid way to investigate dynamic balance.^{18, 25} Nonlinear variability of trunk motion during gait, which evaluates the predictability of

cyclical motion, is higher in PwMS compared to controls^{18, 24} and in elderly fallers compared to elderly non-fallers.²⁵

Specific physiological impairments which may contribute to these dynamic balance impairments in PwMS include slowed neural conduction speed, sensory loss, muscle weakness, and spasticity.^{6, 18} Sensory loss, muscle weakness, and simple reaction time tests are all related to spatiotemporal variability in elderly individuals.²⁶ However, it is unknown which specific physiological impairments are related to dynamic instability in PwMS. Therefore, the first purpose of this study is to determine if physiological impairments are different between PwMS with a history of falls and PwMS with no fall history. The second purpose of this study is to examine the relationship between physiological impairments and dynamic balance in PwMS. Specific physiological impairments investigated are sensorimotor delays,⁶ foot vibration thresholds,⁷ lower extremity spasticity,⁸ and the pyramidal, cerebellar, and sensory EDSS subscales.²⁰ As PwMS with falls history have shown more impairment on sensory, pyramidal, and cerebellar EDSS subscales than non-fallers,²⁰ and that worse physiological impairments are related to poor static balance in PwMS,⁶⁻⁸ we hypothesize that physiological impairments will be higher in fallers compared to non-fallers and will correlate with poor dynamic balance.

Methods

Participants

Fifty-five PwMS were recruited from the University MS clinic and included in the present study (Table 1). The University Human Research Committee approved this study and all participants gave informed written consent. All subjects were between the ages of 21-60, had relapsing remitting MS, and an EDSS score less than 5.5. The self-reported number of falls in the six months prior to data collection was recorded. PwMS were classified as non-fallers if they did not experience a fall in the previous 6 months (n=28) and as fallers if they experienced 2 or more falls in the previous 6 months (n=27).²¹ Falls were defined as “an event which results in a person coming to rest unintentionally on the ground or lower level”.²⁷ PwMS who fall only once in a year are likely to fall due to extrinsic factors, whereas PwMS who fall 2 or more times are more likely to fall due to intrinsic disease specific factors.²¹ Demographics were compared between groups using independent t-tests (Table 1).

Gait protocol and analysis

All subjects walked on a treadmill at their self-selected preferred pace for 3 minutes. Participants were instructed to walk naturally without holding onto the treadmill side rails. Kinematic data^a was collected at 60 Hz using retroreflective markers placed bilaterally on the anterior and posterior superior iliac spine, heel, lateral malleolus, and top of the second and fifth metatarsal phalangeal joint. Wireless inertial sensors^b measured trunk accelerations at 128 Hz, placed over the midline of the sternum.

^aSuppliers: Motion Analysis, 3617 Westwind Blvd, Santa Rosa, CA 95403

^bOpal, APDM, 2828 SW Corbett Avenue, Portland, OR 97201

MoS was calculated as the distance between the extrapolated CoM and base of support.¹⁵ A visual representation and explanation of how MoS is calculated can be found in Figure 1.^{17, 23} MoS was calculated in the AP and ML direction at each heel strike and averaged over the whole trial. MoS variability was assessed using coefficient of variation, which represents the standard deviation normalized by the average.²⁸ Average MoS and MoS variability were calculated independently for the left and right leg and averaged for each subject.

Linear trunk accelerations were measured in the AP, ML, and vertical (VT) axis, and analyzed independently. Root mean square transforms (RMS) were used to describe the dispersion of each signal.^{18, 29} Temporal structure of trunk accelerations was assessed with Lyapunov Exponents (LyE) and Sample Entropy (SaEn). LyE and SaEn are nonlinear variability measures which describe the predictability of cyclical motion. Less predictable trunk accelerations, represented by larger LyE and SaEn values, is interpreted to reflect a dynamic system which is poorly controlled. Less predictable trunk accelerations have been found in PwMS relative to healthy controls,¹⁸ showing that evaluating trunk variability may be a useful indicator of dynamic balance. To calculate LyE and SaEn, raw acceleration time series were down-sampled to 60 Hz and truncated to the middle 60 strides.³⁰ Delay-embedded state spaces were reconstructed independently in each axis. Embedding dimensions were found using the global false nearest neighbor algorithm, and time delays were found using the average mutual information algorithm.³⁰ Both algorithms were used on each independent time series, and the median of every subject resulted in an embedding dimension of 7 for each axis, and time delays of 6, 8, and 9 for the AP, ML, and VT axis, respectively.³⁰ LyE were calculated using Wolf's algorithm. SaEn³¹ was calculated with the medium time delays from the average mutual information analysis.²⁹ Values of $m=3$ and $r=0.2$ were used, as these have been found to be robust for SaEn calculations of trunk accelerations.²⁹

Physiological deficits protocol and analysis

Foot vibration threshold—Vibration threshold the big toe was assessed using the Vibratron II^c device,³² where the lowest amplitude of vibration detectable was recorded for the left and right foot and averaged for each subject.

Sensorimotor delays—Each subject stood on a servo-controlled motorized treadmill,^d which translated forward causing a backwards body sway.³³ The treadmill translated approximately 4-6 cm at approximately 4 cm/s. Wireless surface electromyography sensors^e were placed bilaterally over the tibialis anterior. Electromyography signals were sampled at 1800 Hz, amplified, band-pass filtered (70-2000 Hz), and stored for off-line analysis. Sensorimotor delays were defined as the time between treadmill onset and the first measurable increase in electromyography activity greater than 2 SD from baseline that was sustained for at least 50 milliseconds.^{6, 33} Latencies for 3 separate trials including both legs

^cVibratron II, Physitemp, 154 Huron Avenue, Clifton, New Jersey 07013

^dBari-Mill, Woodway, W229 N591 Foster Ct., Waukesha, WI 53186

^eDelsys, 23 Strathmore Road, Natick, Massachusetts 01760

were averaged for each subject. Healthy individuals have average sensorimotor delays of 100 milliseconds for postural perturbations.^{6, 34}

Spasticity—Lower limb spasticity was assessed bilaterally in the hamstring, quadriceps, and plantarflexors using the modified Ashworth scale,⁸ which was scored between 0 (no increase in muscle tone) and 4 (the affected part is rigid). A single measure of spasticity was used for each participant representing the average spasticity of each three muscles in each leg.

EDSS subscales—Disease severity was assessed with the Kurtzke's expanded disability status scale (EDSS), administered by a neurologist (author SL).²⁰ The pyramidal, cerebellar, and sensory subscale scores were recorded.

Statistical analysis

As many outcome measures chosen were found to be non-normally distributed, non-parametric statistical tests were used. Physiological impairments were compared between fallers and non-fallers with MS using Mann-Whitney U-Tests with significance set at 0.05. The relationship between physiological impairment measures and dynamic balance measures were first assessed across all subjects with MS using spearman's rank correlation coefficients. If a significant correlation was found, separate correlations were run for the fallers (FA) group and non-fallers (NF) group. A step-wise regression was performed with fall status (FA/NF) as the dependent variable and physiological impairments as the dependent variables. Model inclusion criteria was set at $p < 0.01$. As many comparisons are made in the present study, significance was set at 0.01 for correlations only. All statistics were performed with SPSS software.^f

Results

Compared to non-fallers, fallers had a higher vibration threshold ($p=0.003$), longer sensorimotor delays ($p=0.002$), more spasticity ($p=0.017$), and more impairment in the pyramidal ($p=0.002$) and cerebellar EDSS subscales ($p=0.003$) (Table 2). Correlations between physiological impairments and dynamic balance measures can be found in Table 3 and Table 4. The final model entered into the stepwise logistic regression were the pyramidal and cerebellar EDSS subscales, which together explained only 22.4% of the variance in fall status.

Discussion

The purpose of the present study was to determine if physiological impairments are different between PwMS with a history of falls and PwMS with no fall history, and to examine the relationship between physiological impairments and dynamic balance in PwMS. We hypothesized that fallers would be more physiologically impaired than non-fallers and that greater physiological impairment would correlate with worse dynamic balance. The results of the present study support these hypotheses. As many distinct physiological impairments

^fIBM SPSS Statistics, 1 New Orchard Rd, Armonk, NY 10504.

were found to differentiate fallers from non-fallers with MS and to correlate with dynamic balance, the results of the present study highlight the multifactorial nature of instability in this population and suggest that a combination of impairments is likely a major contributor to dynamic instability and falls. It has been shown that fallers with MS have worse dynamic balance than non-fallers.²⁴ The present study expands on this finding by showing that fallers with MS are also more physiologically impaired than non-fallers and that worse physiological impairment is related to worse dynamic balance. These findings provide novel information demonstrating the relationships between physiological impairments and dynamic instability in PwMS.

Sensorimotor delays were longer in fallers than non-fallers and were significantly, moderately correlated with dynamic balance (AP MoS CV, VT LyE, VT RMS) and trending ($p < 0.05$) toward correlations with AP MoS, MS MoS CV, ML LyE, VT SaEn. Sensorimotor delays evaluate the combined somatosensory and motor response times after a translational postural perturbation so any delay in sensorimotor response time represents both sensory and motor tract conduction impairments.^{33, 35} Lyapunov exponents quantify a systems sensitivity to small local perturbations during gait.³⁶ Deviations in center of mass kinematics (also considered perturbations) during gait are corrected through appropriate step placement.¹⁴ Sensorimotor delays correlated with both Lyapunov exponents of trunk accelerations and MoS variability, showing that individuals with longer sensorimotor delays to postural perturbations during stance also have a decreased ability to correct center of mass deviations during gait and thus have poor dynamic balance and a likely increased risk for falling. These results highlight the importance of quick neural conduction for maintaining balance.

Sensorimotor delays and the cerebellar EDSS subscale both correlated with vertical trunk acceleration variability (vertical LyE, vertical RMS). It is likely that vertical accelerations are useful indicators of trunk control as they reflect not only vertical motion of the trunk, but rotations in both the sagittal and frontal plane.³⁷ Trunk control is crucial during gait as the trunk contains approximately 60% of the bodies mass³⁸ and stabilizes the head which contains vital sensory organs.³⁹ Slower walking speeds with lower magnitudes of trunk accelerations, demonstrated by lower trunk acceleration RMS in individuals with longer sensorimotor delays and worse scores on the cerebellar EDSS subscale, are likely a compensatory strategy to preserve stability in PwMS.

Foot vibration thresholds were found to be worse in fallers compared to non-fallers and were moderately correlated with dynamic balance measures. Healthy individuals with experimentally numbed feet and persons with diabetic peripheral neuropathy also have decreased cutaneous sensitivity and increased gait variability which demonstrates the independent contribution of plantar sensation to dynamic balance.^{40, 41} Older adults also have poor cutaneous sensation, poor dynamic balance, and an elevated risk for falls.²⁶ Less somatosensory feedback in PwMS likely leads to a poor perception of their center of mass kinematics, which is shown here to relate to dynamic instability and falls. However, the sensory EDSS subscale did not differ between fallers and non-fallers and was not correlated with any measures of dynamic balance which may indicate limited sensitivity of the sensory EDSS subscale to plantar sensation. Additionally, previous work found no relationship

between proprioception acuity and gait variability²⁸ or fall risk⁴² in PwMS using a lower limb matching task. It is unclear if discrepancies found relating somatosensory acuity to dynamic instability and falls in PwMS is due to differences in instrumentation sensitivity or the specific sensory receptors examined. Future work should aim to document specific impairments found in different sensory systems in PwMS and evaluate their individual contributions to instability.

In the present study, the pyramidal EDSS subscale scores were higher in fallers compared to non-fallers and correlated moderately with dynamic balance measures. This finding agrees with previous work finding pyramidal impairment significantly alters gait in PwMS.⁴³ Motor impairment is very common in PwMS and is characterized by slowed force production rates, weaker maximal force production, less control of force production, spasticity, and fatigue.^{2, 21, 44} Though lower limb spasticity was greater in fallers compared to non-fallers, spasticity was not correlated with any measures of dynamic balance, likely indicating that other motor impairments, such as muscle weakness and fatigue were larger contributors to dynamic instability in the present study. Previous studies have also found that muscle weakness negatively impacts walking ability in PwMS more than spasticity.⁴⁵ While it is possible that fatigue during the 3-minute treadmill walk influenced the results of the present study, previous studies have shown that spatiotemporal parameters and spatiotemporal variability remain consistent throughout a 6-minute walk in independently ambulatory PwMS.⁴⁶ Figure 2 shows MoS throughout the 3-minute trial for a typical faller and non-faller and demonstrates representative consistency in both groups across the trial. The present study highlights a need for a better understanding of how motor impairments affect dynamic balance and falls in PwMS.

Cerebellar involvement was greater in fallers than non-fallers, and was found to strongly correlate with dynamic balance measures. The cerebellar EDSS subscale is examined through tests of fine motor control and balance, such as alternating finger to nose movements and tandem standing and walking. Previous reports have shown that similar tests of fine motor control significantly contributed to differentiating frequent fallers from infrequent fallers with MS,⁴² and that fallers with MS have a larger lesion load in the cerebellum compared to non-fallers.⁵ The present results indicate that cerebellar damage likely influences dynamic instability; however our present study design is insufficient to determine whether the cerebellar EDSS subscale scores were influenced by other physiological impairments. While the present study found pyramidal and cerebellar to correlate with many dynamic balance measures, a recent study found single limb stance time to be correlated with the sensory and pyramidal subscales, but not with the cerebellar subscale.⁴⁷ These slight differences are likely due to differences between static and dynamic balance, however collectively tell the same story of instability being multifactorial in PwMS.

Study limitations

A limitation of our experimental procedure was the use of a treadmill for data collection, which is known to alter gait compared to over-ground walking. However, the treadmill allowed for continuous walking data over three minutes, which was needed to assess gait variability. Additionally, fallers and non-fallers did not walk at the same speeds. While many

of the outcome variables used in the present study are known to change with walking speed (e.g. MoS and LyE), slow walking is believed to be a primary adaptive mechanism to improve stability,^{17, 48} and therefore was not included as a covariate in the present study.

Conclusion

Distinct physiological impairments found in PwMS are related to dynamic balance. Also, physiological impairments are more severe in PwMS who fall compared to PwMS who have a falls history. These results highlight the multifactorial nature of dynamic instability in PwMS. Future studies should be specifically designed to identify which specific sensory impairments and motor impairments contribute most to dynamic instability and falls through regressions. Evaluating dynamic balance and distinct physiological impairments may provide useful indicators of disease progression, aid in individualizing therapies for intervention, and improve measurement of responsiveness to intervention. Specifically targeting both sensory and motor impairments seems important to improve dynamic balance in PwMS based on the present study findings. For example, manipulating sensory feedback (e.g. removing vision or using a foam support surface) while doing dynamic tasks have been shown to improve balance in PwMS.^{49, 50} Similarly, resistance and aerobic training are known to improve motor impairments and gait in PwMS.⁵¹ Intervention studies should include sensitive measures of physiological impairment and dynamic balance to further our understanding of how much these impairments are modifiable.

Acknowledgments

This work has not been presented or published elsewhere

This work was supported by the National Multiple Sclerosis Society RG 4914A1/2 and the NIH National Center for Advancing Translational Science 1KL2TR00011

References

1. Campbell JD, Ghushchyan V, Brett McQueen R, Cahoon-Metzger S, Livingston T, Vollmer T, et al. Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. *Multiple sclerosis and related disorders*. 2014; 3(2):227–36. [PubMed: 25878010]
2. Noseworthy JH, Lucchinetti C, Rodrigues M, Weinshenker BG. Multiple Sclerosis. *New England Journal of Medicine*. 2000:938–52.
3. Matsuda PN, Shumway-Cook A, Bamer AM, Johnson SL, Amtmann D, Kraft GH. Falls in multiple sclerosis. *PM & R: the journal of injury, function, and rehabilitation*. 2011; 3(7):624–32. quiz 32.
4. Peterson EW, Cho CC, Finlayson ML. Fear of falling and associated activity curtailment among middle aged and older adults with multiple sclerosis. *Multiple Sclerosis*. 2007; 13
5. Prosperini L, Kouleridou A, Petsas N, Leonardi L, Tona F, Pantano P, et al. The relationship between infratentorial lesions, balance deficit and accidental falls in multiple sclerosis. *Journal of the neurological sciences*. 2011; 304(1-2):55–60. [PubMed: 21402386]
6. Huisinga JM, St George RJ, Spain R, Overs S, Horak FB. Postural response latencies are related to balance control during standing and walking in patients with multiple sclerosis. *Archives of physical medicine and rehabilitation*. 2014; 95(7):1390–7. [PubMed: 24445088]
7. Citaker S, Gunduz AG, Guclu MB, Nazliel B, Irkec C, Kaya D. Relationship between foot sensation and standing balance in patients with multiple sclerosis. *Gait & posture*. 2011; 34(2):275–8. [PubMed: 21683600]

8. Sosnoff JJ, Gappmaier E, Frame A, Motl RW. Influence of Spasticity on Mobility and Balance in Persons With Multiple Sclerosis. *Journal of Neurologic Physical Therapy*. 2011; 35(3):129–32. [PubMed: 21934374]
9. Peterson EW, Ben Ari E, Asano M, Finlayson ML. Fall attributions among middle-aged and older adults with multiple sclerosis. *Archives of physical medicine and rehabilitation*. 2013; 94(5):890–5. [PubMed: 23201427]
10. Kang HG, Dingwell JB. A direct comparison of local dynamic stability during unperturbed standing and walking. *Experimental brain research*. 2006; 172(1):35–48. [PubMed: 16432700]
11. Hausdorff J, Nelson M, Kaliton D, Layne J, Bernstein M, Nuernberger A, et al. Etiology and modification of gait instability in older adults: a randomized controlled trial of exercise. *Journal of Applied Physiology*. 2001; 90(6):2117–29. [PubMed: 11356774]
12. Winter D. Human balance and posture control during standing and walking. 1995
13. Rankin BL, Buffo SK, Dean JC. A neuromechanical strategy for mediolateral foot placement in walking humans. *Journal of neurophysiology*. 2014; 112(2):374–83. [PubMed: 24790168]
14. Wang Y, Srinivasan M. Stepping in the direction of the fall: the next foot placement can be predicted from current upper body state in steady-state walking. *Biology letters*. 2014; 10(9)
15. Hof AL, Gazendam MG, Sinke WE. The condition for dynamic stability. *Journal of biomechanics*. 2005; 38(1):1–8. [PubMed: 15519333]
16. Sosnoff JJ, Sandroff BM, Motl RW. Quantifying gait abnormalities in persons with multiple sclerosis with minimal disability. *Gait & posture*. 2012; 36(1):154–6. [PubMed: 22424761]
17. Peebles AT, Reinholdt A, Bruetsch AP, Lynch SG, Huisinga JM. Dynamic margin of stability during gait is altered in persons with multiple sclerosis. *Journal of biomechanics*. 2016; 49(16):3949–55. [PubMed: 27889188]
18. Huisinga JM, Mancini M, St George RJ, Horak FB. Accelerometry reveals differences in gait variability between patients with multiple sclerosis and healthy controls. *Annals of biomedical engineering*. 2013; 41(8):1670–9. [PubMed: 23161166]
19. Zissimopoulos A, Stine R, Fatone S, Gard S. Mediolateral foot placement ability during ambulation in individuals with chronic post-stroke hemiplegia. *Gait & posture*. 2014; 39(4):1097–102. [PubMed: 24582515]
20. Sosnoff JJ, Socie Michael J, Boes Morgan K, Sandroff Brian M, Pula John H, Suh Yoojin, et al. Mobility, Balance and Falls in Persons with Multiple Sclerosis. *PloS one*. 2011; 6(11)
21. Kasser SL, Jacobs JV, Foley JT, Cardinal BJ, Maddalozzo GF. A prospective evaluation of balance, gait, and strength to predict falling in women with multiple sclerosis. *Archives of physical medicine and rehabilitation*. 2011; 92(11):1840–6. [PubMed: 21840497]
22. Hof AL, Vermerris SM, Gjaltema WA. Balance responses to lateral perturbations in human treadmill walking. *Journal of Exp Biol*. 2010; 213(Pt 15):2655–64. [PubMed: 20639427]
23. McAndrew Young PM, Wilken JM, Dingwell JB. Dynamic margins of stability during human walking in destabilizing environments. *Journal of biomechanics*. 2012; 45(6):1053–9. [PubMed: 22326059]
24. Peebles AT, bruetsch A, Lynch SG, Huisinga JM. Dynamic balance in persons with multiple sclerosis who have a falls history is altered compared to non-fallers and to healthy controls. *Journal of biomechanics*. 2017 In press.
25. Toebes MJP, Hoozemans MJM, Furrer R, Dekker J, van Dieën JH. Local dynamic stability and variability of gait are associated with fall history in elderly subjects. *Gait & posture*. 2012; 36(3):527–31. [PubMed: 22748312]
26. Callisaya ML, Blizzard L, McGinley JL, Schmidt MD, Srikanth VK. Sensorimotor Factors Affecting Gait Variability in Older People--A Population-Based Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2009; 65A(4):386–92.
27. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *New England journal of medicine*. 1988; 319(26):1701–7. [PubMed: 3205267]
28. Moon Y, Wajda DA, Motl RW, Sosnoff JJ. Stride-Time Variability and Fall Risk in Persons with Multiple Sclerosis. *Mult Scler Int*. 2015; 2015:964790. [PubMed: 26843986]
29. Craig JJ, Bruetsch A, Huisinga JM. Relationship between trunk and foot accelerations during walking in healthy adults. *Gait & posture*. 2016; 49:25–9. [PubMed: 27344450]

30. van Schooten KS, Rispens SM, Pijnappels M, Daffertshofer A, van Dieen JH. Assessing gait stability: the influence of state space reconstruction on inter- and intra-day reliability of local dynamic stability during over-ground walking. *Journal of biomechanics*. 2013; 46(1):137–41. [PubMed: 23159098]
31. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology-Heart and Circulatory Physiology*. 2000; 278(6): 2039–49.
32. Newsome SD, Wang JI, Kang JY, Calabresi PA, Zackowski KM. Quantitative measures detect sensory and motor impairments in multiple sclerosis. *Journal of the neurological sciences*. 2011; 305(1-2):103–11. [PubMed: 21458828]
33. Cameron MH, Horak FB, Herndon RR, Bourdette D. Imbalance in multiple sclerosis: a result of slowed spinal somatosensory conduction. *Somatosensory & motor research*. 2008; 25(2):113–22. [PubMed: 18570015]
34. Horak FB, Diener HC, Nashner LM. Influence of central set on human postural responses. *Journal of neurophysiology*. 1989; 62(4):841–53. [PubMed: 2809706]
35. Horak FB, Macpherson JM. Postural orientation and equilibrium. *Comprehensive Physiology*. 2011:255–92.
36. Dingwell JB, Kang HG. Differences between local and orbital dynamic stability during human walking. *Journal of biomechanical engineering*. 2007; 129(4):586–93. [PubMed: 17655480]
37. Rispens SM, van Schooten KS, Pijnappels M, Daffertshofer A, Beek PJ, van Dieen JH. Identification of fall risk predictors in daily life measurements: gait characteristics' reliability and association with self-reported fall history. *Neurorehabilitation and neural repair*. 2015; 29(1):54–61. [PubMed: 24759809]
38. Winter DA, Ruder GK, MacKinnon CD. Control of Balance of Upper Body During Gait. *Multiple muscle systems*. 1990:534–41.
39. Kavanagh J, Barrett R, Morrison S. The role of the neck and trunk in facilitating head stability during walking. *Experimental brain research*. 2006; 172(4):454–63. [PubMed: 16489437]
40. Menz HB, Lord SR, St George R, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. *Archives of physical medicine and rehabilitation*. 2004; 85(2):245–52. [PubMed: 14966709]
41. Manor B, Wolenski P, Guevaro A, Li L. Differential effects of plantar desensitization on locomotion dynamics. *Journal of electromyography and kinesiology: official journal of the International Society of Electrophysiological Kinesiology*. 2009; 19(5):e320–8. [PubMed: 18682330]
42. Hoang PD, Cameron MH, Gandevia SC, Lord SR. Neuropsychological, balance, and mobility risk factors for falls in people with multiple sclerosis: a prospective cohort study. *Archives of physical medicine and rehabilitation*. 2014; 95(3):480–6. [PubMed: 24096187]
43. Kalron A, Givon U. Gait characteristics according to pyramidal, sensory and cerebellar EDSS subcategories in people with multiple sclerosis. *J Neurol*. 2016; 263(9):1796–801. [PubMed: 27314963]
44. Davies BL, Hoffman RM, Healey K, Zabad R, Kurz MJ. Errors in the ankle plantarflexor force production are related to the gait deficits of individuals with multiple sclerosis. *Human Movement Sciences*. 2017; 51:91–8.
45. Wagner JM, Kremer TR, Van Dillen LR, Naismith RT. Plantarflexor weakness negatively impacts walking in persons with multiple sclerosis more than plantarflexor spasticity. *Archives of physical medicine and rehabilitation*. 2014; 95(7):1358–65. [PubMed: 24582617]
46. Socie MJ, Motl RW, Sosnoff JJ. Examination of spatiotemporal gait parameters during the 6-min walk in individuals with multiple sclerosis. *International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation*. 2014; 37(4):311–6. [PubMed: 25117855]
47. Fry DK, Huang MH, Rodda BJ. Predictors of static balance in ambulatory persons with multiple sclerosis. *International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation*. 2016; 39(1):42–7. [PubMed: 26579696]

48. Dingwell JB, Cusumano JP. Nonlinear time series analysis of normal and pathological human walking. *Chaos*. 2000; 10(4):848–63. [PubMed: 12779434]
49. Cattaneo D, Jonsdottir J, Zocchi M, Regola A. Effects of balance exercises on people with multiple sclerosis: a pilot study. *Clinical rehabilitation*. 2007; 21(9):771–81. [PubMed: 17875557]
50. Kasser SL, Jacobs JV, Ford M, Tourville TW. Effects of balance-specific exercises on balance, physical activity and quality of life in adults with multiple sclerosis: a pilot investigation. *Disability and rehabilitation*. 2015; 37(24):2238–49. [PubMed: 25738911]
51. Donze C. Update on rehabilitation in multiple sclerosis. *Presse medicale*. 2015; 44(4 Pt 2):e169–76.

Abbreviations

MS	multiple sclerosis
PwMS	persons with multiple sclerosis
CoM	center of mass
MoS	margin of stability
AP	anterior-posterior
ML	mediolateral
VT	vertical
RMS	root mean square
LyE	Lyapunov exponents
SaEn	sample entropy
EDSS	expanded disability status scale
FA	fallers with multiple sclerosis
NF	non-fallers with multiple sclerosis

Figure 1.

Visual representation of the MoS calculation in the (A) anterior-posterior (AP) and in the (B) mediolateral (ML) direction. First the position of the center of mass (X_{CoM}) and the anterior and lateral edges of the base of support (BoS) have to be defined and second the velocity of the CoM calculated (V_{CoM}). The position of the CoM was estimated using the geometric center of the pelvic markers, and the edge of the base of support in the AP and ML direction was estimated using the toe and lateral MTP markers respectively. Note that the position and velocity of the CoM are two dimensional (AP and ML). The extrapolated center of mass ($xCoM$) is then calculated independently in the AP and ML direction, which includes the position and velocity of the CoM as well as the acceleration due to gravity (g) and length of the leg (L). MoS is then calculated as the distance between the $xCoM$ and the edge of the BoS, again independently in the AP and ML directions.

Figure 2. Margin of stability values throughout the entire 3 minute walking trial for a representative non-faller (left) and faller (right).

Table 1

Sample demographics for the entire population (n = 55), non-fallers (n=27), and faller (n=28) groups, and t-tests comparing non-fallers and fallers with bolded values representing significant ($p<0.05$) group differences. Values presented as mean (standard deviation).

	All PwMS (n=55)	Non-fallers (n=28)	Fallers (n=27)	Independent t-tests
Age	46.2 (9.7)	45.9 (9.5)	46.6 (10.1)	1.000
Gender (F/M)	39/16	20/8	19/8	0.931 [#]
BMI	28.3 (7.4)	28.0 (6.5)	28.6 (8.4)	1.000
T25FW (sec)	5.5 (1.6)	4.7 (0.9)	6.3 (1.8)	<0.001
EDSS	2.3 (1.2)	1.8 (0.9)	2.8 (1.2)	0.001
Berg Balance Scale	51.9 (6.3)	54.11 (3.07)	49.63 (7.81)	0.007
Years since diagnosis	11.1 (8.5)	10.5 (8.5)	11.7 (8.5)	0.625
Falls in previous 6 months	3.8 (9.5)	0.0 (0.0)	7.8 (12.5)	0.002
Preferred Walking Speed (m/s)	1.62 (0.29)	0.73 (0.23)	0.51 (0.30)	0.012

[#] gender compared using chi-squared test. BMI – body mass index; 25FTW – timed 25-foot walk; EDSS – Kurtzke's expanded disability status scale.

Table 2

Physiological impairment differences between fallers and non-fallers; values are presented as Median (IQR), with z- and p-values based on Mann-Whitney U-Test. Bolded values represent significant ($p < 0.05$) group differences. Due to data collection issues, motion capture data from one faller was excluded, spasticity from one faller was not collected, sensory EDSS subscale score was not collected for two fallers, and EDSS subscale scores were not recorded for three non-fallers.

	Non-Fallers (n=28)	Fallers (n=26)	Z	p
Vibration Threshold	3.0 (2.0)	5.5 (5.2)	-2.972	0.003
Sensorimotor Delays	118.57 (25.65)	143.20 (41.43)	-3.131	0.002
Spasticity	0.33 (0.66)	0.66 (0.66)	-2.397	0.017
Pyramidal	1 (1)	2 (1)	-3.054	0.002
Cerebellar	0 (1)	1 (2.5)	-2.958	0.003
Sensory	1 (1)	1 (2)	-1.223	0.221

Table 3

Correlation coefficient [spearman rho (p-value)] between sensorimotor impairment measures and Margin of Stability (MoS) dynamic balance measures for all groups. Bolded* values represent significant (p<0.01) correlations. Within group correlations are presented for significant group correlations only; FA – Fallers, NF – Non-fallers

	AP MoS (cm)		AP MoS CV (%)		ML MoS (cm)		ML MoS CV (%)
Vibration Threshold	-0.393 (0.003)*	FA: -0.372 (0.062) NF: -0.234 (0.234)	0.568 (<0.001)*	FA: 0.536 (0.005)* NF: 0.445 (0.018)	-0.039 (0.782)	0.507 (<0.001)*	FA: 0.256 (0.207) NF: 0.427 (0.023)
Sensorimotor Delays	-0.292 (0.032)		0.440 (0.001)*	FA: 0.329 (0.101) NF: 0.264 (0.175)	0.134 (0.336)	0.314 (0.021)	
Spasticity	-0.346 (0.011)		0.339 (0.013)		-0.130 (0.353)	0.100 (0.477)	
Pyramidal	-0.456 (0.001)*	FA: -0.408 (0.039) NF: -0.450 (0.024)	0.556 (<0.001)*	FA: 0.494 (0.010)* NF: 0.414 (0.040)	0.045 (0.755)	0.384 (0.005)*	FA: 0.107 (0.603) NF: 0.289 (0.161)
Cerebellar	-0.662 (<0.001)*	FA: -0.724 (<0.001)* NF: -0.288 (0.163)	0.639 (<0.001)*	FA: 0.721 (<0.001)* NF: 0.302 (0.142)	-0.025 (0.859)	0.259 (0.067)	
Sensory	-0.260 (0.072)		0.315 (0.027)		0.283 (0.049)	0.248 (0.086)	

AP – anterior-posterior; ML – mediolateral; CV – coefficient of variation.

Table 4

Correlation coefficient [spearman rho (p-value)] between sensorimotor impairment measures and nonlinear trunk variability measures for all groups. Bolded* values represent significant (p<0.01) correlations. Within group correlations are presented for significant group correlations only; FA – Fallers, NF – Non fallers

	AP LyE	ML LyE		VT LyE		AP SaEn	ML SaEn	VT SaEn		AP RMS	ML RMS	VT RMS	
Vibration Threshold	-0.013 (0.929)	0.408 (0.002)*	FA: 0.098 (0.628) NF: 0.569 (0.002)*	0.284 (0.038)		0.045 (0.747)	0.217 (0.111)	0.273 (0.043)		0.089 (0.520)	-0.178 (0.192)	-0.335 (0.013)	
Sensorimotor Delays	0.199 (0.158)	0.277 (0.041)		0.378 (0.005)*	FA: 0.246 (0.216) NF: 0.363 (0.063)	0.016 (0.908)	0.098 (0.479)	0.299 (0.027)		0.018 (0.897)	0.152 (0.268)	-0.355 (0.008)*	FA: -0.108 (0.601) NF: -0.135 (0.493)
Spasticity	0.119 (0.401)	0.150 (0.279)		0.214 (0.124)		0.019 (0.892)	0.189 (0.171)	0.309 (0.023)		-0.067 (0.629)	-0.214 (0.120)	-0.334 (0.015)	
Pyramidal	0.202 (0.160)	0.125 (0.367)		0.334 (0.017)		0.189 (0.179)	-0.143 (0.312)	0.477 (<0.001)*	FA: 0.329 (0.094) NF: 0.474 (0.017)	-0.093 (0.510)	-0.105 (0.459)	-0.485 (<0.001)*	FA: -0.196 (0.338) NF: -0.407 (0.047)
Cerebellar	0.180 (0.212)	0.344 (0.013)		0.412 (0.003)*	FA: 0.423 (0.028) NF: 0.278 (0.174)	-0.026 (0.857)	0.218 (0.120)	0.472 (<0.001)*	FA: 0.540 (0.004)* NF: 0.249 (0.230)	0.064 (0.651)	-0.316 (0.023)	-0.451 (0.001)*	FA: -0.284 (0.160) NF: -0.197 (0.334)
Sensory	0.195 (0.180)	-0.002 (0.988)		0.196 (0.177)		-0.051 (0.726)	-0.099 (0.493)	0.214 (0.136)		0.170 (0.239)	-0.113 (0.433)	-0.265 (0.066)	

AP – anterior-posterior; ML – medial-lateral; VT – vertical; RMS – root mean square; LyE – Lyapunov exponents; SaEn – sample entropy.