Hausdorff JM, Hillel I, Shustak S, Del Din S, Bekkers E, Pelosin E, Nieuwhof F, Rochester L, Mirelman A.

Everyday stepping quantity and quality among older adult fallers with and without mild cognitive impairment: Initial evidence for new motor markers of cognitive deficits?

***Journals of Gerontology. Series A: Biological Sciences & Medical Sciences* 2017**

DOI: https://doi.org/10.1093/gerona/glx187

The Journals of Gerontology: Series A: Brief Report

DOI: https://doi.org/10.1093/gerona/glx187

Published: 08 October 2017

Everyday stepping quantity and quality among older adult fallers with and without mild cognitive impairment: Initial evidence for new motor markers of cognitive deficits?

JM Hausdorff[1,2,4,5], I Hillel[1], S Shustak[1], S Del Din[6], E MJ Bekkers[7,8], E Pelosin[9,10], F Nieuwhof1[1], L Rochester[6], A Mirelman[1,3]

1 Center for the study of Movement, Cognition and Mobility, Department of Neurology, Tel Aviv Sourasky Medical Center

2 Department of Physical Therapy, and 3 Department of Neurology & Neurosurgery, Sackler School of Medicine. Tel Aviv University

4 Sagol School of Neuroscience, Tel Aviv University

5 Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center

6 Institute of Neuroscience, Clinical Ageing Research Unit, Newcastle University, Newcastle upon Tyne

7 KU Leuven, Department of Rehabilitation Sciences, Neuromotor Rehabilitation Research Group, Leuven, Belgium

8 Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Parkinson Centre Nijmegen (ParC), Nijmegen, The Netherlands

9 Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genova, Genova, Italy; 10 IRCCS San Martino Teaching Hospital, Genoa, Italy

11 Departments of Geriatric Medicine and Neurology, Radboud university medical center

Corresponding Author

Prof. Jeffrey Hausdorff

Center for the Study of Movement, Cognition, and Mobility

Department of Neurology Tel Aviv Sourasky Medical Center Tel Aviv, Israel

Email: jhausdor@tlvmc.gov.il

ABSTRACT

Background: Recent work demonstrated that the gait of people with mild cognitive impairment (MCI) differs from that of age-matched controls and, in general, that walking ability, as measured in the clinic, does not necessarily reflect actual, daily performance. We evaluated if the quantity and quality of everyday walking (i.e., community ambulation) differs in older adults with MCI, compared to age-matched controls.

Methods: Inclusion criteria included: age 65-90 years, able to walk at least 5 minutes unassisted, and >2 falls in the past 6 months. Subjects with MCI were included if they scored 0.5 on the Clinical Dementia Rating Scale. To assess stepping quantity and quality, subjects wore a tri-axial accelerometer on the lower-back for 7 days.

Results: Age and gender were similar ($p>0.10$) in MCI (n=36, 77.8±6.4 yrs; 27.8% men) and controls (n=100, 76.0±6.2 yrs; 22.0% men). As expected, Montreal Cognitive Assessment scores were lower ($p<0.001$) in MCI (21.31±4.05), compared to controls (25.81±2.64). Walking time was lower ($p=0.016$) in MCI (0.74±0.48 hrs/day), compared to controls (1.05±0.66 hrs/day). Within-bout walking (e.g., stride regularity) was less consistent ($p=0.024$) in MCI (0.51±0.14), compared to controls (0.58±0.14). Changes in stride regularity across bouts were lower ($p<0.001$) in MCI (0.13±0.04), compared to controls (0.17±0.01).

Conclusions: Older adults with MCI walk less and with a more variable within-bout and less variable across-bout walking pattern, as compared to cognitively-intact subjects matched with respect to age and gender. These findings extend previous clinical work and suggest that MCI affects both the quantity and quality of community ambulation.

Key words: gait, cognitive aging, physical activity, risk factors, accelerometers

INTRODUCTION

Cognitive deficits are the hallmark of mild cognitive impairment (MCI), a translational state between normal aging and dementia. Nonetheless, balance, gait and mobility are also altered in older adults with MCI (1, 2). Compared to controls, gait speed is reduced and gait variability is increased in older adults with MCI (3-5). In addition, gait apparently helps to predict cognitive decline and dementia (5-10), underscoring the relationship between motor and cognitive function in aging. While there is some indication that daily physical activity is also altered in MCI and that these changes may assist with the prediction of cognitive decline (11), little is known about the everyday, community ambulation stepping patterns of older adults with MCI.

Recent work demonstrated that the one-time assessment of gait and mobility in the clinic, i.e., mobility capacity, is only modestly correlated with daily life mobility function (12-16). At the same time, measures of daily life mobility function may help to capture risk of falls and neurodegeneration that are not reflected in a conventional, one-time clinical assessment of mobility (14-16). Based on these reports, we speculated that the everyday stepping pattern might also be affected by MCI. In this exploratory study, we addressed the following questions: 1) Is the amount of daily-living walking different in older adults with MCI and age-matched controls? 2) Is the quality of the walking pattern different in older adults with MCI and controls? and 3) Is everyday walking mobility related to performance on clinical tests of gait and balance?

METHODS

Participants

The present analysis is based on the baseline assessment of subjects who participated in a randomized controlled trial designed to reduce fall rates in older adults (17, 18). Briefly,

older adults at five clinical centers across five countries (Belgium, Israel, Italy, the Netherlands, and UK) were studied. Subjects were included if they were: a) age 65-90 years, b) self-report ability to walk at least 5 minutes unassisted, c) on stable medications, and d) had at least 2 falls in the previous 6 month, a requirement of the parent study, the RCT. Subjects with MCI were included if they scored 0.5 on the Clinical Dementia Rating Scale. Subjects were excluded if they had other significant comorbidities or clinical diagnosis of dementia or severe cognitive impairment.

For example, subjects were excluded if they had psychiatric co-morbidity (e.g., major depressive disorder as determined by DSM IV criteria), clinical diagnosis of dementia or other severe cognitive impairment, history of stroke, traumatic brain injury, Parkinson's disease, or other neurological disorders (other than MCI, for that group), acute lower back or lower extremity pain, peripheral neuropathy, rheumatic and orthopaedic diseases, or if they had an unstable medical condition including cardiovascular instability in the past 6 months. In addition, to avoid complications due to wear time of the accelerometer, we only included subjects with 7 day recordings. The study was approved by each clinical site's ethics committee. All participants provided informed written consent prior to testing.

Demographics and lab-based measures

Age and sex were recorded for each participant along with other subject characteristics. The Montreal Cognitive Assessment (MOCA) evaluated general cognitive function and sub-items were used to estimate visualspatial/executive function and attention. Gait speed, stride length, and stride time variability were measured during usual walking and the SF-36 was used to evaluate general health and physical function (17). The Short Physical Performance Battery, the two minute walk test, Mini-Balance Evaluation Systems Tests, and the Four Square Step Test assessed different aspects of balance, gait and mobility capacity in the lab (17).

Everyday walking data collection

At the end of the laboratory testing session, participants wore a water-proof, tri-axial accelerometer (Axivity AX3, York, UK; 23.0×32.5×7.6 mm; weight: 11 grams; 100 Hz sampling rate) for one week. The accelerometer was placed on the fifth lumbar vertebrae, held in place with a hydrogel adhesive, and covered with a Hypafix bandage. Participants were asked to continue their activities as usual. Upon completion of the recording, participants removed the device and sent it back to the local clinical site.

As previously described, we identified each bout of walking (as well as lying, standing, and sitting) throughout the week-long recording and then extracted measures that reflect the quantity and quality of walking (14, 15). To focus on steady-state walking and to compare in-lab walking with community ambulation, we focused on bouts that were at least 60 seconds long (14, 15). To evaluate the quality of the walking pattern, we extracted the step regularity and the peak value of the Fourier transformed acceleration in the vertical direction in each bout (14, 15); for both metrics, higher values reflect greater walking consistency. These measures can be determined without the need to identify individual steps and are related to the known increase in gait variability in MCI. Each subject's median value over the week was determined. In addition, to assess bout-to-bout variations over the week, we calculated the standard deviation of these two measures of walking quality for each subject.

Statistical analysis

Normality of data was tested with a Shapiro-Wilk test. Descriptive statistics are reported as means and standard deviations (SD). Spearman's correlations assessed the relationship between measures and multiple regression analyses evaluated the effect of covariates and the independence of measures. For the within-bout and across-bout measures of community ambulation walking quality, we used a Bonferonni corrected cut-off of $p=0.025$ to define the

level of significance; otherwise, a two-tailed p-value < 0.05 was considered statistically significant. Cohen's d was used to estimate effect size of group differences. Statistical analyses were performed using SPSS Version 22 (SPSS Inc.).

RESULTS

Age, sex, height, weight, body-mass-index and general health were similar in the two groups (Table 1). As expected, MOCA scores were lower in the MCI group. Measures of gait and mobility capacity, i.e., when tested in the lab, were worse or tended to be worse in the subjects with MCI, compared to the controls (Table 2).

Figure 1A shows an example of the bar code summary of the walking and other bouts recorded in an example subject with MCI and a control subject. As seen in this example, on a group level, the MCI group spent less time walking, as compared to the controls (see Table 3). Figure 1B-D shows an example walking bout of a subject with MCI and a control subject, along with the corresponding autocorrelation plot and frequency domain analyses. Stride time regularity and the peak in the frequency domain were lower in the subject with MCI, as compared to the control subject. Similar results were seen on a group level (see Table 3). Within bout walking consistency, as measured by both stride regularity and the peak in the frequency domain, were significantly lower in the MCI subjects than in the controls. For both measures of stepping quality, the across bout variability was lower in the subjects with MCI, compared to the controls (see Table 3).

The correlations between the mobility capacity and mobility function measures were generally modest to moderate (see Figure 2), suggesting that the mobility function measures captured different aspects of mobility than the in-lab, one-time measures. This possibility was also explored using multiple regression analyses. When included in the same regression model, measures of mobility capacity and mobility function were both independently

associated with group assignment (i.e., MCI vs. controls). For example, the Four Square Step Test ($p=0.025$) and the SD of the peak amplitude ($p=0.005$) were both related to group (i.e., MCI vs. controls).

Finally, we explored if the observed group differences in everyday stepping were related to cognitive function. When MOCA scores were added to the regression models, several of the group differences in everyday walking were no longer significant (see Table 3), suggesting the cognitive function may have influenced or mediated the across group changes in everyday stepping. We also explored if MCI subtype (amnestic vs. non-amnestic) might impact the stepping measures by dividing the subjects into those who scored above or below the MCI group's median value (and into a tertile split, comparing the worst and best groups) for visualspatial/ executive and attention sub-scores. There were no differences in the everyday walking pattern between these sub-groups both for the visualspatial/executive items and the attention items ($p>0.47$).

DISCUSSION

Consistent with previous findings (1-5), we observed that older adults with MCI performed poorer on in-lab measures of balance, gait and mobility than age-matched older adults who did not have MCI or dementia. Here, we find that not only is mobility capacity altered, but mobility function, as reflected in daily life ambulation, is also changed in MCI. Everyday stepping quantity and stepping quality were reduced in MCI, compared to age-matched controls. In addition, mobility capacity and mobility function were only moderately related to each other, similar to findings in other cohorts (12-16). We also found that measures of mobility capacity and function were independently associated with group assignment. Taken together, these results suggest that measures of everyday walking reflect aspects of mobility that are not simply a mirror-image of the gait and balance changes measured in the lab

setting. Interestingly, while MCI is conventionally defined by a lack of impact of the cognitive changes on activities of daily living, the present findings suggest that subtle, but measurable changes in everyday ambulation can be detected in MCI.

Several hypotheses putatively explain the association between gait changes, as measured in the lab, and cognitive impairment in older adults, in MCI, and in dementia (1-5). Some suggest that the relationship is simply a manifestation of changes in brain areas common to both the control of walking and to cognitive functioning. For example, reduced grey and white matter volumes and white matter hyper-intensities are observed in brain regions that contribute to gait dysfunction and to cognitive deficits. There is, however, increasing evidence that gait in aging relies on specific, higher-level cognitive functioning and that deficits in these brain regions (e.g., dorsal lateral pre-frontal cortex) contribute to the gait changes seen in MCI and dementia (7, 19).

The present work was not designed to probe mechanisms. Still, we found that changes in everyday (within-bout) walking consistency were no longer significant in models that adjusted for MOCA scores and that the everyday walking measures were only moderately correlated with in-lab measures. These findings suggest that brain regions and networks related to cognitive function are likely involved in the observed changes in daily walking and, further, that the specific mechanisms that contribute to changes in community ambulation are not identical to those that contribute to the changes quantified in the lab-setting. Perhaps other factors that were not measured (e.g., affect) explain these findings. Future work is needed to assess this question.

The present study has several limitations. For example, we used the Clinical Dementia Rating Scale to identify subjects with MCI, while other criteria are available. Our use of this definition may affect generalizability. In the future, it will be interesting to see if the observed findings are affected by the exact definition of MCI and if the results vary with MCI-subtype

(e.g., amnestic vs. non-amnestic). In exploratory analyses, when the MCI subjects were divided into those with relatively better or worse visualspatial/executive function or attention, there were no differences in everyday walking. suggesting that the results may be insensitive to MCI type. Still, a larger sample and other ways of characterizing subjects as amnestic or non-amnestic should be investigated in the future. Because subjects in the present study were recruited to participate in a falls intervention study, all of the subjects had a history of multiple falls. While this history was controlled for in that subjects in both groups met this criteria, and falls are common in MCI (20), in the future, it will be important to assess whether the observed findings generalize to people with MCI who do not have a history of falls. The cross sectional nature of the present analyses also needs to be kept in mind. Finally, while we applied previously validated methods to detect everyday walking (14, 15), it is possible that other activities may have been identified as walking.

The present findings suggest that everyday stepping quantity and stepping quality, both within and across bout metrics, are related to MCI and are not strongly related to in-lab measures of gait and balance. Prospective studies are needed to determine if and how these measures of everyday walking can augment the prediction of cognitive decline and the progression to dementia, potentially addressing the need for additional markers of future cognitive impairment in older adults (7, 19, 20).

REFERENCES

1. Mirelman A, Weiss A, Buchman AS, Bennett DA, Giladi N, Hausdorff JM. Association between performance on Timed Up and Go subtasks and mild cognitive impairment: further insights into the links between cognitive and motor function. J Am Geriatr Soc. 2014;**62**:673-678.

2. Pedersen MM, Holt NE, Grande L, Kurlinski LA, Beauchamp MK, Kiely DK, *et al.* Mild cognitive impairment status and mobility performance: an analysis from the Boston RISE study. J Gerontol A Biol Sci Med Sci. 2014;**69**:1511-1518.

3. Allali G, Launay CP, Blumen HM, Callisaya ML, De Cock AM, Kressig RW, *et al.* Falls, Cognitive Impairment, and Gait Performance: Results From the GOOD Initiative. J Am Med Dir Assoc. 2017;**18**:335-340.

4. Montero-Odasso M, Bergman H, Phillips NA, Wong CH, Sourial N, Chertkow H. Dualtasking and gait in people with mild cognitive impairment. The effect of working memory. BMC Geriatr. 2009;**9**:41.
5. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, *et al.* Gait dysfunction in mild cognitive impairment syndromes. J Am Geriatr Soc. 2008;**56**:1244-1251.
6. Montero-Odasso MM, Sarquis-Adamson Y, Speechley M, Borrie MJ, Hachinski VC, Wells J, *et al.* Association of Dual-Task Gait With Incident Dementia in Mild Cognitive Impairment: Results From the Gait and Brain Study. JAMA Neurol. 2017.
7. Kikkert LH, Vuillerme N, van Campen JP, Hortobagyi T, Lamoth CJ. Walking ability to predict future cognitive decline in old adults: A scoping review. Ageing Res Rev. 2016;**27**:1-14.
8. Savica R, Wennberg AM, Hagen C, Edwards K, Roberts RO, Hollman JH, *et al.* Comparison of Gait Parameters for Predicting Cognitive Decline: The Mayo Clinic Study of Aging. J Alzheimers Dis. 2017;**55**:559-567.
9. Verghese J, Wang C, Lipton RB, Holtzer R. Motoric cognitive risk syndrome and the risk of dementia. J Gerontol A Biol Sci Med Sci. 2013;**68**:412-418.
10. Marquis S, Moore MM, Howieson DB, Sexton G, Payami H, Kaye JA, *et al.* Independent predictors of cognitive decline in healthy elderly persons. Arch Neurol. 2002;**59**:601-606.
11. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology. 2012;**78**:1323-1329.
12. Giannouli E, Bock O, Mellone S, Zijlstra W. Mobility in Old Age: Capacity Is Not Performance. Biomed Res Int. 2016;**2016**:3261567.
13. van Lummel RC, Walgaard S, Pijnappels M, Elders PJ, Garcia-Aymerich J, van Dieen JH, *et al.* Physical Performance and Physical Activity in Older Adults: Associated but Separate Domains of Physical Function in Old Age. PLoS One. 2015;**10**:e0144048.
14. Weiss A, Brozgol M, Dorfman M, Herman T, Shema S, Giladi N, *et al.* Does the evaluation of gait quality during daily life provide insight into fall risk? A novel approach using 3-day accelerometer recordings. Neurorehabil Neural Repair. 2013;**27**:742-752.
15. Weiss A, Herman T, Giladi N, Hausdorff JM. Objective assessment of fall risk in Parkinson's disease using a body-fixed sensor worn for 3 days. PLoS One. 2014;**9**:e96675.
16. van Schooten KS, Pijnappels M, Rispens SM, Elders PJ, Lips P, van Dieen JH. Ambulatory fall-risk assessment: amount and quality of daily-life gait predict falls in older adults. J Gerontol A Biol Sci Med Sci. 2015;**70**:608-615.
17. Mirelman A, Rochester L, Reelick M, Nieuwhof F, Pelosin E, Abbruzzese G, *et al.* VTIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled trial. BMC Neurol. 2013;**13**:15.
18. Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, *et al.* Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. Lancet. 2016;**388**:1170-1182.
19. Belghali M, Chastan N, Davenne D, Decker LM. Improving Dual-Task Walking Paradigms to Detect Prodromal Parkinson's and Alzheimer's Diseases. Front Neurol. 2017;**8**:207.
20. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. Arch Phys Med Rehabil. 2012;**93**:293-299.

Table 1: Subject characteristics			
	Controls (n=100)	**MCI (n=36)**	**P-value**
Age (yrs)	76.0±6.2	77.8±6.4	0.145
Gender (% men)	22.0%	27.8%	0.506
Education (yrs)	13.4±3.9	10.9±2.9	<0.001
Height (m)	1.65±0.01	1.64±0.08	0.897
Weight (kg)	70.5±13.4	70.9±13.9	0.883
Body-mass-index (kg/m^2)	25.9±4.2	26.2±4.6	0.787
Montreal Cognitive Assessment: Total score	25.8±2.6	21.3±4.1	<0.001
Montreal Cognitive Assessment: visuospatial/executive score	4.13±0.1	3.11±0.21	<0.00001
Montreal Cognitive Assessment: Attention score	5.65±0.6	4.89±0.21	<0.001
Number of falls (in past 6 months)	2.96± 2.14	2.08±0.68	0.166
SF-36 General Health	62.12±1.94	57.90±3.48	0.143
SF-36 Total Physical Health	62.97±1.73	58.71±3.04	0.221
SF-36 Physical Function	67.75±2.38	60.15±4.28	0.188

Table 2: In lab measures of gait and mobility capacity				
	Controls (n=100)	**MCI (n=36)**	**P-value**	**Effect Size**
Gait speed (m/sec)	1.06±0.24	0.90±0.29	0.017	0.601
Stride Length (m)	1.16±0.20	1.02±0.22	0.004	0.666
Stride time variability (%)	2.24±1.92	2.78±2.35	0.117	0.252
Short Physical Performance Battery (SPPB)	9.42±2.03	8.44±2.74	0.070	0.406
Mini Best test of balance (MiniBest)	23.0±5.87	19.8±6.4	0.008	0.521
Two min walk distance (m)	133.1±32.0	118.2±33.1	0.019	0.457
Four Square Step Test (sec) (FSST)	11.2±5.1	15.7±10.1	0.002	0.562

Table 3: Measures of mobility function derived from the 7 day recordings					
		Controls (n=100)	**MCI (n=36)**	**P-value**	**Effect Size**
Walking quantity	Time spent walking (hrs/day) [from walking bouts≥60 sec]	1.05±0.66	0.74±0.48	0.016 [b]	0.537
Within Bout Walking Quality	Stride Regularity (unitless)	0.58±0.14	0.51±0.14	0.024	0.500
	Peak amplitude (g^2/Hz)	0.72±0.21	0.62±0.21	0.015	0.476
Across Bout Variability of Walking Quality	SD of stride regularity (unitless)	0.17±0.01	0.13±0.04	<0.001 [a, b, c]	1.372
	SD of peak amplitude (g^2/Hz)	0.18±0.01	0.12±0.05	<0.001 [a, b, c]	1.664

a, b, c: Group differences persisted after adjusting for the MOCA total score (or the visuospatial/executive score or attention score; all 3 MOCA scores behaved similarly), years of education and two minute walk distance (a proxy for cardiovasvular function), respectively.

FIGURES

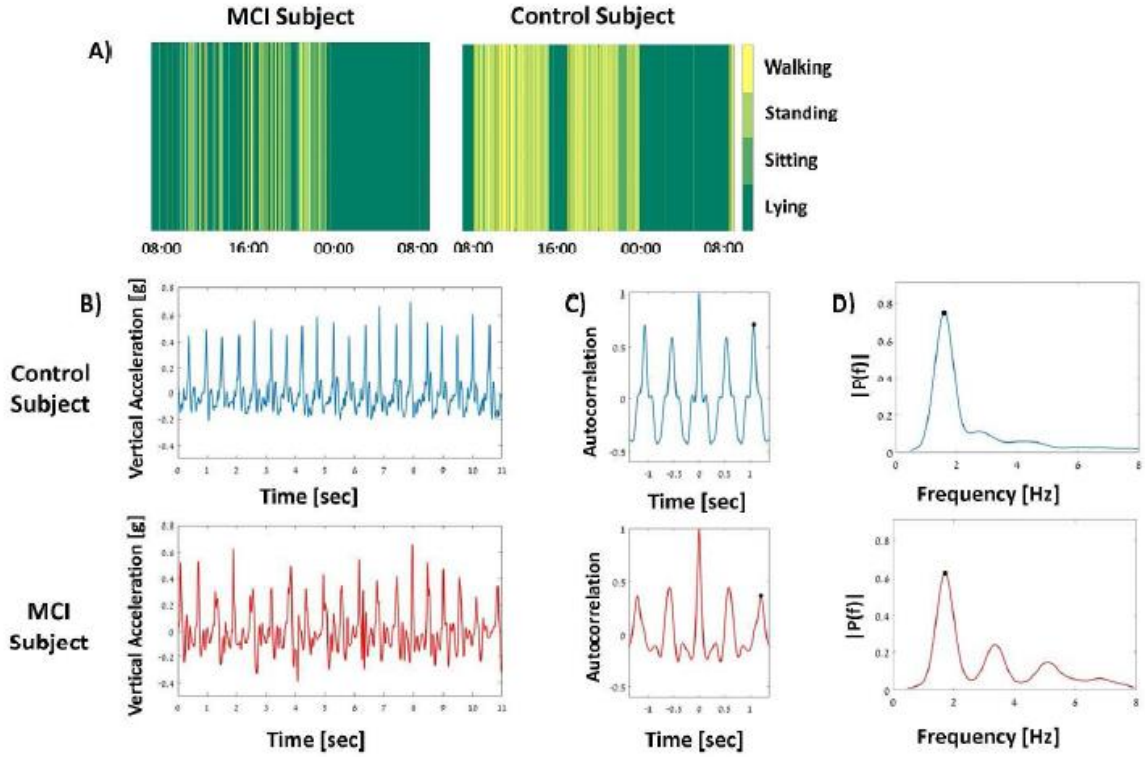

Figure 1: Example steps in the processing of the 7 day accelerometer data for a subject with MCI and a control subject. A) Barcode plot illustrating daily activity for one day; B) Raw vertical acceleration signal in one bout of walking; C) Autocorrelation plot used to determine stride regularity in a bout; D) Frequency domain plot used to determine the peak in the frequency domain for a bout of walking.

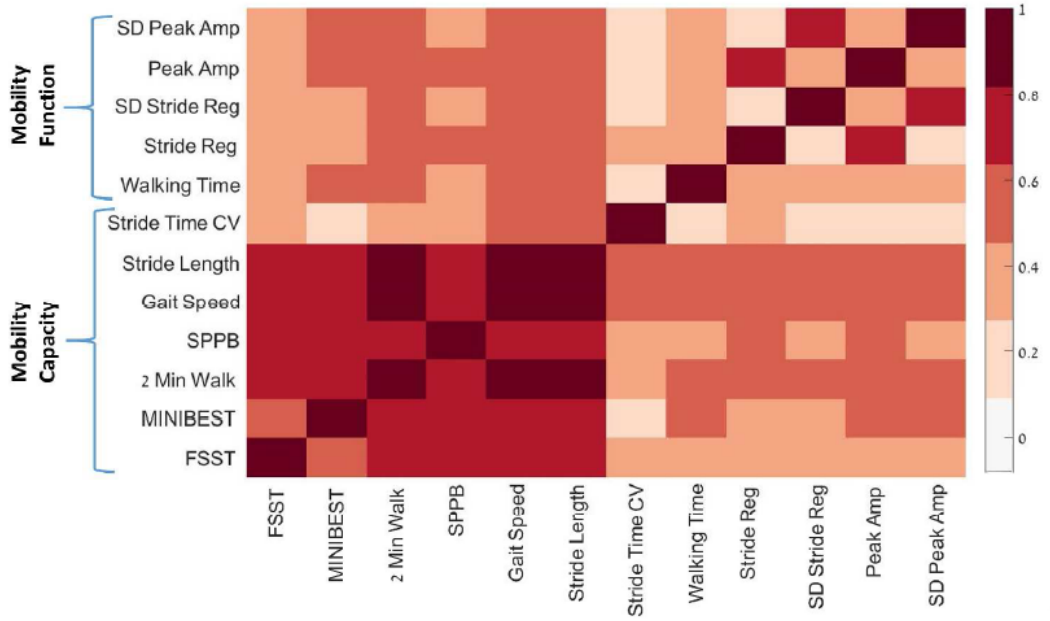

Figure 2: Heat map showing the Spearman correlation coefficients between measures of mobility capacity (i.e., those measured in the lab) and mobility function (metrics derived from the 7 day recordings). Darker pixels reflect higher correlation values. Note that while the mobility capacity measures tended to be moderate to highly correlated with each other, they were not strongly correlated with the mobility function measures (see, for example, the top left quadrant of the map). Stride reg: stride regularity; amp: amplitude.