Published in final edited form as:

Arch Phys Med Rehabil. 2017 November ; 98(11): 2160–2166. doi:10.1016/j.apmr.2017.07.004.

How do pain, fatigue, depressive, and cognitive symptoms relate to well-being and social and physical functioning in the daily lives of individuals with multiple sclerosis?

Anna L. Kratz, PhD¹, Tiffany J. Braley, MD, MS³, Emily Foxen-Craft, PhD⁴, Eric Scott, PhD⁴, John Murphy III¹, and Susan L. Murphy, ScD^{1,2}

¹Department of Physical Medicine & Rehabilitation, University of Michigan, Ann Arbor, MI

²VA Ann Arbor Health Care System, Geriatric Research, Education, and Clinical Center, GRECC, Ann Arbor, MI

³Department of Neurology, University of Michigan, Ann Arbor, MI

⁴Department of Anesthesiology, University of Michigan, Ann Arbor, MI

Abstract

Objective—To examine the relative association between daily change in pain, fatigue, depressed mood, and cognitive function, and four outcomes (positive affect and well-being, ability to participate in social roles and activities, upper extremity (UE) functioning, and lower extremity (LE) functioning).

Design—Repeated-measures observational study including a baseline lab visit, followed by seven days of home monitoring that included ecological momentary assessment (EMA) of symptoms (pain, fatigue, depressed mood, and cognitive function) and end-of-day diary surveys of outcomes of interest. Multilevel mixed models were used to test study hypotheses.

Setting—General community.

Participants—Ambulatory adults (n=102) with MS recruited through [masked] and the surrounding community.

Interventions—Not applicable.

Main Outcome Measure(s)—Customized short-forms of the Neuro-QOL Positive Affect and Well-Being, Upper Extremity Functioning, and Lower Extremity Functioning item banks and the PROMIS Ability to Participate in Social Roles and Activity item banks, adapted for daily use and administered as end-of-day diaries.

Corresponding Author: Anna L. Kratz, Ph.D., Department of Physical Medicine and Rehabilitation, University of Michigan, NCRC B14 G218, 2600 Plymouth Rd., Ann Arbor, MI, 48101, phone: 734-647-5982, alkratz@med.umich.edu.
Contact Dr. Kratz for article reprints.

Conflicts of Interest: The authors have no conflicts of interest to declare.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—Above and beyond the effects of demographic and clinical covariates, daily pain was associated with three of the four outcomes; days of higher pain were related to lower same-day social participation ($B=-1.00$, $p=0.002$), UE functioning ($B=-1.04$, $p=0.01$), and LE functioning ($B=-0.71$, $p=0.04$). Daily fatigue and depressed mood were independently related to daily positive affect and well-being; days of worse fatigue ($B=-0.54$, $p=0.006$) and depressed mood ($B=-1.17$, $p<0.0001$) were related to lower same-day well-being.

Conclusions—Results demonstrate the role of fluctuations in symptoms in daily functioning and quality of life of individuals with MS. Daily increases in pain intensity are related to social and physical functioning, whereas increases in fatigue and depressed mood is related to daily lower levels of well-being. Findings implicate a person-centered approach to monitoring and treating symptoms.

Keywords

multiple sclerosis; symptoms; social participation; well-being; ecological momentary assessment

Multiple Sclerosis (MS) is a progressive autoimmune disease of the central nervous system¹ that is associated with physical impairment and chronic pain^{2–5}, fatigue^{6–11}, depressed mood^{12–14}, and cognitive problems^{15–20}. Research has demonstrated associations between these symptoms and numerous outcomes, including employment, disability, social impairment, life satisfaction, interference with daily activities, general mental and physical health, and community integration^{2,17,21–29}.

Despite recent advances, important questions remain regarding how symptoms relate to functioning and well-being in MS. Current cross-sectional research is limited to addressing between-level questions such as, “do people *who* report higher pain also report lower social functioning?” However, other questions, such as “*when* a person has a day of higher than usual pain, how does that person’s social functioning change?” are highly clinically relevant and important to patients for whom comparisons of their experience to other people with MS are not as salient as how their experience compares day-to-day. Additionally, many studies have focused on the association between one or two symptoms on an outcome in isolation³⁰; examination of complex daily interrelations between multiple symptoms and functional outcomes is needed to inform and tailor symptom management, including approaches to self-management.

To address limitations of the current literature regarding association of symptoms and functional and affective outcomes in MS, we used a combination of *ecological momentary* (real-time) *assessment* (EMA) of symptoms, and *end-of-day (EOD) diary* surveys of functional and affective outcomes. These methods can increase measurement reliability and facilitate better understanding of daily relations between symptoms and functioning. The main aim of this paper was to examine the relative associations of four common MS symptoms – pain, fatigue, depressed mood, and cognitive function – to affective and functional outcomes in the daily lives of individuals with MS. Specifically, we examined how daily fluctuations in symptoms related to daily positive affect and well-being (PAWB), ability to participate in social roles and activities (SRA), and upper-extremity (UE) and lower-extremity (LE) functioning. *Based on findings from previous research, we predicted*

that: 1) greater daily fatigue would be associated with worse same-day SRA and UE and LE functioning^{21,23,26,27}; 2) greater daily pain would be associated with worse same-day SRA and UE and LE functioning^{21,22}; 3) greater daily depressed mood would be associated with worse same-day SRA and UE and LE functioning^{21,24}; and 4) worse daily cognitive function would be associated with worse same-day SRA^{17,26,28,29}. The literature does not clearly delineate which symptoms relate to PAWB in MS; however, given the inverse relationship between PAWB and depression in clinical practice, we expected that daily depressive symptoms would be the strongest predictor of same-day PAWB.

Methods

Participants

Adults with medically-confirmed MS were recruited. Inclusion criteria were: 18 years old; able to speak/read English at a 6th grade level; and ambulatory with minimal assistance (e.g. cane/walker). Exclusion criteria were: MS exacerbation within the past 30 days; atypical sleep/night wake/day pattern; diagnosis of rheumatological disease or fibromyalgia; and changes in disease-modifying therapy during the study. Participants were recruited through flyers in community and clinics, an existing research participant registry, electronic medical record queries followed by opt-out letters to eligible patients, physician referrals, and outreach efforts at community events (e.g. National MS Society walks).

Study Procedures

The primary aim of the broader observational, repeated measures week-long study was to examine the daily variability³¹, covariance³², and association of MS symptoms with functional outcomes. The study was conducted at [masked]; data were collected between October 2014 and March 2016. Institutional Review Board approval was granted prior to starting the study.

Volunteers were screened over the telephone and eligible individuals attended an in-person visit where they underwent informed consent procedures, completed baseline surveys, and were trained on how to complete the “home monitoring” phase of data collection. At the end of the visit, participants were given a PRO-Diary^a (wrist-worn accelerometer enhanced with a user interface for self-report data entry; CamNtech, Cambridge, United Kingdom), logbook, and prepaid box for returning the PRO-Diary. The home monitoring period began on the day following the in-person visit.

During the 7-day home monitoring, participants wore the PRO-Diary on their non-dominant wrist continuously, except while swimming or bathing, and entered pain, fatigue, depressed mood, and cognitive functioning ratings five times a day: upon waking, 11AM, 3PM, 7PM, and at bed time. The PRO-Diary collected and stored accelerometer data and timestamped self-report data until it was returned to the lab, where the data was downloaded. Participants were alerted by alarm when it was time to enter 11AM, 3PM, and 7PM ratings; participants initiated ratings at wake and bed times.

^aCamNtech Ltd., Upper Pendrill Court, Ermine Street North, Papworth Everard, Cambridge, CB23 3UY, United Kingdom

Each night of home monitoring, participants completed a brief EOD diary of validated survey measures by logging onto Qualtrics, an online research tool that enables secure data entry and storage³³. Participants without internet access were provided with 7 paper EOD diaries and completed one diary each night. To validate paper diaries, participants mailed the previous night's diary the following day; post office date stamps confirmed the timing of diary completion. Participants were compensated for their study participation.

Measures

Baseline Demographic and Clinical Measures—On a demographic survey, participants self-reported their age, sex, race, and the year that their MS was diagnosed. Each person's MS subtype was retrieved from their medical records.

Ecological Momentary Assessment Measures—As described elsewhere, four EMA measures were developed for this study; they demonstrated good convergent with standardized surveys in this sample³¹.

Pain: Participants rated their “level of pain right now” on a scale where 0 = “no pain” to 10 = “worst pain imaginable.”

Fatigue: Participants rated their level of fatigue right now” on a scale from 0 = no fatigue” to 10 = “extremely severe fatigue.”

Depressed Mood: Participants rated their “level of depression right now” on a scale from 0 = “not at all depressed” to 10 = “extremely depressed.”

Cognitive Function: Participants rated their perceived “level of cognitive functioning right now” on a scale from 0 = “Good: my thinking is sharp and quick” to 10= “Bad: my thinking is very difficult or slow.”

End-of-Day Diary Measures—Scores on all diary measures described below were calculated by summing the item responses and converting the total score to a T-Score metric (Mean=50, SD=10) via the scoring service provided by AssessmentCenter.net.

Ability to Participate in Social Roles and Activities (SRA): Social participation was assessed with four items from the Patient Reported Outcomes Measurement Information System (PROMIS) v2.0 Ability to Participate in Social Roles and Activities item bank, which has demonstrated good psychometric qualities in multiple clinical conditions^{34–36}, adapted for daily use. Participants were asked to indicate, for “Today” the frequency (=never to 5=always) with which they experienced problems: “doing all of the family activities that I want to do”, “doing all of the activities with friends that are really important to me”, “doing all the leisure activities with others that I want to do”, “doing all of the work that I feel I should do (include work at home)”. Items were reverse-scored; higher scores indicated higher SRA.

Positive Affect and Well-Being (PAWB): Nine items from the Quality of Life in Neurological Disorders (Neuro-QOL) v1.0 Positive Affect and Well-Being item bank³⁷ were

used to assess daily PAWB. Respondents indicated, for “Today” the frequency (1=never to 5=always) with which: “I had a sense of well-being,” “I felt hopeful,” “My life was satisfying,” “My life had purpose,” “My life had meaning,” “I felt cheerful,” “My life was worth living,” “I had a sense of balance in my life,” and “Many areas of my life were interesting to me.” Items responses were summed; higher scores indicated higher PAWB.

Upper Extremity (UE) Functioning: Eight items from the Neuro-QOL Upper Extremity Functioning item bank³⁸ were used to assess daily UE functioning. Respondents indicated their daily level of difficulty completing UE motor tasks on a scale from 1=without any difficulty to 5=unable to do. Tasks were: turn a key in a lock; brush your teeth; make a phone call using a touch tone key pad; pick up coins from a table top; write with a pen or pencil; open and close a zipper; wash and dry your body; and shampoo your hair. Items were reverse-scored so that higher scores indicated greater ability..

Lower Extremity (LE) Functioning: Eight items from the Neuro-QOL Lower Extremity Functioning item bank³⁸ assessed daily LE functioning. Respondents indicated their daily level of difficulty completing LE motor tasks on a scale from 1=without any difficulty to 5=unable to do. Tasks were: get on and off the toilet; step up and down curbs; get in and out of a car; get out of bed into a chair; push open a heavy door; run errands and shop; get up off the floor from lying on your back without help; and go for a walk of at least 15 minutes. Items were reverse scored so that higher scores indicated greater ability; responses were summed and converted to T-Scores. Both the Neuro-QOL UE and LE measures showed evidence of good validity in terms of correspondence with physical performance tasks in MS³⁹.

Data Analyses

Preliminary Data Analyses—Descriptive statistics were generated for all variables. Difference scores for maximum and minimum daily values of study variables were calculated for each person; descriptive statistics of difference scores characterizes within-person variability. In addition, relative amounts of between- and within-person variance (i.e., proportion of total variance accounted for by the intercept versus residual variance) in EOD diary measures were calculated to determine whether there was adequate within-person variance to support primary analyses. Rates of missing data were calculated.

Multilevel random effects modeling (MLM; SAS PROC MIXED software) was used to examine same-day associations between EMA-reported symptoms and PAWB, SRA, and UE and LE functioning. MLM retains cases with missing within-person data, accounts for autocorrelation between observations, and allows for modelling of fixed and random effects. EMA variables were person-day-centered, by subtracting average EMA values for a day from a person’s weekly average, to create deviation scores for daily pain, fatigue, depressed mood, and cognitive function. Centered values indicated daily change relative to each person’s own weekly average (e.g., a higher or lower pain day than usual)^{32,33}, which allows for the examination of within-person and between-person variance separately^{40,41}. Prior to conducting primary analyses, which included all symptoms in the same model, bivariate analyses examining associations between each symptom and daily outcome were conducted.

Primary Data Analyses—Four MLMs for same-day associations, one for each outcome, were constructed. The predictors of interest were the same-day centered values for the four EMA symptom ratings. Person-averaged EMA symptom were included in all models to account for between-person symptom levels. Clinical and demographic variables (age, sex, MS duration, MS subtype) that were deemed clinically-relevant to symptom experience were included as covariates. Dummy codes⁴² were created for sex (male=reference) and MS subtype (all progressive types=reference). SAS version 9.4^b (SAS Institute, Cary, NC, USA) was used.

Results

Preliminary Results

One hundred and eight participants enrolled and completed baseline measures. Of these, six did not complete any of the EOD diaries; analyses were completed on the remaining 102 participants who had complete EMA and diary data. Sixty-two participants had no missing diaries and 21 had one missing diary; across the whole sample 87.1% (628/721) of the EOD diaries were completed. For EMA, 84.9% (3031/3570 [35 points X 102 participants]) of possible data points were complete. Rates of missing data in this study were low and similar to those in other clinical studies^{43–46}. Within-person variance accounted for 25% of the total variance in PAWB, 33% of the variance in SRA, 28% of the variance in UE functioning, and 18% of the total variance in LE functioning.

The average age of the sample was ~45 years and most were white, females, with relapsing remitting MS (Table 1). Relative to the general population (M=50, SD=10), sample scores on Neuro-QOL and PROMIS measures indicated slightly higher than average PAWB, much lower SRA, and somewhat lower UE and LE functioning; however, there was a wide range for all of outcomes represented in the sample.

Within-person daily associations between symptoms and functioning

Bivariate results—In isolation, each symptom was significantly related to PAWB and SRA. Days of higher pain, fatigue, depressed mood, and cognitive function were related to lower PAWB and SRA (Table 2). Pain and depressed mood were both significantly inversely related to both UE and LE functioning. In contrast, fatigue and cognitive function were only significantly inversely related to LE functioning.

Multivariable results—Results for PAWB indicate that those who reported greater depressed mood (i.e. average depressed mood) reported lower daily well-being ($B=-3.01$, $p<0.001$; Table 3). Day-level fatigue ($B=-0.54$, $p=0.006$) and depressed mood ($B=-1.17$, $p<0.0001$) were both associated with well-being; days of higher fatigue or depressed mood were related to lower same-day PAWB.

Progressive MS subtype and older age were both related to lower SRA (Table 3). Average levels of fatigue ($B=-1.73$, $p=0.005$) and depressed mood ($B=-1.55$, $p=0.006$) were related

^bSAS, SAS Campus Drive, Building T, Cary, NC 27513

to SRA; those who were more fatigued or more depressed in general reported lower daily SRA. On a daily basis, however, only changes in pain intensity related to same-day participation ($B=-1.00$, $p=0.002$), with days of higher pain associated with significantly lower same-day SRA.

Progressive MS was related to lower UE functioning (Table 4) and average pain and daily change in pain were the only symptom variables that predicted LE functioning. People who reported generally higher levels of pain ($B=-1.04$, $p=0.01$) reported worse LE functioning and days of higher pain ($B=-0.71$, $p=0.04$) were significantly related to worse same-day LE functioning.

Discussion

Building on previous studies showing between-person associations among symptoms and emotional, physical, and social functioning, this study is the first to demonstrate *within-person* associations of symptoms with diverse, clinically-relevant outcomes in the daily lives of people with MS^{2,21–27}. Pain played a prominent role in daily social and physical functioning, but no notable role in same-day variation in emotional well-being. Increased daily pain intensity was independently associated with lower social, UE, and LE functioning above and beyond the effects of demographic and clinical variables, and between- and within-person levels of all other symptoms. As expected, increases in daily depressed mood were related to decreased PAWB. Daily fatigue was also negatively related to well-being, but was not related to any other daily outcomes.

Findings for daily pain are consistent with previous studies showing that pain is highly prevalent in MS and very impactful^{2–5}. By using a within-person design, this study provided new information about the associations between symptoms and functional/affective variables. For instance, between-person studies have demonstrated an association between pain and poorer mental health but not community integration²⁷, whereas findings for daily pain in this study were not associated with daily changes in affect, but were associated with daily changes in social participation. Overall findings for fatigue were consistent with previous cross-sectional studies showing that fatigue is related to poorer mental health and lower social participation at home;²⁷ however, daily fluctuations in fatigue were not linked with same-day PAWB and SRA.

An unexpected outcome was the lack of same-day association between perceived cognitive function and any of the outcomes. Cognitive problems, both the subjective experience of cognitive decline and objectively documented decline, are common among people with MS, and are associated with worse psychosocial and physical quality of life^{47,48,27}. Although we expected fatigue to be the strongest predictor of daily outcomes, we did expect that days of slow or foggy thinking might be related to worse affective and functional outcomes. In previous cross-sectional work in MS, perceived memory problems were only related to “productive” aspects of community integration, not to mental health or social or home aspects of integration²⁷. Thus, it may be that daily fluctuations in perceived cognitive function are related to relatively narrow aspects of functioning that were not assessed in this study, such as the ability to effectively do one’s job or complete schoolwork.

Clinically, there are several implications to better assess and monitor symptoms to improve affective, social, and physical functioning in those with MS. The first is that scores on standard surveys of symptoms often used to screen for “clinically significant” symptoms, fail to provide a full clinical picture of how symptoms may be interfering with daily quality of life for any given patient. Rather, a patient-centered approach is necessary to assess how fluctuations from a person’s own “baseline” may be more consequential in terms of how they feel and are able to function on a daily basis. From this perspective, a person who scores in the sub-clinical range on a pain survey (an indicator of their pain status relative to other patients), but describes having occasional “bad pain days”, may benefit from interventions to help them self-manage their pain, through physical, medical, and psychosocial means. A second clinical implication is the importance of assessing a broad range of symptoms because of their inter-relationships with various aspects of well-being and function²⁷. For example, a patient whose primary complaint is severe fatigue may also be experiencing the impact of fluctuations of lower-level symptoms, which should not be overlooked by the clinician.

Study Limitations

Predominance of white, female participants with low average symptom levels may limit generalizability to more diverse samples or those with more severe symptoms burden. However, this sample is similar to previous MS study samples in terms of average scores on standardized symptom surveys³¹. Although we measured four common MS symptoms, not all clinically-relevant symptoms (e.g., weakness) were considered. Studies that examine a more comprehensive range of symptoms and social, emotional, and physical outcomes are sorely needed in order to fully elucidate the daily association between symptoms and quality of life in MS. Additionally, future studies that incorporate longer monitoring periods may provide more information about how symptoms and functioning are associated in MS.

Conclusions

In this first-of-its-kind study of same-day links between symptoms and indicators of quality of life in MS, fluctuations in pain emerged as an independent predictor of both social and physical functioning. In contrast, daily fluctuations in fatigue and depressed mood were linked only to same-day emotional well-being. Findings indicate the need for more person-centered or individualized assessment and treatment of symptoms and symptom impact.

Acknowledgments

Sources of Funding: Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health under award number R03NR014515; PI: Kratz. Dr. Kratz was supported during manuscript preparation by a grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (award number K01AR064275). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The manuscript submitted does not contain information about medical device(s).

Abbreviations

DMT	disease-modifying therapy
EMA	ecological momentary assessment

EOD	end-of-day
MS	multiple sclerosis
PROMIS	Patient Reported Outcomes Measurement Information System
Neuro-QOL	Quality of Life in Neurological Disorders
p PAWB	positive affect and well-being
SRA	Ability to participate in social roles and activities
UE	Upper extremity
LE	Lower extremity

References

1. National Multiple Sclerosis Society. 2011, 2012. <http://www.nationalmssociety.org/index.aspx>
2. Ehde DM, Gibbons LE, Chwastiak L, Bombardier CH, Sullivan MD, Kraft GH. Chronic pain in a large community sample of persons with multiple sclerosis. *Mult Scler*. Dec; 2003 9(6):605–611. [PubMed: 14664474]
3. Ehde DM, Osborne TL, Hanley MA, Jensen MP, Kraft GH. The scope and nature of pain in persons with multiple sclerosis. *Mult Scler*. Oct; 2006 12(5):629–638. [PubMed: 17086910]
4. Ehde DM, Osborne TL, Jensen MP. Chronic pain in persons with multiple sclerosis. *Phys Med Rehabil Clin N Am*. May; 2005 16(2):503–512. [PubMed: 15893684]
5. Hirsh AT, Turner AP, Ehde DM, Haselkorn JK. Prevalence and impact of pain in multiple sclerosis: physical and psychologic contributors. *Arch Phys Med Rehabil*. Apr; 2009 90(4):646–651. [PubMed: 19345781]
6. Kos D, Kerckhofs E, Nagels G, D'Hooghe MB, Ilsbroux S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair*. Jan-Feb;2008 22(1):91–100. [PubMed: 17409388]
7. Krupp LB. Fatigue in multiple sclerosis: definition, pathophysiology and treatment. *CNS Drugs*. 2003; 17(4):225–234. [PubMed: 12665396]
8. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol*. Apr; 1988 45(4):435–437. [PubMed: 3355400]
9. Krupp LB, Christodoulou C. Fatigue in multiple sclerosis. *Curr Neurol Neurosci Rep*. May; 2001 1(3):294–298. [PubMed: 11898532]
10. Krupp LB, Serafin DJ, Christodoulou C. Multiple sclerosis-associated fatigue. *Expert Rev Neurother*. Sep; 2010 10(9):1437–1447. [PubMed: 20819014]
11. MacAllister WS, Krupp LB. Multiple sclerosis-related fatigue. *Phys Med Rehabil Clin N Am*. May; 2005 16(2):483–502. [PubMed: 15893683]
12. Minden SL, Orav J, Reich P. Depression in multiple sclerosis. *Gen Hosp Psychiatry*. Nov; 1987 9(6):426–434. [PubMed: 3692149]
13. Patten SB, Beck CA, Williams JV, Barbui C, Metz LM. Major depression in multiple sclerosis: a population-based perspective. *Neurology*. Dec 9; 2003 61(11):1524–1527. [PubMed: 14663036]
14. Sadovnick AD, Remick RA, Allen J, et al. Depression and multiple sclerosis. *Neurology*. Mar; 1996 46(3):628–632. [PubMed: 8618657]
15. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Arch Neurol*. Oct; 2001 58(10):1602–1606. [PubMed: 11594918]
16. Bagert B, Camplair P, Bourdette D. Cognitive dysfunction in multiple sclerosis: natural history, pathophysiology and management. *CNS Drugs*. 2002; 16(7):445–455. [PubMed: 12056920]

17. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol.* Dec; 2008 7(12):1139–1151. [PubMed: 19007738]
18. Huijbregts SC, Kalkers NF, de Sonnevile LM, de Groot V, Reuling IE, Polman CH. Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. *Neurology.* Jul 27; 2004 63(2):335–339. [PubMed: 15277630]
19. Kesselring J, Klement U. Cognitive and affective disturbances in multiple sclerosis. *J Neurol.* Mar; 2001 248(3):180–183. [PubMed: 11355150]
20. Lazeron RH, Boringa JB, Schouten M, et al. Brain atrophy and lesion load as explaining parameters for cognitive impairment in multiple sclerosis. *Mult Scler.* Oct; 2005 11(5):524–531. [PubMed: 16193889]
21. Motl RW, McAuley E, Snook EM, Gliottoni RC. Physical activity and quality of life in multiple sclerosis: intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. *Psychol Health Med.* Jan; 2009 14(1):111–124. [PubMed: 19085318]
22. Archibald CJ, McGrath PJ, Ritvo PG, et al. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients. *Pain.* Jul; 1994 58(1):89–93. [PubMed: 7970843]
23. Hemmett L, Holmes J, Barnes M, Russell N. What drives quality of life in multiple sclerosis? *QJM : monthly journal of the Association of Physicians.* Oct; 2004 97(10):671–676. [PubMed: 15367738]
24. Skerrett TN, Moss-Morris R. Fatigue and social impairment in multiple sclerosis: The role of patients' cognitive and behavioral responses to their symptoms. *Journal of Psychosomatic Research.* Nov; 2006 61(5):587–593. [PubMed: 17084135]
25. Pittion-Vouyovitch S, Debouverie M, Guillemin F, Vandenberghe N, Anxionnat R, Vespignani H. Fatigue in multiple sclerosis is related to disability, depression and quality of life. *J Neurol Sci.* Apr 15; 2006 243(1–2):39–45. [PubMed: 16434057]
26. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology.* May; 1991 41(5):692–696. [PubMed: 1823781]
27. Kratz AL, Ehde DM, Hanley MA, Jensen MP, Osborne TL, Kraft GH. Cross-Sectional Examination of the Associations Between Symptoms, Community Integration, and Mental Health in Multiple Sclerosis. *Arch Phys Med Rehabil.* Oct 31.2015
28. Ben Ari Shevil E, Johansson S, Ytterberg C, Bergstrom J, von Koch L. How are cognitive impairment, fatigue and signs of depression related to participation in daily life among persons with multiple sclerosis? *Disabil Rehabil.* 2014; 36(23):2012–2018. [PubMed: 24524439]
29. Hughes AJ, Hartoonian N, Parmenter B, et al. Cognitive Impairment and Community Integration Outcomes in Individuals Living With Multiple Sclerosis. *Arch Phys Med Rehabil.* Nov; 2015 96(11):1973–1979. [PubMed: 26189203]
30. Kramer AM. Rehabilitation care and outcomes from the patient's perspective. *Medical care.* Jun; 1997 35(6 Suppl):JS48–57. discussion JS58–63. [PubMed: 9191714]
31. masked. Ecological momentary assessment of pain, fatigue, depressive and cognitive symptoms reveals significant daily variability in multiple sclerosis. *Arch Phys Med Rehab.* under review.
32. masked. Temporal associations between pain, fatigue, depressive, and cognitive symptoms within- and across-days in multiple sclerosis. *Arch Phys Med Rehab.* under review.
33. Qualtrics. Qualtrics Security White Paper: Why should I trust Qualtrics with my Sensitive Data? [pdf]. 2011. Version 1.0 [Accessed July 3, 2014]
34. Hahn EA, DeVellis RF, Bode RK, et al. Measuring social health in the patient-reported outcomes measurement information system (PROMIS): item bank development and testing. *Qual Life Res.* Sep; 2010 19(7):1035–1044. [PubMed: 20419503]
35. Castel LD, Williams KA, Bosworth HB, et al. Content validity in the PROMIS social-health domain: a qualitative analysis of focus-group data. *Qual Life Res.* Jun; 2008 17(5):737–749. [PubMed: 18478368]
36. Bartlett SJ, Orbai AM, Duncan T, et al. Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. *PloS one.* 2015; 10(9):e0138543. [PubMed: 26379233]

37. Salsman JM, Victorson D, Choi SW, et al. Development and validation of the positive affect and well-being scale for the neurology quality of life (Neuro-QOL) measurement system. *Qual Life Res*. Nov; 2013 22(9):2569–2580. [PubMed: 23526093]
38. Miller DM, Bethoux F, Victorson D, et al. Validating Neuro-QoL short forms and targeted scales with people who have multiple sclerosis. *Mult Scler*. May; 2016 22(6):830–841. [PubMed: 26238464]
39. Miller DM, Mamone B, Mourany L, Rao SM, Rudick RA. Validity of the Neuro-QOL lower extremity and upper-extremity scales in persons with MS with a range of cognitive disability as measured by the SDMT. *Mult Scler J*. Sep.2014 20:407–407.
40. Enders CK, Tofighi D. Centering predictor variables in cross-sectional multilevel models: a new look at an old issue. *Psychol Methods*. Jun; 2007 12(2):121–138. [PubMed: 17563168]
41. Enders, CK. Centering predictors and contextual effects. In: Scott, MA.Simonoff, JS., Marx, BD., editors. *The SAGE Handbook of Multilevel Modeling*. Thousand Oaks, CA: Sage Publications Inc; 2013. p. 89-107.
42. Cohen, J., Cohen, P., West, SG., Aiken, LS. *Applied Multiple Regression/Correlation Analyses for the Behavioral Sciences*. 3. Mahwah, NJ: Lawrence Erlbaum Associates; 2003.
43. Kratz AL, Davis MC, Zautra AJ. Attachment predicts daily catastrophizing and social coping in women with pain. *Health Psychol*. May; 2012 31(3):278–285. [PubMed: 21859214]
44. Kratz AL, Ehde DM, Bombardier CH, Kalpakjian CZ, Hanks RA. Pain Acceptance Decouples the Momentary Associations Between Pain, Pain Interference, and Physical Activity in the Daily Lives of People With Chronic Pain and Spinal Cord Injury. *J Pain*. Mar; 2017 18(3):319–331. [PubMed: 27919770]
45. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. *Brit Med J*. May 18; 2002 324(7347):1193–1194. [PubMed: 12016186]
46. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient compliance with paper and electronic diaries. *Controlled clinical trials*. Apr; 2003 24(2):182–199. [PubMed: 12689739]
47. Hoogs M, Kaur S, Smerbeck A, Weinstock-Guttman B, Benedict RH. Cognition and physical disability in predicting health-related quality of life in multiple sclerosis. *International journal of MS care*. Summer;2011 13(2):57–63. [PubMed: 24453706]
48. Vasconcelos AG, Haase VG, de Lima EP, Lana-Peixoto MA. Maintaining quality of life in multiple sclerosis: fact, fiction, or limited reality? *Arquivos de neuro-psiquiatria*. Oct; 2010 68(5):726–730. [PubMed: 21049183]

Table 1

Descriptive statistics for demographic and baseline study variables (n = 102)

Variable	Mean (SD)	Min-Max
Age	44.85 (11.72)	23 – 67
MS Duration (years)	9.26 (8.25)	0 – 44
NQ Positive Affect & Well-being	54.95 (8.33)	31.74 – 68.00
Person-level daily max-min	7.83 (5.26)	0.00 – 29.30
PROMIS Ability to Participate in Social Roles	39.41 (9.42)	27.30 – 64.50
Person-level daily max-min	11.72 (8.35)	0.00 – 37.20
NQ Upper Extremity Functioning	44.59 (9.95)	12.80 – 53.80
Person-level daily max-min	5.26 (10.07)	0.00 – 41.00
NQ Lower Extremity Functioning	45.41 (9.71)	18.81 – 58.60
Person-level daily max-min	5.29 (7.64)	0.00 – 42.10
EMA Pain (0–10)	2.45 (1.73)	0.00 – 6.73
Person-level daily max-min	2.07 (1.38)	0.00 – 6.00
EMA Fatigue (0–10)	3.48 (1.92)	0.00 – 8.10
Person-level daily max-min	2.48 (1.24)	0.00 – 6.10
EMA Depressive Symptoms (0–10)	1.19 (1.64)	0.00 – 8.37
Person-level daily max-min	1.41 (1.61)	0.00 – 7.50
EMA Cognitive Problems	1.82 (1.78)	0.00 – 8.25
Person-level daily max-min	1.68 (1.31)	0.00 – 7.50
<u>N (%)</u>		
Sex (Female)	71 (69.6%)	
MS Subtype		
Relapsing Remitting	78 (76.5%)	
Primary Progressive	11 (10.8%)	
Progressive Relapsing	1 (1.0%)	
Secondary Progressing	12 (11.8%)	
Race		
White	84 (82.3%)	
Black	8 (7.8%)	
Asian	6 (5.8%)	
Native	2 (2%)	
Biracial (Black/White)	1 (1%)	
Hispanic	1 (1%)	

Note. EMA variables are person-averaged (aggregated across the week of home monitoring for each person): PROMIS = Patient Reported Outcomes Measurement Information System; NQ = Neuro-QoL; Both PROMIS and Neuro-QoL measures are on a T-score metric, Mean=50, SD=10; Person-level daily max-min is the difference between the maximum daily score and minimum daily score for each repeated measures for each person

Table 2

Results from multilevel models examining same-day bivariate associations between each symptom and each daily outcome.

Outcome	B	SE	<i>p</i>
Positive Affect & Well-being			
Pain	−0.62	0.28	0.03
Fatigue	−0.96	0.23	<0.0001
Depressive Symptoms	−1.52	0.30	<0.0001
Cognitive Problems	−1.14	0.32	<0.001
Ability to Participate in Social Roles & Activities			
Pain	−1.36	0.29	<0.0001
Fatigue	−1.08	0.24	<0.0001
Depressive Symptoms	−1.23	0.51	0.02
Cognitive Problems	−1.38	0.30	<0.0001
Upper Extremity Functioning			
Pain	−0.90	0.38	0.02
Fatigue	−0.16	0.22	0.49
Depressive Symptoms	−0.53	0.21	0.01
Cognitive Problems	−0.47	0.25	0.06
Lower Extremity Functioning			
Pain	−0.75	0.29	0.01
Fatigue	−0.39	0.20	0.05
Depressive Symptoms	−0.51	0.23	0.03
Cognitive Problems	−0.36	0.15	0.004

Note. Output is simplified to improve readability of bivariate associations of primary interest;

Output for covariates (sex, MS subtype, age, MS duration, and average levels of the EMA-measured symptom of interest) is not included; B = unstandardized beta; SE = standard error;

= person-day centered variable representing daily deviation (change) from a person's average; (df = 93 between-person, 512 within-person)

Table 3

Results of multivariable multilevel models examining same-day associations between symptoms, positive affect and well-being and ability to participate in social roles and activities, controlling for age, sex, MS subtype, and time since MS diagnosis.

Random Effects						
Positive Affect & Well-being			Ability to Participate in Social Roles & Activities			
Est.	SE	p	Est.	SE	p	
Intercept	39.86	6.54	<0.0001	40.16	7.83	<0.0001
AR(1)	0.34	0.07	<0.0001	0.38	0.07	<0.0001
Residual	14.34	1.37	<0.0001	37.11	3.71	<0.0001
Fixed Effects						
Positive Affect & Well-being (df = 512)			Ability to Participate in Social Roles & Activities (df = 512)			
B	SE	p	B	SE	p	
Between-Person Variables (time invariant) df = 93						
Intercept	58.16	3.71	<0.001	62.97	3.76	<0.001
Female	1.69	1.48	0.25	0.87	1.43	0.54
MS Type	-0.49	1.78	0.78	5.36	2.14	0.01
Age	-0.002	0.06	0.98	-0.20	0.08	0.02
MS Duration	0.04	0.09	0.65	-0.04	0.12	0.74
Pain *	0.11	0.42	0.79	-0.14	0.53	0.80
Fatigue *	-0.27	0.50	0.59	-1.73	0.59	0.005
Depressive *	-3.01	0.47	<0.001	-1.55	0.55	0.006
Cognitive *	-0.02	0.58	0.97	-0.47	0.73	0.52
Within-Person Predictor Variables – Symptoms (same day)						
Pain	0.03	0.28	0.90	-1.00	0.32	0.002
Fatigue	-0.54	0.20	0.006	-0.30	0.33	0.36
Depressive	-1.17	0.26	<0.0001	-0.63	0.60	0.30
Cognitive	-0.33	0.24	0.18	-0.56	0.42	0.18

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Note. Est. = covariance parameter estimate; B = unstandardized beta; SE = standard error;
* = person-average of EMA values over the week-long home monitoring period;
= person-day centered variable representing daily deviation (change) from a person's average. An (AR) autoregressive matrix was used to model the error variance. Female = Male was reference category;
MS Type = relapsing remitting MS subtype, progressive subtypes was reference category

Table 4

Results of multivariable multilevel models examining same-day associations between symptoms and upper extremity and lower extremity physical functioning, controlling for age, sex, MS subtype, UE strength and coordination (for UE outcome), walking ability (for LE outcome) and time since MS diagnosis.

Random Effects						
Upper Extremity Functioning			Lower Extremity Functioning			
Est.	SE	p	Est.	SE	p	
Intercept	59.44	10.96	<0.0001	32.50	5.85	<0.0001
AR(1)	0.50	0.07	<0.0001	0.44	0.07	<0.0001
Residual	32.50	4.23	<0.0001	19.27	2.13	<0.0001

Fixed Effects						
Upper Extremity Functioning (df = 2088)			Lower Extremity Functioning (df = 2087)			
B	SE	p	B	SE	p	
Between-Person Variables (time invariant) df = 98						
Intercept	54.85	3.86	<0.0001	61.06	3.09	<0.0001
Female	0.43	1.68	0.80	−0.99	1.31	0.45
MS Type	5.78	2.44	0.02	6.47	1.56	<0.0001
Age	−0.06	0.10	0.55	−0.23	0.07	0.002
MS Duration	0.15	0.14	0.29	0.11	0.09	0.21
Pain *	−0.69	0.76	0.37	−1.49	0.56	0.009
Fatigue *	−0.29	0.66	0.66	−0.56	0.50	0.27
Depressive *	−0.36	0.56	0.53	0.25	0.47	0.59
Cognitive *	−0.22	0.81	0.78	−0.26	0.36	0.47
Within-Person Predictor Variables – Symptoms (same day)						
Pain	−1.04	0.41	0.01	−0.71	0.36	0.04
Fatigue	0.44	0.22	0.05	−0.006	0.23	0.99
Depressive	−0.38	0.20	0.06	−0.29	0.26	0.27

Random Effects						
Upper Extremity Functioning			Lower Extremity Functioning			
	Est.	SE	p	Est.	SE	p
Cognitive	-0.23	0.21	0.28	-0.11	0.25	0.67

Note. Est. = covariance parameter estimate; B = unstandardized beta; SE = standard error;

* = person-average of EMA values over the week-long home monitoring period;

= person-day centered variable representing daily deviation (change) from a person's average. An (AR) autoregressive matrix was used to model the error variance. Female = Male was reference category; MS Type = relapsing remitting MS subtype, progressive subtypes was reference category