Published in final edited form as:

Psychosom Med. 2002 ; 64(5): 803–809.

Moderating Effects of Coping on the Relationship Between Stress and the Development of New Brain Lesions in Multiple Sclerosis

David C. Mohr, PhD, Donald E. Goodkin, MD, Sarah Nelson, DrRerNat, Darcy Cox, PsyD, and Michael Weiner, MD

From the University of California, San Francisco, CA.

Abstract

Objective—Many patients with multiple sclerosis (MS) report that stress can trigger disease exacerbations. Considerable research has supported a relationship between stress and both clinical exacerbation and the development of new brain lesions. However, these relationships are not always consistent either within patients or across patients, suggesting the presence of moderators. This study examined the hypothesis that coping moderates the subsequent relationship between stress and the development of new brain lesions in MS.

Methods—Thirty-six patients (mean age = 44.4; 22 women, 14 men) with relapsing forms of MS were assessed once every 4 weeks for 28–100 weeks. New brain lesions were identified using monthly Gd+ MRI. Stress was measured within 24 hours before MRI using a modified version of the Social Readjustment Rating Scale that assessed Conflict and Disruption in Routine. Coping was measured at baseline using the Coping with Health Injuries and Problems questionnaire, which produces four scales: distraction, instrumental, palliative, and emotional preoccupation. Data were analyzed using mixed effects logistic regression to account for within-subject correlations. Analyses were lagged such that stress assessments predicted new Gd+ MRI brain lesions 8 weeks later.

Results—As reported previously, stress was significantly related to the development of new Gd+ brain lesions 8 weeks later ($OR = 1.62, p = .009$). Greater use of distraction was found to be a significant moderator of the relationship between stress and new Gd+ lesions ($OR = 0.69, p = .037$) such that greater use of distraction was associated with a decreased relationship between stress and new Gd+ lesions. Increased instrumental coping was marginally associated with a decreased relationship between stress and new Gd+ lesions ($OR = 0.77, p = .081$), while increased emotional preoccupation was marginally associated with an increased relationship between stress and new Gd+ lesions ($OR = 1.46, p = .088$). There was no significant moderating effect for palliative coping ($p = .27$) and no significant main effects for any coping variables and the subsequent development of new Gd+ brain lesions (p values $> .21$).

Conclusions—These findings provide modest support for the hypothesis that coping can moderate the relationship between stress and the MS disease activity. Several limitations in this study are discussed. While these findings suggest areas of potentially fruitful research, readers are cautioned that these are preliminary results; inferences regarding the clinical importance of these findings are premature.

Keywords

stress; multiple sclerosis; coping; mind-body

INTRODUCTION

Multiple sclerosis is a chronic, often disabling disease of the central nervous system that affects approximately 350,000 people in the United States (1). It is believed that the disease is caused by autoimmune activity that results in the destruction of the myelin sheath around the axons of the CNS (2). Prevalence among women is about twice that found in men. MS is usually diagnosed between the ages of 20 and 40. MS can produce a wide variety of symptoms, including, but not limited to, loss of function or feeling in limbs, loss of bowel or bladder control, sexual dysfunction, debilitating fatigue, blindness due to optic neuritis, loss of balance, pain, loss of cognitive functioning, and emotional changes (3–5). There are several types of MS, differentiated in part by the presence or absence of exacerbations (6). Exacerbation refers to a sudden increase in disease activity that results in new or increased symptoms within a 24-hour period that remits partially or fully, usually after a period of weeks or months. A history of exacerbations is required for the diagnosis of RRMS or SPMS.

The belief that stress causes exacerbation is widespread among people with MS. The notion that psychological stress may trigger disease activity was first considered by Charcot, who speculated that grief, vexation, and adverse changes in social circumstance were related to the onset of MS (7). Since that time, the potential relationship between stressful life events, psychological distress, and clinical exacerbations has been examined empirically. Although early case-control studies failed to detect a significant relationship between stressful life events, psychological distress, and first symptoms or clinical exacerbations of MS (8,9), a number of more recent studies have suggested that stress may be related to MS disease activity (10).

The nature of any relationship between stress and MS disease activity remains unclear. These relationships are reciprocal (11). MS disease exacerbation is known to result in stress and distress (12). Thus, the retrospective studies examining the effects of stress on MS disease activity (13–15) are difficult to interpret because retrospective reports of stress and distress may be influenced by the stress and distress experienced during exacerbation. However, two prospective studies have found that stress is related to increased risk of clinical exacerbation (16,17) and a third has found a small but significant increase in risk of progression of impairment due to stress (11). In contrast, a prospective study conducted in Israel during the Gulf War found a significant drop in MS exacerbations while patients were under missile attack (18).

To explain these discrepancies, we have suggested that moderate stressors may be related to increased subsequent disease activity, while severe stressors may be unrelated to or even reduce disease activity (19). While it may be that differences in the effects of moderate vs. severe stressors on disease activity may be due to variability in the occurrence of stress, controlled studies of EAE, an animal model of MS, support our hypothesis. In EAE, chronic varied stress (a variety of physical and social stressors) increases exacerbation (20) while severe stress (complete restraint) suppresses clinical manifestations of the disease (21). Similarly, Sibley found marital or job-related stress was followed by clinical MS exacerbation, while severe acute stressors such as a death in the family resulted in no significant change in exacerbation rate (17).

We recently examined the effects of different kinds of stress on MS disease activity, as defined by the appearance of new brain lesions measured by Gd+ magnetic MRI (19). Gd+ MRI has several advantages over clinical ratings of disease exacerbation. Gd+ MRI is up to 10 times more sensitive in detecting MS disease activity than clinical evaluation, which can suffer from a variety of threats to reliability (22). Because Gd+ MRI is a marker of the breakdown of the blood-brain barrier, it can shed light on the biology of the relationship between stress and MS exacerbation.

Our findings were consistent with Sibley's in several ways (17). Conflict and disruptions in routine (consisting mainly of family and job-related problems) predicted the development of new brain lesions 8 weeks later, while major life events (eg, a death in the family) or positive life events were unrelated to the subsequent appearance of Gd+ lesions. The time lag was consistent with emerging literature showing that newer brain imaging techniques (eg, magnetic transfer imaging and spectroscopy) can detect changes in brain tissue at least 1 month before the appearance of Gd+ images (23). While the relationship between conflict and disruptions in routine and subsequent MS disease activity was significant, the effect size (OR = 1.64) was not large. Stressful events were not consistently followed by new Gd+ brain lesions, and relationships between stress and new Gd+ lesions were not consistent across patients. This suggests the presence of moderators in this relationship. Potential moderators include types of stress, MS disease characteristics, environmental factors, and patient biological, social, and psychological characteristics. The purpose of the present study is to examine the potential moderating role of coping on the relationship between stress and the subsequent appearance of new Gd+ brain lesions.

There is a vast literature evaluating the effects of coping on adaptation to illness. While the effects of coping are complex and often situation specific, findings generally show that approach strategies are associated with better adaptation while avoidant strategies are usually associated with less favorable outcomes (24–26). The literature on the effects of coping on disease progression is more limited. Coping has been associated with disease progression in some diseases such as cancer (27–30) but has not been looked at as a predictor of disease activity in MS. Furthermore, the effects of the interaction between stress and coping on disease has rarely been examined. In MS, a patient's ability to successfully cope with stressful life events may moderate the effect of those events on biological disease processes.

This study hypothesized that coping would moderate the relationship between stress and the development of new brain lesions. Specifically, it was hypothesized that higher levels of active cognitive or behavioral coping would be related to a weaker relationship between stress and new brain lesions while higher levels of emotion focused would lead to an increased relationship between stress and new brain lesions.

METHODS

These data were initially presented in a paper reporting the relationship between stress and the development of new Gd+ MRI brain lesions (19). The data on coping have not been previously presented.

Patients

Enrollment was offered to patients at the University of California, San Francisco, MS Center participating in ongoing studies that included monthly MRI and clinical evaluations. These studies included a natural history study of early RRMS (23), in which patients were not taking any MS disease-modifying medication, and a clinical trial of IFN β -1b in patients with SPMS. Patients in the natural history study were not on any MS disease-modifying medication. All patients had an EDSS (31) of less than 7.0. A run-in period was used; patients who had no new Gd+ lesions during the first 24 weeks of MRI scans were excluded.

Overview of Study Procedures

All patients signed an informed consent to participate in this study. Patients completed Gd+ MRI imaging and standardized neurological evaluations every 4 weeks for 28 to 96 weeks. Standardized measures of stressful life events and psychological distress were administered by telephone 24 hours before each monthly MRI scanning session. Length of time in the study

was dependent on remaining duration of enrollment in the parent study at the time stress assessments were initiated and was not due to patient attrition.

MRI Methods

MR data for 17 RRMS patients participating in the natural history study were acquired on a General Electric Signa 1.5T system using a quadrature head coil. MRI data for 19 SPMS patients participating in the clinical trial of IFN β -1b were acquired on a Siemens Vision 1.5T system (Erlangen, Germany) using a quadrature head coil. The differences in image acquisition between these two machines are negligible but are described more fully in the original paper (19). Briefly, the imaging procedures were as follows: Before MR acquisition, the B₀ homogeneity over the entire head was optimized using an automated routine supplied by the manufacturer. Two-dimensional gradient echo scout images, acquired in three planes, were used for positioning of subsequent MRI scans. All subsequent MRI scans were collected with full brain coverage using 3 mm. A T2-weighted spin-echo MRI scan was acquired before (T2W) and 10 minutes after (T1Gd+) intravenous injection of gadodiamide (Omniscan; 0.1 mmol/kg). All monthly scans were coregistered to the baseline image using the Woods algorithm (32).

New lesions appearing on all images were identified by visual inspection of the T1Gd+ images by a single radiologist who was masked to patients' clinical information. New disease activity was defined as the presence of one or more Gd+ lesions not visible on the previous MRI.

Clinical exacerbations that resulted in loss of ability to perform activities of daily living were treated with methylprednisolone 500 to 1000 mg, administered intravenously for 3–5 days. To minimize the known effect of corticosteroids on MRI measures of interest, imaging and assessment procedures were delayed 14 days after methylprednisolone was discontinued (33).

Psychosocial Measures

Stress and coping measures were administered over the telephone. Although formal validation for telephone administration has not been done with these measures specifically, there are many studies indicating that telephone administration of similar psychological and neuropsychological assessments is equivalent to face-to-face administration (34–42).

Stress was measured using a revised version of the Holmes and SRRS (43). The a priori modifications to the SRRS are thoroughly described in Mohr et al. (19) and are similar to modifications that have been used by other investigators (11). Briefly, items possibly confounded with MS symptoms were eliminated, a three-point Likert scale assessing stress severity was added for endorsed items, and three subscales assessing positive stressors, major negative life events, and a scale named Conflict and Disruption in Routine (eg, family or job conflict) were created. Because Conflict and Disruption in Routine was the only scale associated with the subsequent development of new brain lesions, only this scale was used in this study.

Coping was assessed using CHIP (44) at baseline only. The CHIP assesses four basic coping dimensions that are characteristically used by people with health problems: distraction, palliative coping, instrumental coping, and emotional preoccupation. Because this assessment was conducted only once, the goal of the assessment was to identify characteristic or dispositional coping rather than coping responses to any specific stressors. Participants were asked how they usually coped with MS-related symptoms and problem.

Statistical Methods

Mixed effects logistic regression (45) was used to evaluate the moderating effects of coping on the relationship between stress and the appearance of new Gd+ MRI brain lesions 8 weeks after the stressful event. This time frame was selected based on previous work (19). Mixed effects logistic regression was used because it accounts for within-subject correlation. It also provides more interpretable effect estimates than the common generalized estimating equations approach (46). To normalize differences in the scaling of the various psychological measures, ORs were calculated corresponding to an increase in the predictor equal to its standard deviation (SD) observed in this sample: $OR = \exp(SD \times \beta)$. Because the scaling of psychological measures varied, with ranges of 4 to 176 points, this facilitates comparison of different predictors' ORs. To assist interpretation, 95% confidence intervals are also provided for significant ORs. All reported *p* values are two-tailed.

Four analyses were performed. For each analysis, variables were entered sequentially so that the OR for any given variable reflects the OR after the variance for the preceding variables have been accounted for. Initially, variables reflecting a biological or medical influence were entered including presence of new Gd+ MRI lesions 8 weeks before visit date, followed by a dummy-coded variable for treatment with IFN β -1b or no treatment. To account for the main effects of stress on new Gd+ MRI lesions, the Conflict and Disruption in Routine scale of the Holmes and Rahe was entered next. Each analysis then added a term for one coping scale. Finally, a term for the interaction of the respective coping scale and Conflict and Disruption in Routine was entered. This final term represents an interaction between baseline coping and subsequent relationships between stress and new Gd+ lesions and is the term that is of primary interest in examining the hypotheses.

RESULTS

Fifty-two patients were initially available to participate in this study (22 RRMS and 30 SPMS). Of these, 36 patients were enrolled (17 RRMS and 19 SPMS). Eleven patients declined participation in the monthly stress assessments and five patients were excluded because they did not meet MRI activity inclusion criteria. Of the 36 patients who received stress assessments, 17 in the natural history study had clinically definite RRMS and 19 patients in the clinical trial had clinically definite SPMS (6,47) (see Mohr et al. (19) for breakdown of patient characteristics by MS disease type). Among the SPMS patients in the clinical trial, 12 were receiving IFN β -1b and 7 were receiving placebo. Patients had a mean EDSS of 3.4 (range = 0–6.5) and a mean of 42.2% of visits with new Gd+ lesions. Participants were on average 44.4 (SD = 8.7) years old. Twenty-two (61.1%) were women, and 14 (39.9%) were men. Thirty-four (94.4%) of the participants were married or living with a significant other. Thus, the sample was generally representative of the MS population, with the exception of marital status, which was biased in favor of people with partners.

Relationship Between Stress, Coping, and Gd+ MRI Lesions

Odds ratios and confidence intervals are displayed in Table 1. The occurrence of a new Gd+ MRI lesion was significantly related to increased odds of having new Gd+ lesions 8 weeks later (OR = 2.55; 95% CI = 1.38–4.70; *p* = .004). Treatment with IFN β -1b was not significantly related to the odds of the appearance of new Gd+ lesions (*p* = .22). Conflict and Disruption in Routine was significantly related to increased odds of the appearance of new Gd+ lesions 8 weeks later (OR = 1.62; 95% CI = 1.12–2.34; *p* = .009).

Distraction was not significantly related to the odds of the appearance of new Gd+ brain lesions (*p* = .21) or with the subsequent occurrence of stress (*p* = .83). The interaction between Distraction and Conflict and Disruption in Routine was significantly related to the odds of the

appearance of new Gd+ lesions 8 weeks later (OR = 0.69; 95% CI = 0.49–0.98; $p = .037$). Specifically, people who used distraction more frequently were less likely to show a relationship between Conflict and Disruption in Routine and the subsequent appearance of new Gd+ lesions.

Palliative Coping was not significantly related to the odds of the appearance of new Gd+ brain lesions ($p = .69$) or with the subsequent occurrence of stress ($p = .38$). There was no significant interaction between Palliative Coping, Conflict and Disruption in Routine, and the odds of the appearance of new Gd+ lesions 8 weeks later ($p = .27$).

Instrumental Coping was not significantly related to the odds of the appearance of new Gd+ brain lesions ($p = .55$) or with the subsequent occurrence of stress ($p = .29$). The interaction between Instrumental Coping and Conflict and Disruption in Routine and the odds of the appearance of new Gd+ lesions 8 weeks later reached marginal significance (OR = 0.77; 95% CI = 0.57–1.04; $p = .081$). This suggests that people who used instrumental coping more frequently were less likely to show a relationship between Conflict and Disruption in Routine and the subsequent appearance of new Gd+ lesions.

Emotional Preoccupation was not significantly related to the odds of the appearance of new Gd+ brain lesions ($p = .72$) or with the subsequent occurrence of stress ($p = .37$). The interaction between Emotional Preoccupation and Conflict and Disruption in Routine and the odds of the subsequent appearance of new Gd+ lesions reached marginal significance (OR = 1.46; 95% CI = 0.94–2.27; $p = .088$). This suggests that people who more frequently used emotional preoccupation as a coping strategy were more likely to show a relationship between Conflict and Disruption in Routine and the subsequent appearance of new Gd+ lesions.

DISCUSSION

The hypothesis that patient coping moderates the relationship between stress and the subsequent development of new brain lesions in MS received some support. The relationship between stress, in the form of conflict and disruption in routine, and the subsequent development of new brain lesions was reported previously (19). Increases in the characteristic use of distraction were significantly related to a reduction in the subsequent relationship between stress and the risk of developing new brain lesions. A similar trend was seen for the use of instrumental coping. There was also a trend toward the finding that the use of emotional preoccupation may increase the odds that stress will result in subsequent brain lesions. None of the coping variables exerted a main effect on the development of new brain lesions. No main effect was anticipated because coping was not expected to exert an influence in the absence of stress.

The influence of either Type I or Type II errors cannot be ruled out in this study. The small sample size leaves the study underpowered to detect significant effects. On the other hand, this study capitalizes on chance in two ways. The multiple analyses result in some alpha inflation, which, if strictly controlled, would leave the results nonsignificant. It should also be emphasized that these findings are secondary analyses based on the first study to show a relationship between stress and the development of new Gd+ brain lesions in MS (19). As such, it is most appropriate to view these findings as preliminary and in need of replication.

A study design issue regarding the assessment timing should be considered in interpreting the coping data. Due to limitations in the number of assessments we could impose on patients, coping was assessed only once at the outset of the study rather than serially. Thus, coping was treated as a patient characteristic, rather than a situational stressor. The absence of a significant direct relationship between patient coping and new Gd+ brain lesions in these data suggests that coping as a characteristic only exerts an effect in the presence of stress. In other words,

these data suggest that it is the coping responses to stress that are important. However, MS patients often use different coping strategies for different problems (48). Without serial assessment of coping, this design does not permit us to adequately examine the richness and dynamics of coping as a response to situational variables. Future work in this area should include such serial assessment of all relevant variables.

There are several factors related to the sample affecting generalizability. First, the elimination of five patients who had no new Gd+ brain lesions during the 6-month run-in means that these results can only be generalized to those MS patients who have active disease. This sample is also biased on partner status: almost all participants had partners with whom they cohabitated. This skewed sample likely resulted from the burdens associated with participation in this study, which required a full day of MRI scans and medical evaluations every 4 weeks. Several enrolled participants with low social support (eg, not married and living alone) dropped out of the parent studies before being considered for this study. We note that there were no apparent biases in any other variables. The age, gender ratio, and level of impairment are consistent with the MS population. The coping scale scores are also consistent with published norms for both healthy adults as well as people with medical problems (44,49).

Keeping the aforementioned caveats in mind, these findings are generally consistent with existing literature. Emotional coping, such as emotional preoccupation, has generally been associated with worse psychological and health outcomes in MS (24,25,50–53). The effects of problem-focused coping have been somewhat more diverse, with cognitive strategies such as distraction or positive reframing generally being positively associated with health and well being and behavioral or instrumental strategies having more mixed results.

The effect of coping strategies on the relationship between stress and MS disease activity may be direct, indirect, or both. The use of effective coping strategies could have an indirect effect by controlling an emerging stressor, thereby reducing the magnitude of the stressor and any physiological stress response. This would be consistent with instrumental coping; these data only offer qualified support for an indirect pathway. Alternatively, adaptive coping could have direct effects by altering the patient's emotional and cognitive responses to stress, thereby minimizing endocrine and immunological stress responses that are known to be related to MS disease activity (2,54,55). The finding of a moderating influence of the use of distraction supports this second pathway. Clearly, the two pathways are not mutually exclusive, and there is some support for both pathways from other studies as well (5,56–59).

While we believe that there is mounting evidence that stress does have some effect on MS disease activity, not all investigators share this view (10). It is clear that any such relationship is complex and not consistent across patients or within patients over time. There are likely many potential moderators of a relationship between stress and MS disease activity, including MS disease types and processes, the nature of the stressor, environmental context, and the patient's biological, social, and psychological characteristics. This article has examined one set out of many potential moderators. We believe these findings suggest a potentially exciting and important line of research. However, we also caution that these results are preliminary, likely overly simplistic, and should not at this point be considered to have any clear clinical applications.

Acknowledgements

This research was supported by Grants RG2719 A1/2 from the National Multiple Sclerosis Society and R01 MH59708 from the National Institute of Mental Health.

References

1. Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodriguez M, Silberberg DH. Revised estimate of the prevalence of multiple sclerosis in the United States. *Ann Neurol* 1992;31:333–6. [PubMed: 1637140]
2. Hohlfeld RE, Meinl F, Weber F, Zipp S, Schmidt S, Sotgiu S, Boebels R, Voltz S, Spuler A, Iglesias A, Wekerle H. The role of autoimmune T lymphocytes in the pathogenesis of multiple sclerosis. *Neurology* 1995;45 (Suppl 6):S33–8. [PubMed: 7783909]
3. Goodkin, DE. The natural history of multiple sclerosis. In: Rudick, RA.; Goodkin, DE., editors. *Treatment of Multiple Sclerosis: Trial Design, Results and Future Perspectives*. New York (NY): Springer-Verlag; 1992. p. 17-46.
4. Mohr, DC.; Dick, LP. Multiple sclerosis. In: Camic, PM.; Knight, S., editors. *Clinical Handbook of Health Psychology: A Practical Guide to Effective Interventions*. Seattle (WA): Hogrefe and Huber; 1998. p. 313-48.
5. Mohr DC, Cox D. Multiple sclerosis: empirical literature for the clinical health psychologist. *J Clin Psychol* 2001;57:479–99. [PubMed: 11255203]
6. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology* 1996;46:907–11. [PubMed: 8780061]
7. Charcot, JM. *Lectures on Diseases of the Nervous System*. London: New Sydenham Society; 1877.
8. Antonovsky A, Leibowitz U, Medalie JM, Smith A, Halpern L, Alter M. Reappraisal of possible etiologic factors in multiple sclerosis. *Am J Public Health* 1968;58:836–48.
9. Pratt RTC. An investigation of the psychiatric aspects of disseminated sclerosis. *J Neurol Neurosurg Psych* 1951;14:326–36.
10. Goodin DS, Ebers GC, Johnson KP, Rodriguez M, Sibley WA, Wolinsky JS. The relationship of MS to physical trauma and psychological stress: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1999;52:1737–45. [PubMed: 10371517]
11. Schwartz CE, Foley FW, Rao SM, Bernardin LJ, Lee H, Genderson MW. Stress and course of disease in multiple sclerosis. *Behav Med* 1999;25:110–6. [PubMed: 10640224]
12. Dalos NP, Rabins PV, Brooks BR, O'Donnell P. Disease activity and emotional state in multiple sclerosis. *Ann Neurol* 1983;13:573–83. [PubMed: 6870209]
13. Grant I, Brown GW, Harris T, McDonald WI, Patterson T, Trimble MR. Severely threatening events and marked life difficulties preceding onset or exacerbation of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1989;52:8–13. [PubMed: 2709039]
14. Warren S, Greenhill S, Warren KG. Emotional stress and the development of multiple sclerosis: case-control evidence of a relationship. *J Chronic Dis* 1982;35:821–31. [PubMed: 7142361]
15. Warren S, Warren KG, Cockerill R. Emotional stress and coping in multiple sclerosis and exacerbations. *J Psychosom Res* 1991;35:37–47. [PubMed: 2023141]
16. Franklin GM, Nelson LM, Heaton RK, Burks JS, Thompson DS. Stress and its relationship to acute exacerbations in multiple sclerosis. *J Neurol Rehabil* 1988;2:7–11.
17. Sibley, WA. Risk factors in multiple sclerosis. In: Raine, CS.; McFarland, HF.; Tourtellotte, WW., editors. *Multiple Sclerosis: Clinical and Pathogenetic Basis*. London: Chapman and Hall; 1997. p. 141-8.
18. Nisipeanu P, Korczyn AD. Psychological stress as risk factor for exacerbations in multiple sclerosis. *Neurology* 1993;43:1311–2. [PubMed: 8327130]
19. Mohr DC, Goodkin DE, Bacchetti P, et al. Psychological stress and the subsequent appearance of new brain MRI lesions in MS. *Neurology* 2000;55:55–61. [PubMed: 10891906]
20. Correa SG, Rodriguez-Galn MC, Rivero VE, Riera CM. Chronic varied stress modulates experimental autoimmune encephalomyelitis in Wistar rats. *Brain Behav Immun* 1998;12:134–48. [PubMed: 9646938]
21. Whitacre CC, Dowdell K, Griffen AC. Neuroendocrine influences on experimental autoimmune encephalomyelitis. *Ann NY Acad Sci* 1998;840:705–16. [PubMed: 9629297]

22. Grossman, RI. Magnetic resonance imaging: current status and strategies of improving multiple sclerosis clinical trial design. In: Goodkin, DE.; Rudick, RA., editors. *Multiple Sclerosis: Advances in Clinical Trial Design, Treatment and Future Perspectives*. London: Springer; 1996. p. 161-86.
23. Goodkin DE, Rooney WD, Sloan R, et al. A serial study of new MS lesions and the white matter from which they arise. *Neurology* 1998;51:1689–97. [PubMed: 9855524]
24. Mohr DC, Goodkin DE, Gatto N, Van Der Wende J. Depression, coping, and level of neurological impairment in multiple sclerosis. *Multiple Sclerosis* 1997;3:254–8. [PubMed: 9372510]
25. Pakenham KI. Adjustment to multiple sclerosis: application of a stress and coping model. *Health Psychol* 1999;18:383–92. [PubMed: 10431940]
26. Zeidner, M.; Saklofske, D. Adaptive and maladaptive coping. In: Zeidner, M.; Endler, NS., editors. *Handbook of Coping: Theory, Research, Applications*. New York (NY): Wiley; 1996. p. 505-31.
27. Greer S, Morris T, Pettingale KW. Psychological response to breast cancer; effect on outcome. *Lancet* 1979;ii:785–7. [PubMed: 90871]
28. Greer S, Morris T, Pettingale KW, Haybittle J. Psychological response to breast cancer and 15 year outcome. *Lancet* 1990;335:49–50. [PubMed: 1967350]
29. Hislop TG, Waxler NE, Coldman AJ, Elwood JM, Kan L. The prognostic significance of psychosocial factors in women with breast cancer. *J Chronic Dis* 1987;40:729–35. [PubMed: 3597675]
30. Levy SM, Herverman RB, Lippman M, D'Angelo T, Lee J. Immunological and psychosocial predictors of disease recurrence in patients with early-stage breast cancer. *Behav Med* 1991;17:67–75. [PubMed: 1878611]
31. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52. [PubMed: 6685237]
32. Woods RP, Mazziotta JC, Cherry SR. MRI-PET registration with automated algorithm. *J Comput Assist Tomogr* 1993;17:536–46. [PubMed: 8331222]
33. Barkoff F, Tas MW, Frequin S. Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis. *Neuroradiology* 1994;36:382–7. [PubMed: 7936181]
34. Aneshensel CS, Frerichs RR, Clark VA, Yokopenic PA. Measuring depression in the community: a comparison of telephone and personal interviews. *Public Opinion Quart* 1982;46:110–21.
35. Debanne SM, Patterson MB, Dick R, Riedel TM, Schnell A, Rowland DY. Validation of a telephone cognitive assessment battery. *J Am Geriatr Soc* 1997;45:1352–9. [PubMed: 9361661]
36. Desmond DW, Tatemichi TK, Hanzawa L. The telephone interview for cognitive status (TICS): reliability and validity in a stroke sample. *Int J Geriatr Psychiatry* 1994;9:803–7.
37. Gallo JJ, Breitner JCS. Alzheimer's disease in the NAS-NRC registry of ageing twin veterans, IV. Performance characteristics of a two-stage telephone screening procedure for Alzheimer's dementia. *Psychol Med* 1995;25:1211–9. [PubMed: 8637951]
38. Simon GE, Revicki D, Von Korff M. Telephone assessment of depression severity. *J Psychiatr Res* 1993;27:247–52. [PubMed: 8295157]
39. Smith PM, Illig SB, Fielder RC, Hamilton BB, Ottenbacher KJ. Intermodal agreement of follow-up telephone functional assessment using the Functional Independence Measure in patients with stroke. *Arch Phys Med Rehabil* 1996;77:431–5. [PubMed: 8629917]
40. Tunstall N, Prince M, Mann A. Concurrent validity of a telephone-administered version of the Gospel Oak instrument (including the Short-Care). *Int J Geriatr Psychiatry* 1997;12:1035–8. [PubMed: 9395936]
41. Wells KB, Burnam MA, Leake B, Robins LN. Agreement between face-to-face and telephone-administered versions of the depression section of the NIMH diagnostic interview schedule. *J Psychiatr Res* 1988;22:207–20. [PubMed: 3225790]
42. Welsh KA, Breitner JCS, Magruder-Habib KM. Detection of dementia in elderly using telephone screening of cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* 1993;6:103–10.
43. Holmes TH, Rahe RH. The social readjustment scale. *J Psychosom Med* 1967;11:213–8.
44. Endler NS, Parker JDA, Summerfeldt LJ. Coping with health problems: developing a reliable and valid multidimensional measure. *Psychol Assess* 1998;10:195–205.
45. Hedeker D, Gibbons RD. A random-effects ordinal regression model for multilevel analysis. *Biometrics* 1994;50:933–44. [PubMed: 7787006]

46. Lindsey JK, Lambert P. On the appropriateness of marginal models for repeated measurements in clinical trials. *Stat Med* 1998;17:447–69. [PubMed: 9496722]
47. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis. *Ann Neurol* 1983;13:227–31. [PubMed: 6847134]
48. Jean VM, Beatty WW, Paul RH, Mullins L. Coping with general and disease-related stressors by patients with multiple sclerosis: relationships to psychological distress. *Multiple Sclerosis* 1997;3:191–6. [PubMed: 9310965]
49. Endler NS, Courbasson CMA, Fillion L. Coping with cancer: the evidence for the temporal stability of the French-Canadian version of the Coping with Health Injuries and Problems (CHIP). *Personality Individual Differences* 1998;25:711–7.
50. Aikens JE, Fischer JS, Namey M, Rudick RA. A replicated prospective investigation of life stress, coping, and depressive symptoms in multiple sclerosis. *J Behav Med* 1997;20:433–45. [PubMed: 9415854]
51. Mohr DC, Boudewyn AC, Genain CP. Relationship between treatment of depression and interferon-gamma in patients with multiple sclerosis. *Psychosom Med* 1999;61:112.
52. Mohr DC, Dick LP, Russo D, et al. The psychosocial impact of multiple sclerosis: exploring the patient's perspective. *Health Psychol* 1999;18:376–82. [PubMed: 10431939]
53. Wineman NM, Durand EJ, McCulloch BJ. Examination of the factor structure of the Ways of Coping Questionnaire with clinical populations. *Nurs Res* 1994;43:268–73. [PubMed: 7937172]
54. Ackerman KD, Martino M, Heyman R, Moyna NM, Rabin BS. Immunologic response to acute psychological stress in MS patients and controls. *J Neuroimmunol* 1996;68:85–94. [PubMed: 8784264]
55. Ackerman KD, Martino M, Heyman R, Moyna NM, Rabin BS. Stressor-induced alteration of cytokine production in multiple sclerosis patients and controls. *Psychosom Med* 1998;60:484–91. [PubMed: 9710295]
56. Foley FW, Bedell JR, LaRocca NG, Scheinberg LC, Reznikoff M. Efficacy of stress-inoculation training in coping with multiple sclerosis. *J Consult Clin Psychol* 1987;55:919–22. [PubMed: 3693660]
57. Mohr DC, Goodkin DE, Likosky W, et al. Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment. *Multiple Sclerosis* 1996;2:222–6. [PubMed: 9050360]
58. Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol* 1997;54:531–3. [PubMed: 9152109]
59. Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP. Treatment of depression is associated with suppression of non-specific and antigen-specific Th1 responses in multiple sclerosis. *Arch Neurol* 2001;58:1081–6. [PubMed: 11448297]

Glossary

CHIP

Coping with Health Injuries and Problems

CNS

central nervous system

EAE

experimental autoimmune encephalomyelitis

EDSS

Expanded Disability Scale Score

Gd+

gadolinium enhancing

IFNβ-1b	interferon beta-1b
MRI	magnetic resonance imaging
MS	multiple sclerosis
OR	odds ratio
RRMS	relapsing-remitting MS
SPMS	secondary-progressive MS
SRRS	Social Readjustment Rating Scale

TABLE 1

Odds Ratios for the Effects of Coping and Attachment on the Development of New Gd+ Lesions and Interaction Effects Between Coping or Attachment and Stress and New Gd+ Lesions^a

Measure	Odds Ratio	Lower 95% CI	Upper 95% CI	p Value
New Gd+ lesions at time of stress assessment (8 weeks prior)	2.55	1.38	4.70	.004
Treatment with IFN β -1b	0.50	0.16	1.54	.22
Conflict and Disruption in Routine Coping	1.62	1.12	2.34	.009
Distraction	1.54	0.78	3.05	.21
Distraction $\times$ conflict	0.69	0.49	0.98	.037
Palliative	1.14	0.59	2.21	.69
Palliative $\times$ conflict	0.83	0.59	1.17	.27
Instrumental	1.26	0.57	2.74	.55
Instrumental $\times$ conflict	<i>0.77</i>	<i>0.57</i>	<i>1.04</i>	<i>.081</i>
Emotional preoccupation	0.89	0.46	1.72	.72
Emotional preoccupation $\times$ conflict	<i>1.46</i>	<i>0.94</i>	2.27	<i>.088</i>

^aBold = significant relationship; italic = marginal significance.