Published in final edited form as:

Psychol Med. 2014 January ; 44(2): 349–359. doi:10.1017/S0033291713000755.

Do positive or negative stressful events predict the development of new brain lesions in people with Multiple Sclerosis?

Michelle Nicole Burns^{a1}, Ewa Nawacki^{a1}, Mary J. Kwasny^{a1}, Daniel Pelletier^{a2}, and David C. Mohr^{a1,c1}

^{a1}Department of Preventive Medicine, Center for Behavioral Intervention Technologies (CBITs), Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

^{a2}Department of Neurology, Yale School of Medicine, New Haven, CT, USA

Abstract

Background—Stressful life events have long been suspected to contribute to multiple sclerosis (MS) disease activity. The few studies examining the relationship between stressful events and neuroimaging markers have been small and inconsistent. This study examined whether different types of stressful events and perceived stress could predict development of brain lesions.

Methods—This was a secondary analysis of 121 patients with MS followed for 48 weeks during a randomized controlled trial comparing Stress Management Therapy for MS to a waitlist control. Patients underwent MRI's every 8 weeks. Monthly, patients completed an interview measure assessing stressful life events, and self-report measures of perceived stress, anxiety, and depressive symptoms, which were used to predict the presence of gadolinium enhancing (Gd+) and T₂ lesions on MRI's 29–62 days later. Participants classified stressful events as positive or negative. Negative events were considered “major” if they involved physical threat or threat to the patient's family structure, and “moderate” otherwise.

Results—Positive stressful events predicted decreased risk for subsequent Gd+ lesions in the control group (*OR*=.53 for each additional positive stressful event, 95% *CI*=.30–.91) and less risk for new or enlarging T₂ lesions regardless of group assignment (*OR*=.74, 95% *CI*=.55–.99).

Across groups, major negative stressful events predicted Gd+ lesions (*OR*=1.77, 95% *CI*=1.18–2.64) and new or enlarging T₂ lesions (*OR*=1.57, 95% *CI*=1.11–2.23), while moderate negative stressful events, perceived stress, anxiety, and depressive symptoms did not.

Conclusions—Major negative stressful events predict increased risk for Gd+ and T₂ lesions, while positive stressful events predict decreased risk.

Keywords

Multiple Sclerosis; Lesions; Stress; Depression; Anxiety; MRI; Neuroimaging

^{c1}Address for correspondence: D. Mohr, Ph.D., Department of Preventive Medicine, Northwestern University, Feinberg School of Medicine, 680 N Lake Shore Drive, Suite 1220, Chicago, IL 60611, USA. (d-mohr@northwestern.edu).

This study is registered on clinicaltrials.gov (NCT00147446).

DECLARATION OF INTEREST

None.

Studies have consistently demonstrated a relationship between stress and disease activity in people with MS. The vast majority of these studies have examined clinical exacerbations as an indicator of disease activity (Artemiadis *et al.*, 2011). While clinical exacerbation is an important outcome to patients, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, as well as the authors of a recent review, have recommended using MRI to evaluate the relationship between stress and disease activity (Goodin *et al.*, 1999; Artemiadis *et al.*, 2011). Two neuroimaging markers are commonly used. Gadolinium enhancing (Gd+) MRI is a marker of the breakdown of the blood-brain-barrier, an important pathogenic process in MS. T₂ MRI is a marker of more permanent lesions that predict poorer functional outcomes over long-term follow-up (Rudick *et al.*, 2006). Because neurological evaluation of exacerbation includes symptoms that are subjective (e.g., fatigue) or that can be affected by stress and distress (e.g., ambulation speed), clinical exacerbation could potentially be confounded with measures of stress and distress, while MRI is a more objective marker. Additionally, only one out of approximately five to ten Gd+ lesions is associated with a clinical exacerbation (Grossman, 1996), rendering MRI a more sensitive marker of disease activity.

Stressful events or perceived stress may be causally linked to the development of new lesions; indeed, even in healthy people, exposure to an acute stressful event was associated with white matter changes (Chen *et al.*, 2011). A recent randomized controlled trial found that a stress management program reduced the occurrence of Gd+ and T₂ lesions in participants with MS (Mohr *et al.*, 2012). The present study examines in more detail the relationship between different types of stress and the subsequent emergence of new brain lesions. To date, two studies have examined this question. Mohr *et al.* (2000) evaluated the relationship between Gd+ lesions detected on monthly MRI's and major negative, moderate negative, and positive stressful events in 36 patients. Only moderate negative stressors, described as interpersonal conflicts and disruptions in routine, predicted Gd+ lesions four to eight weeks later. In the second study, Yamout *et al.* (2010) conducted a review of patient records. Eighteen of the patients completed MRI's during and one month after the July 2006 Israeli-Lebanese war. These 18 patients were compared to 83 patients who completed MRI's during the same months, but in the years preceding and following the war. Gd+ lesion activity was 2.5 times greater on wartime MRI's, but statistical significance was marginal due to the small sample size.

Thus, the extant studies differ as to whether moderate or major negative stressful events are associated with increased risk for Gd+ lesions. Also, both these seminal studies had methodological weaknesses. Mohr *et al.*'s sample only included 36 patients. The Yamout *et al.* study was cross-sectional and, focusing only on war stress, lacked generalizability to the more common types of stressors encountered by the majority of people with MS. Finally, no studies to our knowledge have examined stress in relation to new or enlarging T₂ lesions.

Current Study

The present study overcame previous methodological limitations in determining whether stressful events are associated with subsequent brain lesions in MS. We used a prospective design following a larger sample of patients, and MRI's were used to detect both Gd+ and

T₂ lesions. We also used assessments of negative (major and moderate) and positive stressful events, as well as subjectively perceived stress. Events were categorized as positive or negative according to the patient's evaluation, rather than researchers' assumptions regarding the valence of particular life events.

We ensured that stressful events were always measured during a specific time window prior to the MRI's, such that findings could be more clearly interpreted. We hypothesized that reports of stressful events would predict the presence of Gd+ and T₂ lesions on MRI's conducted 29–62 days later, above and beyond increases in perceived stress and psychiatric distress that may have accompanied the stressful events. This time window was selected as the average lifespan of a Gd+ lesion is around four weeks (Cotton *et al.*, 2003); at the time of an MRI, any discovered lesions would likely be 0–28 days old. Thus, the stressful events would be unlikely to have been assessed, much less occurred, after the start of a detected Gd+ lesion, and the temporal order of stressful events prior to lesion formation can be established.

Due to the dearth of literature, we did not have pre-existing hypotheses regarding the type of stressful events that would predict Gd+ or T₂ lesions.

METHOD

Study Design

This is a secondary analysis of people with MS who were followed for 48 weeks in a Phase II multi-site, randomized controlled trial (Mohr *et al.*, 2012) comparing Stress Management Therapy for MS (SMT-MS; Mohr, 2010a, b) to a waitlist control. Methods related to the present study are presented here; however, details regarding the trial are available in the primary outcome paper (Mohr *et al.*, 2012). Participants were informed about the study by their physicians, direct contact, and notices in MS specialty clinics at the University of California, San Francisco, Evergreen Hospital Medical Center in Seattle, and Feinberg School of Medicine at Northwestern University in Chicago, as well as through local chapters of the National MS Society. Participants also provided informed consent through these sites. The Institutional Review Boards at all sites approved this study, and a Data Safety Monitoring Board monitored the conduct of the trial and participant safety.

Participants

Individuals interested in the study first completed an initial screening. For those who were potentially eligible, documentation of active MS was then provided by their physician, and a baseline interview and neurological exam were completed with study staff to fully establish eligibility. Inclusion criteria were: 1) diagnosis of a relapsing form of MS (Polman *et al.*, 2005); 2) documentation that MS was active, defined by occurrence of a clinical exacerbation or Gd+ lesion in the past year, occurring 1+ months after beginning any currently used interferon drug and 6+ months after beginning glatiramer acetate to ensure there was active disease while on disease modifying medications; 3) 18+ years old; 4) ability to speak and read English; and 5) a score of 6.5 or less on the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), indicating participants could ambulate. Exclusion criteria

were: 1) current exacerbation; 2) corticosteroid use in the previous 28 days; 3) use of natalizumab or a cytotoxic drug; 4) non-MS autoimmune or endocrine disorder; 5) inability to undergo MRI procedures; 6) pregnancy or intention to become pregnant; 7) severe psychiatric condition; 8) current psychotherapy or intention to pursue psychotherapy; and 9) dementia (Mohr *et al.*, 2012).

Measures

MRI—T₂/T₁-weighted MRI images of the brain, with a single dose injection of Gd, were completed every 8 weeks (i.e., baseline and weeks 8, 16, 24, 32, 40, and 48) using a 3.0-Tesla magnet at each of the sites. For participants taking steroid medication, MRI's were not conducted until at least 28 days after cessation. MRI's were read by two masked neurologists using standardized protocols. All scans within each patient were read by the same neurologist. The two neurologists consulted each other and reached consensus in difficult cases. For the purpose of these analyses, we used a conventional and accepted method to identify: i) the presence of new Gd+ lesions on T1-weighted post-contrast images; and ii) the presence of new or newly enlarging T₂ lesions on T₂-weighted images. The presence of such lesions was determined by visual inspection of all serial images co-registered (re-aligned) to baseline, acquired from a standardized MRI protocol maintained throughout the study. According to accepted definition, the surface area of each lesion had to be > 3 mm² to be counted as a new lesion. No Gd+ lesions were counted twice.

Scans were clinically reviewed by a radiologist for the presence of any potentially dangerous abnormalities that should be brought to the patient or their physician's attention (e.g., possible tumor, high numbers of lesions).

Interview measures were administered monthly via telephone by evaluators who were masked to participants' treatment assignment. Self-reports were administered in-person at baseline and 48 weeks, and either online or via mail at all the other monthly time points.

Stressful Events—The Life Events List (LEL; Cohen *et al.*, 1991) was administered every 4 weeks by telephone interview. The LEL was validated in a U.K. study, where it predicted development of colds after viral exposure and evidenced concurrent validity with perceived stress and negative affect (Cohen *et al.*, 1993). Participants indicated whether or not a variety of stressful events occurred during the three months prior to the baseline LEL assessment, and for subsequent assessments, during the month prior. For each endorsed event, participants rated their subjective evaluation of the event on a 6-point Likert scale. We classified events as negative if they were rated "slightly bad" to "very bad," and we calculated the total positive events by summing the number of events that were evaluated as "slightly good" to "very good." For events missing subjective rating data, the majority evaluation of that event within our sample was used to classify the event as positive or negative.

Negative events were classified as "major" if they involved physical threat (e.g., assault, hospitalization for life threatening illness) to the patient or someone close to them, or if the negative event threatened the structure of the patient's immediate family (e.g., the patient's spouse had an affair). All other negative stressful events were categorized as "moderate,"

and assessed interpersonal conflict (e.g., termination of a friendship), disruptions in the patient's routine (e.g., job change), or reduction in resources (e.g., personal finances became worse).

There were four medical stressful events queried on the LEL. Two of these items (one querying "physical illness, injury, or disability," the other querying "serious diagnosis of illness") were modified to exclude MS. The other two items (one querying accidents necessitating emergency medical care, the other querying hospitalization "for a serious (life threatening) illness") were unlikely to be related to MS.

Perceived Stress—The Brief Inventory of Perceived Stress (BIPS) is a self-report measure of perceived stress that was validated among MS patients in the U.S., most of whom participated in the current study (Lehman *et al.*, 2012). The BIPS queries the frequency of various aspects of perceived stress (e.g., feeling criticized or judged, feeling under pressure from deadlines) over the past month.

Psychiatric Distress—The Hospital Anxiety and Depression Scale anxiety subscale (HADS-A; Zigmond and Snaith, 1983) and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) were administered to assess self-reported anxiety and depressive symptoms, respectively, during the past week. The CES-D was initially validated in the U.S. (Radloff, 1977). We used a 6-item subscale of the CES-D to assess somatic depressive symptoms (i.e., restless sleep), and a 7-item subscale for affective depressive symptoms (i.e., sadness; Shafer, 2006). These depressive symptom clusters have evidenced differential relationships with inflammatory processes (Dantzer *et al.*, 2008; Dantzer *et al.*, 2009). Although the English version of the HADS-A has been used more extensively in the U.K. (Herrmann, 1997), researchers in Canada have validated its use for MS patients (Honarmand and Feinstein, 2009). The HADS-A consists of 7 items querying various anxiety symptoms (e.g., tension, panic, worry).

Treatments

Participants were randomized by the statistician to SMT-MS or a wait list control (WLC) condition. SMT-MS, which features a published therapist manual (Mohr, 2010a) and patient workbook (Mohr, 2010b), is a validated stress management intervention for patients with MS. Participants met individually with a licensed clinical psychologist or social worker for 16 50-minute sessions over 20–24 weeks. Problem solving, relaxation, engagement in positive activities, cognitive restructuring, and increasing social support comprised core skills that were taught during the first six sessions. Optional treatment modules that addressed common comorbidities of depression or MS (e.g., anxiety, sexual dysfunction, cognitive impairments) were then used to tailor the intervention to the patient's needs. Therapists were not allowed to discuss disease modifying or psychiatric medications; participants who presented with questions regarding such issues were advised to consult with their prescribing physician.

The WLC consisted of treatment as usual for the first 40 weeks, followed by an optional 5-hour stress management workshop. Over the 24 week SMT-MS treatment period, patients in SMT-MS experienced significantly fewer cumulative Gd+ and T₂ lesions than those in the

waitlist control. However, the effect of treatment assignment on cumulative Gd+ and T₂ lesions over the 24 week post-treatment follow-up period were both non-significant (Mohr *et al.*, 2012).

Data Analysis

We used SAS 9.2 (SAS Institute Inc., 2008) to create generalized estimating equations (GEE) logistic regression models to predict the presence or absence of Gd+ and T₂ lesions occurring after baseline. The time variant variables were assessed 29–62 days prior to the MRI, and were comprised of the stressful events, perceived stress, and symptoms of depression and anxiety. Given the follow-back period of each measure, Figure 1 shows the timeline of these variables in relationship to the MRI and formation of a Gd+ lesion. As shown, the maximum possible lag between the occurrence of stressful events and the subsequent MRI was 3 months, while the minimum lag was 1 month (i.e., 29 days).

As the waitlist control participants had the opportunity to attend a stress management workshop after week 40, the control group participants' week 48 MRI's were removed from analysis to ensure the data were not contaminated by any effects the workshop may have had on the relationship between stressful events and MS disease activity.

We first modeled lesions on time, age, baseline presence or absence of a Gd+ lesion, treatment group, and the three types of stressful events. To evaluate whether results differed between the treatment versus control condition, we then added interactions between each type of stressor and group assignment one at a time to the models and retained any significant interaction terms. Finally, we added the perceived stress and psychiatric distress measures to ensure results were not better accounted for by these variables as opposed to the stressful events themselves. For each model, we used the covariance structure that produced the lowest Quasi-Likelihood Information Criterion value when run using only the non-imputed (observed) data.

Using IVEware, 20 datasets were created that imputed values for the numbers of stressful events, perceived stress, and symptoms of depression and anxiety if any of those variables were not assessed between 29–62 days prior to the administration of an MRI, based on all other observed data. Results for the 20 datasets were aggregated using SAS PROC MIANALYZE.

RESULTS

Participants were recruited from 2005 through 2008, and baseline characteristics of the resulting sample ($N=121$) are displayed in Table 1. Over the course of 48 weeks, patients self-reported 165 new exacerbations, 77 of which were confirmed. Intravenous and/or oral steroids were prescribed for 27 unique patients during 39 of the confirmed exacerbations.

MRI Data

A t-test revealed a trend for patients in SMT-MS to have missed a greater proportion of MRI's ($M_{\text{treatment}}=.23$, $M_{\text{control}}=.12$, $t(119)=1.86$, $p=.07$). Baseline measures of stressful life events, perceived stress, and depression and anxiety symptoms were not correlated with the

number of MRI's completed in either SMT-MS or WLC ($p>.17$). There was at least one MRI available after baseline for 113 of the 121 participants, and these were the participants included in analyses of our hypotheses ($n=60$ in WLC, $n=53$ in SMT-MS).

Of the 665 MRI's possible after baseline given the assessment schedule and exclusion of week 48 MRI's in the control group, 527 (79%) were completed and had data available regarding Gd+ lesions; 104 (19.7%) of these 527 MRI's were positive for Gd+ lesions. For new or enlarging T₂ lesions, data was available from 542 (82%) of the 665 possible MRI's, and 140 (25.8%) of these 542 MRI's were positive. Data on previous stressful events, perceived stress, anxiety, or depressive symptoms was missing, and thus imputed, for 18% of the MRI's.

Hypotheses

Gd+ lesions—We first considered Gd+ lesions without the perceived stress and distress measures. There was no differential effect of moderate or major negative stressful events by treatment ($p>.30$). However, as seen in Table 2, there was an overall effect of major negative stressful events ($OR=1.77$ for each additional major negative event, 95% CI=1.18–2.64, $p=.006$). Furthermore, there was an interaction between positive stressful events and treatment ($p=.02$). Positive stressors were associated with less risk for a subsequent Gd+ lesion in WLC ($OR=.53$ for each additional positive stressful event, 95% CI=.30–.91, $p=.02$), but not in SMT-MS ($OR=1.15$, 95% CI=.76–1.74, $p=.51$).

When perceived stress, anxiety, and somatic and affective depressive symptoms were added to this model, they were not predictive of Gd+ lesions ($p>.66$), and the main effect of major negative stressful events ($OR=1.76$, 95% CI=1.17–2.65, $p=.007$) and the interaction between positive stressful events and treatment ($p=.02$) remained significant. Again, positive stressful events were associated with reduced risk for a Gd+ lesion in WLC ($OR=.53$, 95% CI=.30–.93, $p=.03$) but not SMT-MS ($OR=1.14$, 95% CI=.75–1.75, $p=.54$). Thus, the relationships of positive and major negative stressors with subsequent Gd+ lesions did not appear to be due to psychiatric distress or perceived stress that may have been associated with the stressful events.

T₂ lesions—When we examined new or enlarging T₂ lesions without the distress measures, no differential effect of the stressful event types by treatment was significant ($p>.26$). Thus, the model without any interaction terms was used (see Table 2), revealing that positive events were associated with less risk for a subsequent new or enlarging T₂ lesion ($OR=.74$ for an increase of one positive stressful event, 95% CI=.55–.99, $p=.04$). Conversely, the odds of a subsequent new or enlarging T₂ lesion increased by a factor of 1.57 for an increase of one major negative stressful event, 95% CI=1.11–2.23, $p=.01$.

After adjusting for the distress and perceived stress measures ($p>.25$), the main effect of positive ($OR=.72$, 95% CI=.54–.96, $p=.03$) events was still significant. The main effect of major negative events ($OR=1.42$, 95% CI=.99–2.04, $p=.06$) retained the same direction as a non-significant trend.

Note. All conclusions remained consistent when only the non-imputed (observed) data was analyzed.

Post-Hoc Analysis

To investigate whether the significant results could be explained by previous MS disease activity generating the stressful events, we reversed the analyses. We separately modeled positive and major negative stressful events as binary variables on time, age, group assignment, baseline values for that type of stressful event, and the number of Gd+ lesions on the most recent MRI completed 29–62 days prior. We then re-ran these two models using T₂ lesions as a predictor rather than Gd+ lesions. We only used MRI data that was included in the analyses for the hypotheses, and no MRI data was used to predict more than one stressful event assessment. We also removed week 40 MRI's for the control group; these participants may have attended a stress management workshop after week 40 and therefore their subsequent stressful event assessments may have been affected.

Neither Gd+ nor T₂ lesions predicted positive events or major negative events (p 's > .70). We then added interactions between lesion and group assignment to the four models. Group assignment did not significantly modify the relationship between Gd+ or T₂ lesions and major negative events, or between Gd+ lesions and positive events (p 's > .23). There was, in contrast, an interaction effect of T₂ lesions and group assignment on positive events (p = .045); however, the main effect of T₂ lesions on positive events was not significant in SMT-MS (p = .21) or WLC (p = .13). Thus, there was no evidence to suggest that MS disease activity as indicated by neuroimaging was predictive of major negative or positive stressful events. All conclusions remained consistent when only the non-imputed (observed) stressful event data was analyzed.

We also examined whether missing data patterns may have influenced the results. Most MRI's that matched with observed stressful event data were completed at the assessment point 4 or 8 weeks after the stressful event assessment point. Thus, to examine stressful events and missingness of subsequent MRI data, we coded whether or not any major negative or positive stressful events (observed, non-imputed) were reported at the assessments 4 or 8 weeks prior to each MRI assessment point. In Table 3, we present the percentage of missing lesion data by group assignment and prior stressful events. Chi-square tests revealed that participants receiving SMT-MS were more likely than those receiving WLC to have missing lesion data in the absence of both major negative and positive stressful events (p 's < .05). Within SMT-MS, major negative events predicted a lower likelihood of missing Gd+ and T₂ lesion data (p 's < .05). There was also a non-significant trend for positive events to predict increased missing Gd+ data in WLC (p = .06).

DISCUSSION

Patients with MS showed an increased risk of new Gd+ lesions and new or enlarging T₂ lesions on MRI's 29–62 days (4–9 weeks) after the report of major negative life events. During the same timeframe, positive stressful events were associated with less risk for subsequent new or enlarging T₂ lesions in the overall sample, as well as lower risk for Gd+ lesions among MS patients who were not exposed to a stress management intervention.

Results were similar when controlling for measures of perceived stress, anxiety, and affective and somatic depressive symptoms; thus, the relationships found between stressful events and subsequent brain lesions do not appear to be driven by psychiatric distress associated with stressful events. The temporal relationship between stressful events and brain lesions was further established by demonstrating that brain lesions did not predict subsequent positive or major negative stressful events.

The finding that major negative stressful events were associated with increased risk for brain lesions is consistent with evidence of increased Gd+ lesion activity in MS patients during wartime (Yamout *et al.*, 2010), as well as studies demonstrating a relationship between negative stressful events and MS clinical exacerbations (Artemiadis *et al.*, 2011) and a study showing that the absence of positive events predicted shorter time to MS clinical exacerbation (Brown *et al.*, 2006). However, current results are inconsistent with Mohr *et al.* (2000), who found that only moderate negative stressful events—not major negative or positive stressful events—predicted risk for subsequent Gd+ lesions. Differences in methodology may explain these inconsistencies; in the current study the sample size was considerably larger and, rather than relying on classifications of positive or negative events by the researcher, events were classified as positive versus negative according to participants' subjective evaluation.

The latency between MRI's and reports of the stressful events was selected to ensure that stressful events occurred prior to the lesions, and thus were not the result of as-yet undetected Gd+ or T₂ lesions. Given the one month follow-back period of the stressful events interview and assuming a four week lifespan for Gd+ lesions, results suggest stressful events confer risk for development of lesions immediately to three months later (see Figure 1). However, as changes to normal appearing white matter have been observed up to 3 months prior to the appearance of Gd+ lesions (Filippi *et al.*, 1998; Goodkin *et al.*, 1998), our results do not necessarily imply that stressful events trigger the pathogenic factors that result in Gd+ and T₂ lesions. Rather, stressful events may be one set of factors among many that determine whether underlying pathogenic processes are successfully regulated or whether they cascade to the point of detectable brain lesions (Mohr and Pelletier, 2006). For example, chronically elevated cortisol levels associated with major negative stressful events may have led to glucocorticoid receptor resistance, thereby decreasing immunoregulatory capacity (Mohr and Pelletier, 2006; Cohen *et al.*, 2012). Although literature on positive stressful events and cortisol is scarce, positive events have been linked to lower cortisol levels in pregnant women (Pluess *et al.*, 2012); thus, future studies should explore whether positive events may have decreased risk for MS brain lesions by lowering participants' risk for glucocorticoid receptor resistance.

Although the stress management therapy provided to half the participants in this study resulted in fewer Gd+ and T₂ lesions and fewer reported negative stressful events (Mohr *et al.*, 2012), the treatment did not alter the relationship between negative stressful events and subsequent development of new lesions. Although SMT-MS may have improved patients' strategies for coping with stressors, perhaps its beneficial effect on lesion activity was achieved by helping patients learn to avoid negative stressors altogether. This interpretation is supported by the finding that psychiatric distress and perceived stress, the putative

sequelae of negative stressful events, were unrelated to lesion activity. This is also consistent with previous work, which has found negative stressful events, but not distress, are predictive of new lesions (Mohr *et al.*, 2000). These findings suggest that stress management interventions aimed at reducing the development of new brain lesions should focus more on teaching patients to prevent major negative stressful events and increase positive engagement, even if positive events involve some amount of stress.

The finding that positive stressful events were only related to subsequent Gd+ lesions in the control arm and not the SMT-MS arm was unexpected. We speculate that treatment itself may have been a positive stressor that overwhelmed the variability in other positive stressors, thereby decreasing the relationship between measured positive stressors and Gd+ lesions. However, this moderating effect of treatment was not seen for T₂ lesions, and further study is needed to clarify these inconsistent results.

Limitations

In a post-hoc analysis, we found patterns of missing data relating to treatment and stressful events. Among participants who did not report any major negative and positive stressful events, those receiving SMT-MS were more likely to subsequently have missing MRI data than WLC participants. As none of the primary results pertained specifically to the SMT-MS group, however, this pattern is unlikely to influence the interpretation of the results. Within SMT-MS, major negative events predicted missing MRI data. However, major negative events predicted lesions across both groups, indicating this missing data pattern also fails to provide an adequate alternative explanation for the primary results. Finally, there was a trend for positive events in WLC to predict missing Gd+ lesion data. For this missing data pattern to negate the relationship found between positive events and decreased Gd+ lesions in WLC, the WLC participants with positive events who missed their MRI's would need to also be more likely to be experiencing Gd+ lesions. Thus, it is possible but perhaps unlikely that even this one primary result can be explained by missing data.

There are also limitations to this study in terms of methodology. As participants in this study were enrolled in a trial involving a stress management therapy, their experiences with stress may differ from the general population of individuals with MS. Our instrumentation was also unable to detect the changes to normal appearing white matter that precede the emergence of Gd+ and T₂ lesions, and we were thus unable to determine whether stressful events preceded or followed these early pathogenic processes. More frequent MRI's and assessments of stressful life events would also have allowed greater precision in determining the time lag between the occurrence of events and changes in risk for lesion development.

It is possible that the relationship between positive and major negative stressful events and subsequent lesion activity may differ based on a patient's stage of MS disease progression. Future studies should examine this possibility, as all participants in the current study were in the relapsing stage. Finally, although neuroimaging markers of MS disease activity were not predictive of stressful events, the experience of MS symptoms, or a subset thereof, may affect the occurrence and/or reporting of stressful events. It was beyond the scope of this paper to examine relationships between clinical symptoms of MS and stressful events. However, it should be acknowledged that the progression of MS can in itself generate

stressful events, and future studies should tease apart the predictive utility of stressful events versus clinical symptoms of MS on subsequent lesion activity.

Conclusion

This is the largest longitudinal study to date examining the relationship between stressful events and neuroimaging markers of MS. Major negative stressful events were associated with increased risk for subsequent Gd+ and new or enlarging T₂ lesions in patients with MS, while positive stressful events were associated with decreased risk. Future studies should evaluate potential moderators. For example, if positive events occur that are incongruent with the individual's self-concept, they may exert a detrimental rather than beneficial effect on health (Shimizu and Pelham, 2004), and particular coping styles may ameliorate or aggravate the effect of negative stressful events on Gd+ lesions (Mohr *et al.*, 2002). Research that identifies patients who are most vulnerable to the effects of major negative stressful events, and most responsive to the potential benefits of positive life events, can shed light on the pathogenesis of brain lesions in MS and assist with prognosis in clinical settings.

The finding that perceived stress and distress were not statistically associated with the development of new lesions is consistent with a prior study in people with MS (Mohr *et al.*, 2000), but inconsistent with common models of stress that posit perceived stress and/or negative affect as mediators between stressful events and health outcomes (Lazarus and Folkman, 1984; Cohen *et al.*, 1995; McEwen and Gianaros, 2010). This indicates the need to develop and evaluate MS-specific biobehavioral models to explain the relationship between stress and neuroimaging markers of MS disease activity.

Acknowledgments

This study was funded by National Institute of Child Health and Human Development grant R01-HD043323 and National Institute of Mental Health Grant K08-MH094441-01A1.

References

- Artemiadis AK, Anagnostouli MC, Alexopoulos EC. Stress as a risk factor for multiple sclerosis onset or relapse: A systematic review. *Neuroepidemiology*. 2011; 36:109–120. [PubMed: 21335982]
- Brown RF, Tennant CC, Sharrock M, Hodgkinson S, Dunn SM, Pollard JD. Relationship between stress and relapse in multiple sclerosis: part I. Important features. *Multiple Sclerosis*. 2006; 12:453–464. [PubMed: 16900759]
- Chen L, Lui S, Wu QZ, Zhang W, Zhou D, Chen HF, Huang XQ, Kuang WH, Chan RC, Mechelli A, Gong QY. Impact of acute stress on human brain microstructure: An MR diffusion study of earthquake survivors. *Human Brain Mapping*. 2011
- Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences of the United States of America*. 2012
- Cohen, S.; Kessler, RC.; Gordon, UL. Strategies for measuring stress in studies of psychiatric and physical disorder. In: Cohen, S.; Kessler, RC.; Gordon, UL., editors. *Measuring Stress: A Guide for Health and Social Scientists*. Oxford University Press; New York: 1995. p. 3–26.
- Cohen S, Tyrrell DAJ, Smith AP. Psychological stress and susceptibility to the common cold. *New England Journal of Medicine*. 1991; 325:606–612. [PubMed: 1713648]

- Cohen S, Tyrrell DAJ, Smith AP. Negative Life Events, Perceived Stress, Negative Affect, and Susceptibility to the Common Cold. *Journal of Personality and Social Psychology*. 1993; 64:131–140. [PubMed: 8421249]
- Cotton F, Weiner HL, Jolesz FA, Guttmann CRG. MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. *Neurology*. 2003; 60:640–646. [PubMed: 12601106]
- Dantzer R.; O'Connor, JC.; Castanon, N.; Lestage, J.; Kelley, KW. Cytokines and depression: experimental evidence and intermediate mechanisms. In: Pariante, CM.; Nesse, RM.; Nutt, D.; Wolpert, L., editors. *Understanding Depression: A Translational Approach*. Oxford University Press Inc; New York: 2009. p. 123-138.
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*. 2008; 9:46–56.
- Filippi M, Rocca MA, Martino G, Horsfield MA, Comi G. Magnetization transfer changes in the normal appearing white matter precede the appearance of enhancing lesions in patients with multiple sclerosis. *Annals of Neurology*. 1998; 43:809–814. [PubMed: 9629851]
- 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]
- Goodkin DE, Rooney WD, Sloan R, Bacchetti P, Gee L, Vermathen M, Waubant E, Abundo M, Majumdar S, Nelson S, Weiner MW. A serial study of new MS lesions and the white matter from which they arise. *Neurology*. 1998; 51:1689–1697. [PubMed: 9855524]
- 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*. Springer; London: 1996. p. 161-186.
- Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *Journal of Psychosomatic Research*. 1997; 42:17–41. [PubMed: 9055211]
- Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Multiple Sclerosis*. 2009; 15:1518–1524. [PubMed: 19965520]
- Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983; 33:1444–52. [PubMed: 6685237]
- Lazarus, RS.; Folkman, S. *Stress, Appraisal, and Coping*. Springer Pub. Co; New York: 1984.
- Lehman KA, Burns MN, Gagen EC, Mohr DC. Development of the Brief Inventory of Perceived Stress. *Journal of Clinical Psychology*. 2012
- McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Annals of the New York Academy of Sciences*. 2010; 1186:190–222. [PubMed: 20201874]
- Mohr, DC. *The Stress and Mood Management Program for Individuals with Multiple Sclerosis: Therapist Guide*. Oxford Press; New York: 2010a.
- Mohr, DC. *The Stress and Mood Management Program for Individuals with Multiple Sclerosis: Workbook*. Oxford Press; New York: 2010b.
- Mohr DC, Goodkin DE, Bacchetti P, Boudewyn AC, Huang L, Marrietta P, Cheuk W, Dee B. Psychological stress and the subsequent appearance of new brain MRI lesions in MS. *Neurology*. 2000; 55:55–61. [PubMed: 10891906]
- Mohr DC, Goodkin DE, Nelson S, Cox D, Weiner M. Moderating effects of coping on the relationship between stress and the development of new brain lesions in multiple sclerosis. *Psychosomatic Medicine*. 2002; 64:803–9. [PubMed: 12271111]
- Mohr DC, Lovera J, Brown T, Cohen B, Neylan T, Henry R, Siddique J, Jin L, Daikh D, Pelletier D. A randomized trial of stress management for the prevention of new brain lesions in MS. *Neurology*. 2012; 79:412–419. [PubMed: 22786596]
- Mohr DC, Pelletier D. A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis. *Brain, Behavior, and Immunity*. 2006; 20:27–36.

- Pluess M, Wurmser H, Buske-Kirschbaum A, Papousek M, Pirke K-M, Hellhammer D, Bolten M. Positive life events predict salivary cortisol in pregnant women. *Psychoneuroendocrinology*. 2012
- Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 Revisions to the "McDonald Criteria". *Annals of Neurology*. 2005; 58:840–846. [PubMed: 16283615]
- Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1:385–401.
- Rudick RA, Lee JC, Simon J, Fisher E. Significance of T2 lesions in multiple sclerosis: A 13-year longitudinal study. *Annals of Neurology*. 2006; 60:236–242. [PubMed: 16786526]
- SAS Institute Inc. SAS Version 9.2. SAS Institute Inc; Cary, NC: 2008.
- Shafer AB. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. *Journal of Clinical Psychology*. 2006; 62:123–46. [PubMed: 16287149]
- Shimizu M, Pelham BW. The unconscious cost of good fortune: implicit and explicit self-esteem, positive life events, and health. *Health Psychology*. 2004; 23:101–5. [PubMed: 14756609]
- Yamout B, Itani S, Hourany R, Sibaii AM, Yaghi S. The effect of war stress on multiple sclerosis exacerbations and radiological disease activity. *Journal of the Neurological Sciences*. 2010; 288:42–4. [PubMed: 19892371]
- Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*. 1983; 67:361–370. [PubMed: 6880820]

Figure 1.

Time windows during which stressful events, perceived stress, and distress occurred per the follow-back periods of each instrument, relative to the start of a Gd+ lesion and its detection by MRI. Assumes a four week maximum lifespan for Gd+ lesions.

Table 1

Demographics and baseline measures of hypothesis-relevant variables

Age [†]	42.7 (9.8)
Years of Education [†]	15.7 (2.3)
Expanded Disability Status Scale [†]	3.1 (1.5)
Years since MS Diagnosis [†]	7.05 (7.45)
MS Diagnostic Status	
Relapsing-Remitting	118 (98%)
Secondary-Progressive	2 (2%)
Disease Modifying Medication	
Interferon beta 1-a (Avonex)	18 (15%)
Interferon beta 1-b (Betaseron)	10 (8%)
Interferon beta 1-a (Rebif)	17 (14%)
Glatiramer Acetate (Copaxone)	49 (41%)
None	27 (22%)
Female	101 (83%)
Ethnicity	
Caucasian	100 (83%)
Hispanic/Latino	6 (5%)
Native American	3 (3%)
African American	2 (2%)
Asian/Pacific Islander	1 (1%)
Mixed/Other	9 (7%)
Employment Status	
Working	65 (54%)
Unemployed	20 (17%)
Receiving Disability Benefits	22 (18%)
Other (e.g., retired)	14 (12%)
Marital Status	
Married	75 (62%)
Single	26 (22%)
Divorced	11 (9%)
Cohabiting with Partner	7 (6%)
Widowed or Separated	2 (2%)
Has at least one Gd+ Lesion (at baseline)	23 (19%)
Num. of Positive Stressful Events (in the 3 months prior to baseline) [†]	1.23 (1.41)
Num. of Moderate Negative Stressful Events (in the 3 months prior to baseline) [†]	.48 (.72)
Num. of Major Negative Stressful Events (in the 3 months prior to baseline) [†]	1.28 (1.48)

Note. Data are provided as number (percentage) unless otherwise noted. Percentages may not total 100 due to rounding.

[†]Data are provided as mean (SD).

Table 2

Parameter estimates for the prediction of presence or absence of lesions

<i>Non-Time Varying Variables</i>	Gd+ Lesions N=113, 527 Observations			New or Enlarging T ₂ Lesions N=113, 542 Observations		
	<i>B</i>	<i>SE</i>	<i>p</i>	<i>B</i>	<i>SE</i>	<i>p</i>
Intercept	.02	.71	.98	1.41	.60	.02*
Week 16 (Relative to Week 8)	.61	.43	.16	-.10	.36	.78
Week 24 (Relative to Week 8)	.84	.42	.049*	.18	.35	.61
Week 32 (Relative to Week 8)	.72	.43	.09	.03	.36	.93
Week 40 (Relative to Week 8)	.90	.43	.04*	.12	.36	.74
Week 48 (Relative to Week 8) ^a	.11	.63	.87	.04	.50	.93
Age	-.05	.01	<.001**	-.06	.01	<.001**
Treatment ^b	-.92	.32	.004**	-.69	.23	.003**
Baseline Gd+ Lesion (Y/N)	1.42	.27	<.001**	1.23	.25	<.001**
<i>Time-Varying Variables</i>						
Positive Stressful Events	-.64 ^c	.28 ^c	.02* ^c	-.30	.15	.04*
Moderate Negative Stressful Events	.16	.13	.22	.11	.12	.34
Major Negative Stressful Events	.57	.20	.006**	.45	.18	.01*
Positive Stressful Events* Treatment	.78	.33	.02*	-	-	-

^a Week 48 data was excluded for the control group, as it could have been contaminated by the workshop

^b Control = 0, Treatment = 1

^c Given the presence of the interaction effect in the model predicting Gd+ lesions, this parameter constitutes the effect of positive stressful events in the control group

* $p < .05$,

** $p < .01$

Table 3

Percentage of lesion data missing, by group assignment and whether the participant reported at least one stressful life event 4 or 8 weeks prior to the scheduled scan.

Group	Percentage Missing Gd+ Lesion Data			Percentage Missing T2 Lesion Data		
	No Major Negative Events	1+ Major Negative Events	p	No Major Negative Events	1+ Major Negative Events	p
Treatment	21.2%	12.8%	.047*	17.1%	9.4%	.046*
Control	7.8%	11.0%		8.5%	8.1%	
p	<.001**	.65		.02*	.70	
Group	No Positive Events	1+ Positive Events	p	No Positive Events	1+ Positive Events	p
<hr/>						
Treatment	17.5%	17.1%	.93	15.9%	11.9%	.31
Control	5.4%	11.9%	.06	5.4%	10.2%	.15
p	.004**	.15	.009**	.009**	.59	

*
p < .05,

**
p < .01