Multiple Sclerosis and Related Disorders 36 (2019) 101399

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Emotion dysregulation in multiple sclerosis: Impact on symptoms of depression and anxiety

R.S. Prakash[a,*], B. Schirda[a], T.R. Valentine[a], M. Crotty[a], J.A. Nicholas[b]

[a] Department of Psychology, The Ohio State University, 139 Psychology Building 1835 Neil Avenue, Columbus, OH 43210, USA
[b] Division of Neuroimmunology & Multiple Sclerosis, Ohio Health Multiple Sclerosis Center, Columbus, OH, USA

ARTICLE INFO

Keywords:
Multiple sclerosis
Depression
Anxiety
Emotion dysregulation
Quality of life

ABSTRACT

Background: There is consistent evidence for higher prevalence of affective disorders, specifically mood and anxiety disorders, in people with MS (PwMS).
Purpose: The goal of this study was to examine the role of emotion dysregulation in explaining symptoms of depression and anxiety in PwMS.
Methods: Data from 100 PwMS and 98 community controls (CC) were analyzed. Participants completed survey measures assessing symptoms of depression and anxiety, difficulties in emotion regulation, general and health-related quality of life, and use of emotion regulation strategies during emotionally evocative situations in the previous two weeks.
Results: PwMS had higher scores on depression, endorsed greater difficulty regulating emotions, and reported lower health-related quality of life compared with CC. Higher scores on both measures of depression and anxiety were associated with difficulties in emotion regulation and greater use of maladaptive emotion regulation strategies. Additionally, emotion dysregulation - quantified via use of maladaptive strategies and difficulties in regulating emotions - mediated the effect of MS on symptoms of depression.
Conclusions: Emotion dysregulation is associated with symptoms of depression and anxiety in PwMS. Given the malleability of this construct, this study underscores the importance of further investigating emotion dysregulation, and possibly adopting it as a surrogate endpoint in interventions targeting affective disorders in PwMS.

1. Introduction

Multiple sclerosis (MS) is one of the most frequently diagnosed neurological diseases, with 200 new cases each week in the United States, and 2.3 million individuals affected worldwide (National Multiple Sclerosis Society, 2011). People with MS (PwMS) experience a constellation of debilitating and limiting physical symptoms, including difficulties in walking and gait, balance issues, neuropathic pain, spasticity, fatigue, and weakness. Adding to these physical challenges, there is now consistent evidence for a decline in affective functioning in PwMS (Phillips et al., 2014; Prakash et al., 2008).

Specifically, symptoms of depression and anxiety: (1) show the largest effect sizes in between-group investigations (Dahl et al., 2009; Marrie et al., 2013; Patten et al., 2003); (2) are relatively stable over a follow-up period of 4 years for depressive symptoms (Koch et al., 2015) and 2 years for symptoms of anxiety (Janssens et al., 2006); and (3) have critical ramifications for everyday functioning in PwMS, impacting cognitive functioning (Arnett et al., 1999; Diamond et al., 2008), social and occupational functioning (Amato et al., 2001), adherence to disease-modifying therapies (Treadaway et al., 2009), and reducing quality of life (Schirda et al., 2015). Thus, given the importance of these psychiatric disorders in MS, the current study was designed to better understand MS-related group differences on measures of depression and anxiety.

Given the co-occurrence of these two symptoms in PwMS (Hoang et al., 2016; Korostil and Feinstein, 2007), as well as in the general population (Brown et al., 2001; Mineka et al., 1998), there is increasing recognition for the importance of understanding and targeting transdiagnostic factors that explain critical variance in both mood and anxiety disorders (Mansell et al., 2008). Emotion dysregulation – referring to maladaptive patterns of emotional experience and/or expression resulting in interference with goal-directed behavior – is one such construct that is increasingly being employed in the affective sciences as a key player in understanding many forms of psychopathology, especially mood and anxiety disorders (Aldao et al., 2010; Fernandez et al., 2016; Kring and Sloan, 2009). Emotion dysregulation

* Corresponding author.
E-mail address: prakash.30@osu.edu (R.S. Prakash).

https://doi.org/10.1016/j.msard.2019.101399
Received 4 March 2019; Received in revised form 9 September 2019; Accepted 16 September 2019

can be captured either through self-report measures that assess difficulties experienced by participants in regulating emotion-eliciting situations or through an examination of context-inappropriate emotion regulation strategies. One of the widely used multi-faceted measures that assesses limited abilities in regulating emotions is the Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004). The six facets of DERS total together to provide a metric for emotion dysregulation that can be investigated for group and individual differences. In fact, there is emerging evidence for PwMS to endorse higher scores on DERS, reflecting the challenges experienced by those with this chronic condition in regulating emotions in an adaptive way (Phillips et al., 2014). Moreover, emotion dysregulation has been linked with both symptoms of depression and anxiety in a French sample of PwMS, suggesting that this transdiagnostic factor could be helpful in our understanding of affective disorders in MS (Gay et al., 2017).

Emotion dysregulation can also be examined in terms of a failure to recruit context-appropriate processes or strategies resulting in an exaggerated/disproportionate emotional response (Cole et al., 2004; Cole et al., 2017). According to Gross's seminal Process Model of Emotion Regulation (Gross, 1998, 2015), five families of such emotion regulation processes or strategies can be invoked at any stage of the emotion generative cycle that allow for an opportunity to regulate or modulate the emotional response. Over the years, this model has generated a wealth of research, categorizing these strategies as putatively adaptive or putatively maladaptive, based on their implications for symptoms of psychopathology and overall well-being. For example, emotion regulation strategies of cognitive reappraisal (altering the meaning of the situation to reduce the negative intensity), problem-solving (alternate, pragmatic solutions to current emotion-eliciting problems), and acceptance (acknowledgment of current emotional state in response to emotion-eliciting situations) are negatively associated with self-reported symptoms of psychopathology, especially measures of depression and anxiety (Aldao et al., 2010). In contrast, use of maladaptive strategies, like thought avoidance (intentional withdrawal from thoughts associated with the emotional situation), self-criticism (personally criticizing), expressive suppression (intentional withholding of affective experiences from others), and worry/rumination (self-referential negative thinking pertaining to events of the future or the past), on average, are positively associated with symptoms of depression and anxiety (Joormann and Gotlib, 2010; Nolen-Hoeksema, 2000; Segerstrom et al., 2000). Although the literature examining strategy use within PwMS is in its infancy, there is evidence of increased maladaptive strategy use, such as elevated chronic worry (Bruce and Arnett, 2009) and rumination (Sarisoy et al., 2013). Further, lower reported use of the putatively adaptive strategy cognitive reappraisal is linked with reduced quality of life in PwMS (Phillips et al., 2009).

The current study was thus designed to further investigate differences between PwMS and CC on measures of depression and anxiety and examine the contributing role of emotion dysregulation. Based on presented evidence, we hypothesized PwMS to report higher symptoms of depression and anxiety, higher emotion dysregulation, and lower quality of life, both general and health-related. Additionally, we hypothesized PwMS to report using greater maladaptive strategies and fewer adaptive strategies compared with CC. Critically, in this study, we were also interested in examining the extent to which emotion dysregulation – assessed via strategy use and DERS – mediated the impact of MS on symptoms of depression and anxiety (See Fig. 1). We hypothesized that emotion dysregulation would play a critical role in explaining higher symptoms of depression and anxiety in PwMS, such that greater use of maladaptive strategies and infrequent use of adaptive strategies would be associated with higher DERS scores, which would further explain variance in symptoms of depression and anxiety in MS.

2. Methods

2.1. Participants, procedure, and measures

The current online study was administered using Qualtrics and was advertised via online forums, ResearchMatch, and flyers. The title for advertisements targeting individuals with MS was "Online Study Looking at Emotion Regulation in Multiple Sclerosis," and the title for advertisements targeting healthy controls was "Online Study Looking at Emotion Regulation." A detailed phone interview was conducted with every participant after they filled out the online screening survey. The phone interview involved a series of structured questions designed to inquire about demographic characteristics, like age, sex, and education. Additionally, PwMS were administered questions to inquire about the specific characteristics associated with the MS disease course. Specifically, in here, we inquired about when they were diagnosed with MS, the type of MS they had, specific symptoms they were experiencing, last relapse, and their current medications. Additional questions about other neurological disorders or psychiatric disorders were also administered. After determining eligibility following this phone interview, eligible participants were sent the link to Qualtrics surveys.

Self-report measures of depression and anxiety (Hospital Anxiety and Depression Scale; HADS-D and HADS-A, Zigmond and Snaith, 1983); emotion dysregulation (Difficulties in Emotion Regulation Scale; DERS, Gratz and Roemer, 2004); general quality of life (Satisfaction with Life Scale; SWLS, Diener et al., 1985); and health-related quality of life (World Health Organization Quality of Life-BREF; WHOQOL-BREF, WHOQOL Group, 1998) were administered via Qualtrics. Additionally, PwMS completed a measure of disease severity (self-reported Expanded Disability Status Scale; EDSS, (Kurtzke, 1983). For details on these measures, please see the Supplementary Materials.

Emotion regulation strategy use and success of use was obtained through a modified, health-related version of the Contextual Emotion Regulation Assessment (CERA; Aldao and Nolen-Hoeksema, 2012). Overall, this survey required participants to generate twenty-four emotion-eliciting situations that they may have encountered over the previous two weeks across three types of contexts: emotion-elicited (anxiety, anger, sadness, happiness), environment (health, social), and intensity (low, moderate, high). Eight of these situations, spread across various contexts, were presented back to the participants to inquire about use of different ER strategies. For each of these seven different emotion regulation strategies (three adaptive, four maladaptive), participants were then asked to rate their use on a scale of 0 (“not at all”) to 3 (“a lot”). Specifically, strategies that were defined as putatively adaptive were acceptance (“allowing or being accepting of the feelings that you are experiencing, even if they are uncomfortable”), cognitive reappraisal (“think of the situation in a different, more positive way, in order to change how you feel”), and problem-solving (“come up with ideas to fix the problem or change the situation”). Those defined as putatively maladaptive were expressive suppression (“hide your feelings from others”), self-criticism (“criticize yourself for the way you feel”), thought avoidance (“‘avoid thinking about the situation”), and worry/rumination (“worry or ruminate about the situation”). For all group-based differences using GEE analyses, raw scores for the emotion regulation strategies were employed. For situations that were rated 1 or higher, indicating use of that strategy, participants were additionally asked to provide a rating from 0 (“not at all”) to 3 (“very”) on how successful they were at implementing that emotion regulation strategy.

132 individuals with a self-reported diagnosis of MS and 130 age- and sex-matched community controls signed the online consent form and were deemed eligible for the study. Of the consented and eligible participants, a total of 100 PwMS and 98 CC had complete data and were included in all analyses. All participants provided consent, were compensated with a $10 Amazon.com gift card, and the study was approved by the Institutional Review Board of The Ohio State University.

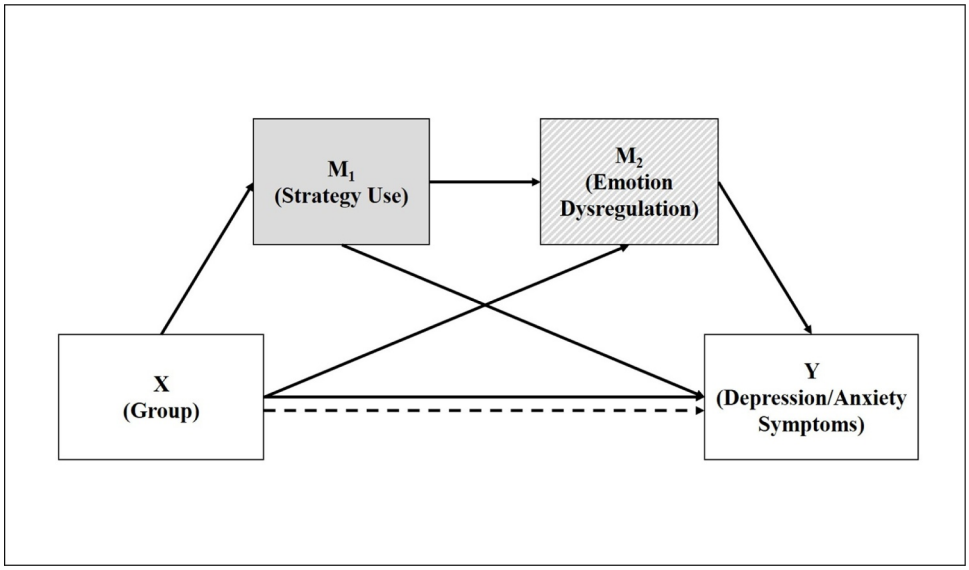

Fig. 1. Serial meditation model depicting the hypothesized effects of group (PwMS, CC) on depression and anxiety symptoms via the indirect pathway of strategy use and emotion dysregulation.

2.2. Statistical analyses

Analyses were conducted in SPSS version 22 and the PROCESS macro for SPSS. Self-report measures of HADS-D, HADS-A, DERS, SWLS, and WHOQoL-BREF were outlier corrected to 2.5 *SD* from the mean in the MS and CC groups separately and checked for normality using the Shapiro–Wilk test of normality. Differences on demographic variables of age and education were examined via the Mann–Whitney *U* test and group differences on sex were examined using chi square. To examine differences between PwMS and CC on self-report measures of depression, anxiety, and quality of life, we employed analysis of covariance (ANCOVA) tests to control for the between group differences on education.

For self-reported ER strategy use, a factor analysis employing principal axis extraction with a direct oblimin rotation (Costello and Osborne, 2005), confirmed our hypothesized bifurcation of ER strategies into a maladaptive cluster (Factor 1) and an adaptive cluster (Factor 2). The maladaptive cluster included expressive suppression, self-criticism, thought suppression, and worry/rumination, whereas the adaptive cluster included acceptance, cognitive reappraisal, and problem solving. See the Supplementary Materials for additional details. We then employed a generalized estimating equation (GEE) approach to examine multivariate MS-related differences in use of self-reported ER strategies. We compared adaptive and maladaptive strategies in a single GEE model with strategy type (ER Type) as a within-subjects factor, Group (PwMS, CC) as a between-subjects factor, and age, sex, and education as covariates. All main effects and interactions were assessed using a full-factorial design. Post-hoc pairwise comparisons were conducted to probe significant interactions. Bonferroni correction was applied to adjust for multiple comparisons. Additionally, we constructed three GEE models to examine the moderating role of context. Details on these three GEE analyses as well as results related to them are presented in the Supplementary Materials.

Lastly, we examined bivariate associations among depression and anxiety symptoms and emotion dysregulation, adaptive and maladaptive strategy use, health-related and general quality of life in the total sample. Of note, emotion regulation strategy use variables were created by first averaging the ratings across situations for each of the seven strategies separately, and then averaging the corresponding strategies, identified in the factor analysis, for adaptive and maladaptive strategy use. To examine whether emotion dysregulation mediated the group-related differences on affective symptoms, we planned to construct serial mediation models for both symptoms of depression and anxiety. However, after controlling for education, we only found differences on symptoms of depression between PwMS and CC, with non-significant between-group differences on anxiety. As such, this mediation model was only constructed to help explain group-related differences in symptoms of depression. Specifically, we constructed a serial mediation model to examine the pathway through which MS-group (*X*) is modeled to have an effect on symptoms of depression (*Y*) indirectly through strategy use (M_1) and DERS (M_2) sequentially (Hayes, 2017; Fig. 1). Serial mediation models are essentially path analyses that allow for multiple mediators to explain the variance between the independent and dependent variables. There are three indirect effects tested in the serial multiple mediation model, reflecting the effect of group on depression explained by: (1) strategy use; (2) DERS scores; and (3) strategy use and DERS scores. We only examined the impact of maladaptive strategies in this model, given the significant bivariate correlation between maladaptive strategy use and symptoms of depression. We employed the bias-corrected bootstrapping technique with 5000 bootstrapping samples. This bootstrapping procedure does not assume a normally distributed indirect effect, rendering it a robust tool with which to examine such effects (Preacher and Hayes, 2004). Reported point estimates are unstandardized coefficients and were considered significant if the 95% confidence intervals (CI) did not contain zero.

3. Results

Our final sample consisted of 100 PwMS (*M* age = 45.51 years; 85.0% female) and 98 CC (*M* age = 45.96 years; 87.8% female). Descriptive statistics for these two samples are presented in Table 1. Given that the two groups were significantly different on years of education, this variable was included in all subsequent analyses that compared group-related differences on self-reported measures of depression, anxiety, emotion dysregulation, quality of life (general and health-related), and strategy use.

3.1. Group differences on symptoms, ER strategy use, and quality of life

As can be seen in Table 2, PwMS, compared with CC, reported significantly higher levels of depressive symptoms, greater emotion dysregulation, as well as lower health-related quality of life, after controlling for education (Table 2). There was no significant difference between the two samples in anxiety symptoms or general quality of life.

Table 1
Demographic and clinical characteristics for 100 MS and 98 CC participants.

		MS participants Mean (SD) or %	Range	CC participants Mean (SD) or %	Range	Group comparisons
Age (y)		45.51 (9.49)	30–59	45.96 (9.43)	30–59	$U = 4758.50$
Female		85.0%		87.80%		$X^2 = .32$
Education (y)		16.03 (2.93)	12–24	17.46 (2.78)	10–26	$U = 3397.00^{**}$
MS Type	RRMS	91.0%		N/A		
	PPMS	5.0%				
	SPMS	4.0%				
Disease Duration (y)		9.38 (7.78)	0–34	N/A		
EDSS		4.64 (1.28)	0–7			

Note: RRMS = Relapsing-remitting MS, SPMS = Secondary Progressive MS, PPMS = Primary Progressive MS
$^{*}p \leq .05$;$^{**}p \leq .01$.

In assessing group-related differences in overall frequency of ER strategy use, the main effect of ER type (Wald $\chi^2 = 188.55$, $p < .001$) was significant. Post-hoc comparisons for the main effect of ER Type indicated adaptive strategies ($M = 1.61$) were employed across groups to a greater extent than maladaptive strategies ($M = .94$, $p < .001$). For group-related differences in success of strategy use, ER Type (Wald $\chi^2 = 299.60$, $p < .001$) and Group X ER Type (Wald $\chi^2 = 4.92$, $p = .03$) were found to be significant predictors of success of strategy use. Post-hoc analysis of the main effect of ER Type indicated that both groups, across situations, had more success implementing adaptive strategies ($M = 2.98$) compared with maladaptive strategies ($M = 2.11$, $p < .001$). When probing the Group X ER Type interaction, we compared the simple effects of adaptive and maladaptive strategy success for the groups separately and found adaptive strategies were implemented more successfully than maladaptive strategies in both MS (M = 2.91 vs. M = 2.15) and CC (M = 3.05 vs. M = 2.07, *ps* < .001) groups. We additionally examined group differences for success of using adaptive and maladaptive strategies. Here, we found a non-significant between-group effect for both adaptive ($p = .08$) and maladaptive ($p = .38$) strategies. Please see Table 3 for additional statistics on the GEE analyses, including covariates and non-significant effects. Also, see the Supplementary Materials for analyses examining the moderating role of context on strategy implementation and success of use.

Table 3
Generalized estimating equations statistics for strategy use and success of use in MS participants vs. community controls.

	Wald χ^2	d*f*	*p*
Strategy use model (QICC: 10087.50)			
(Intercept)	60.14	1	<.001
Age	0.87	1	0.35
Sex	0.48	1	0.49
Education	3.47	1	0.06
Group	2.66	1	0.1
ER Type	188.54	1	<.001
Group X ER Type	1.19	1	0.28
Success of use model (QICC: 4407.37)			
(Intercept)	78.84	1	<.001
Age	0.61	1	0.44
Sex	1.50	1	0.22
Education	0.94	1	0.33
Group	0.13	1	0.72
ER Type	299.60	1	<.001
Group X ER Type	4.92	1	0.03

Note: ER = Emotion Regulation.

3.2. The role of emotion dysregulation

As hypothesized, both depression and anxiety symptoms were associated with greater maladaptive strategy use ($r_s = .41$, $r_s = .48$, respectively; *ps* < .001), greater emotion dysregulation as measured by the DERS ($r_s = .56$, $r_s = .62$, respectively *ps* < .001), lower general quality of life measured by SWLS ($r_s = -.67$, $r_s = -.43$, respectively; *ps* < .001), and health-related quality of life measured by WHOQoL-BREF ($r_s = -.79$, $r_s = -.56$, respectively; *ps* < .001) . However, there was no significant association between depression or anxiety and adaptive strategy use ($r_s = -.06$, $r_s = -.13$; *ps* > .08).

One of the aims of this study was to understand whether emotion dysregulation explained the group-related differences on symptoms of depression and anxiety. Controlling for the effects of education, we found significant differences between PwMS and CC on symptoms of depression, but not anxiety. Thus, we only constructed one serial mediation model, to examine whether the impact of MS-group on depression would be indirectly explained through metrics of emotion dysregulation. Further, given the significant associations of maladaptive strategies with depression, the model only included maladaptive strategies.

Table 2
Group comparisons for measures of depression, anxiety, emotion dysregulation, and quality of life.

	MS participants ($n = 100$) Mean (SD)	Range	CC participants ($n = 98$) Mean (SD)	Range	Group comparisons[a]
HADS-D	5.91 (4.03)	0–15.98	3.76 (3.61)	0–13.28	$F(1,195) = 10.47^{**}$
HADS-A	8.01 (4.15)	0–17	6.98 (4.43)	0–18.12	$F(1,195) = 2.73$
DERS	78.58 (24.58)	36–140.10	69.15 (21.20)	36–126.37	$F(1,195) = 6.51^{**}$
SWLS	20.87 (8.21)	5–35	23.57 (8.27)	5–35	$F(1,195) = 2.49$
WHOQoL	54.96 (11.42)	29–78	62.33 (9.42)	38.01–80	$F(1,195) = 19.30^{**}$
Physical	13.36 (3.44)	6–20	16.49 (2.62)	7–20	
Psychological	12.93 (3.45)	4–19	14.64 (2.86)	7–20	
Social	13.11 (4.09)	4–20	14.43 (3.73)	4–20	
Environmental	15.56 (2.95)	7–20	16.67 (2.65)	8–20	

Note: HADS-D = Hospital Anxiety and Depression Scale – Depression, HADS-A = Hospital Anxiety and Depression Scale – Anxiety, DERS = Difficulties in Emotion Regulation Scale, QoL composite = Quality of Life composite of the World Health Organization – BREF (WHOQoL) and Satisfaction with Life Scale (SWLS).
$^{*}p \leq .05$; $^{**}p \leq .01$.
[a] Education included as a covariate.

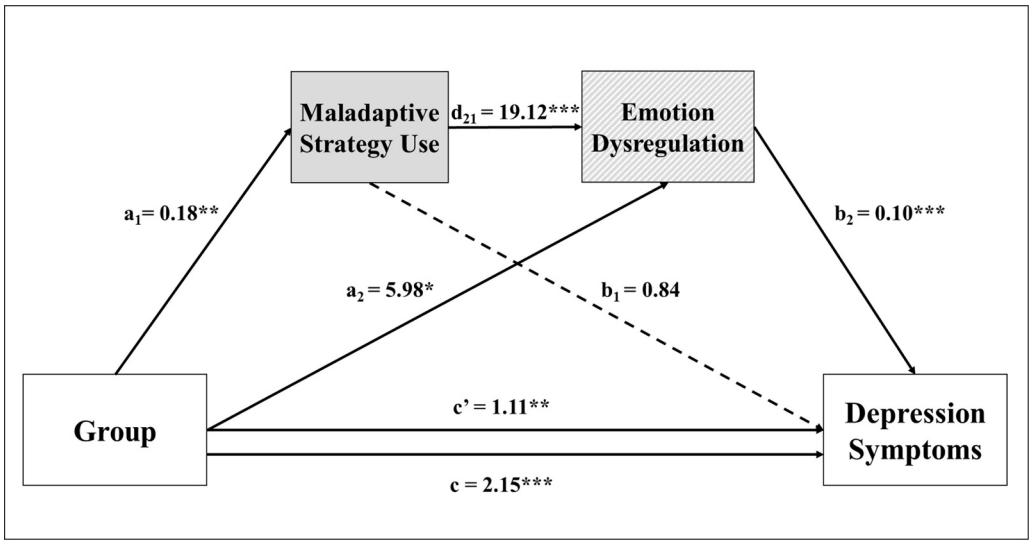

Fig. 2. Depiction of the serial mediation model for group predicting depression symptoms via the indirect pathways including maladaptive strategy use and emotion dysregulation. *Note*: Solid lines represent significant pathways and dashed-line represent non-significant pathways. The total effect (*c*) and the direct effect is (*c'*) are shown in the model.

The serial multiple mediation model revealed a significant total indirect effect of group on depression through maladaptive strategy use and DERS (point estimate = 1.05, 95% CI = [0.38, 1.75]; Fig. 2). Specifically, we observed a significant path through use of maladaptive strategies and DERS ($a_1d_{21}b_2$ = 0.33, 95% CI = [0.09, 0.62]), such that group differences in depression symptoms were explained by the observed differences in PwMS endorsing use of a greater number of maladaptive strategies and higher DERS. Further, the path through DERS (a_2b_2 = 0.57, 95% CI = [0.01, 1.16]) alone was significant. The inclusion of maladaptive strategy use and DERS scores in the model resulted in a decrease of the significant total effect estimate (c = 2.15, 95% CI = [1.08, 3.23]) of MS-group differences on depression (c' = 1.11 vs. c = 2.15) to the direct effect (c' = 1.11, 95% CI = [0.24, 1.97]), suggesting that these two variables critically accounted for the observed group differences on symptoms of depression. Of note, the direct effect remained significant, suggesting the possible involvement of additional mediating variables not examined in the study.

4. Discussion

Our goal in the current study was to understand the role of emotion dysregulation in explaining variance in symptoms of depression and anxiety in individuals diagnosed with MS. With lifetime prevalence rates of 31% and 22% for mood and anxiety disorders, respectively (Boeschoten et al., 2017), and the evidence that comorbidity of these two disorders is associated with increased hospitalizations and worse prognosis (Marrie et al., 2015), the study of transdiagnostic factors like emotion dysregulation, becomes critical within this population. Our results, corroborating previous literature, demonstrated reduced health-related quality of life, and significant elevations in symptoms of depression in PwMS compared with controls. However, after controlling for education, we did not find significant differences between the two groups in either symptoms of anxiety or general quality of life. Although these results are surprising, given the higher prevalence of anxiety disorders in the MS population (Marrie et al., 2015; Boeschoten et al., 2017), there is also increasing evidence for a negative relationship between low anxiety and higher education, both in the general population (Bjelland et al., 2008) and in individuals with MS (Pham et al., 2018). Thus, although the mean HADS-A score in our sample of MS individuals was comparable to that of previous studies (see Pham et al., 2018), controlling for between-group effects on education, resulted in non-significant effects on both measures of anxiety and general quality of life.

However, both depression and anxiety symptoms were associated with reduced quality of life. These findings corroborate the existent literature reporting a consistently negative association between symptoms of depression and anxiety and quality of life (Butler et al., 2016; Fernandez-Jimenz and Arnett, 2015; Hayter et al., 2016; Korostil and Feinstein, 2007). In fact, depression, across many studies, has been found to be the strongest predictor of quality of life, over and above disease severity, suggesting the need to better understand and integrate psychiatric health in treatment models for PwMS (Fernandez-Jimenz and Arnett, 2015; Karatepe et al., 2011).

This study, to our knowledge, is the first to examine differences between PwMS and community controls in the frequency of use of various emotion regulation strategies. Given the elevated prevalence of mood and anxiety disorders and the chronic nature of the MS disease course, we hypothesized greater use of maladaptive strategies compared with adaptive strategies in PwMS. We did not find support for group-related differences in use of strategies, thus suggesting that individuals with MS utilize similar strategies to age- and sex-matched controls. Interestingly, there were also no significant group differences in success of strategy implementation, thus suggesting that PwMS are successfully able to engage in volitional regulation of emotion.

Contributing critically to the existent literature, our study demonstrated the importance of investigation emotion dysregulation in PwMS. Both anxiety and depression scores were associated with difficulties in emotion regulation and use of maladaptive strategies, thus corroborating previous literature providing a strong link between symptoms of psychopathology and emotion dysregulation (Gay et al., 2017; Aldao et al., 2010). Given the lack of significant between-group differences on anxiety, we only constructed our a priori serial mediation model to help explain differences between PwMS and CC on symptoms of depression. In the current study, we found group-related differences in symptoms of depression were explained by a pathway of greater use of maladaptive strategies, such as worry and rumination, expressive suppression, and thought avoidance, and greater perceived emotion dysregulation. Specifically, our results support an indirect pathway of PwMS endorsing greater use of maladaptive strategies, which was then associated with higher emotion dysregulation, and the greater emotion dysregulation was associated with higher symptoms of depression. Collectively, these results point to the importance of maladaptive strategy use in linkages with psychopathology in MS. These results corroborate the broader emotion regulation literature where a consistent, positive relationship has been reported between use of maladaptive strategies and symptoms of psychopathology (Michl et al., 2013; Muris et al., 2005; Nolen-Hoeksema, 2000) as well as in the MS literature, where maladaptive coping strategies have stronger implications for adjustment to MS, compared with adaptive coping strategies (Dennison et al., 2009). Moreover, use of these maladaptive strategies

has been linked with cognitive difficulties (Beaudreau and O'Hara, 2008; Demeyer et al., 2012), decreases in heart rate variability (Aldao et al., 2013; Brosschot et al., 2007), and reduced social support (Gross and John, 2003), thus suggesting a more global, negative relationship between these strategies on cognitive and physical health.

Multiple sclerosis is a chronic disease, with an average onset in the mid-30s, thereby necessitating significant adjustments to the limitations imposed in the physical, cognitive, and affective domains of functioning. Moreover, the immune-mediated inflammatory response has been found to induce a cascade of alterations in the neurobiological circuitry supporting "sickness behaviors," resulting in many of the symptoms of depression observed in PwMS (Gold and Irwin, 2009). Thus, given the chronic nature of the disease and the associated inflammatory response, it is imperative that psychiatric health be considered in integrative care models of MS. Our results suggest that emotion dysregulation, and specifically use of maladaptive strategies, play a critical role in the explaining variances in depression symptoms in MS. We encourage future intervention studies, especially ones designed to improve psychiatric health in PwMS, to incorporate measures of emotion dysregulation as surrogate endpoints in their clinical trials.

It is important to interpret the results of the study in the context of some key limitations. Firstly, this was an online study and although, we completed both online and phone screens, we cannot entirely validate participant authenticity. Additionally, the cross-sectional design of the study precludes us from drawing causal inferences. Future intervention studies targeting a reduction in maladaptive strategy use would be better equipped to answer whether a reduction in use of maladaptive strategies improves symptoms of depression in PwMS

Declaration of Competing Interest

Prakash, R.S. has received honorarium from Sanofi-Genzyme. Nicholas, J.A has received research funding from PCORI, Novartis, Biogen Idec, Sanofi-Genzyme, and Alexion. Nicholas, J.A. has received honoraria for speaking and consulting from MSAA, EMD Serono, Biogen Idec, and Genzyme.

Acknowledgments

This work was supported by the National Multiple Sclerosis Society [grant number PP2183].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.101399.

References

Aldao, A., Nolen-Hoeksema, S., Schweizer, S., 2010. Emotion-regulation strategies across psychopathology: a meta-analytic review. Clin. Psychol. Rev. 30 (2), 217–237. https://doi.org/10.1016/j.cpr.2009.11.004.

Aldao, A., Mennin, D.S., McLaughlin, K.A., 2013. Differentiating worry and rumination: evidence from heart rate variability during spontaneous regulation. Cogn. Ther. Res. 37 (3), 613–619. https://doi.org/10.1007/s10608-012-9485-0.

Aldao, A., Nolen-Hoeksema, S, 2012. The influence of context on the implementation of adaptive emotion regulation strategies. Behav. Res. Ther. 50 (7–8), 493–501. https://doi.org/10.1016/j.brat.2012.04.004.

Amato, M.P., Ponziani, G., Rossi, F., et al., 2001. Quality of life in multiple sclerosis: the impact of depression, fatigue, and disability. Mult. Scler. J. 7, 340–344.

Arnett, P.A., Higginson, C.I., Voss, W.D., Bender, W.I., Wurst, J.M., Tippin, J.M., 1999. Depression in multiple sclerosis: relationship to working memory capacity. Neuropsychology 13 (4), 546–556. https://doi.org/10.1037/0894-4105.13.4.546.

Beaudreau, S.A., O'Hara, R., 2008. Late-life anxiety and cognitive impairment: a review. Am. J. Geriatr. Psychiatry 16 (10), 790–803. https://doi.org/10.1097/JGP.0b013e31817945c3.

Bjelland, I., Krokstad, S., Mykletun, A., Dahl, A.A., Tell, G.S., Tambs, K., 2008. Does a higher educational level protect against anxiety and depression? The HUNT study. Soc. Sci. Med. 66 (6), 1334–1345.

Boeschoten, R.E., Braamse, A.M., Beekman, A.T., Cuijpers, P., van Oppen, P., Dekker, J., Uidehaag, B.M., 2017. Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. J. Neurol. Sci. 372.

Brosschot, J.F., Van Dijk, E., Thayer, J.F., 2007. Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. Int. J. Psychophysiol. 63 (1), 39–47.

Brown, T.A., Campbell, L.A., Lehman, C.L., Grisham, J.R., Mancill, R.B., 2001. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J. Abnorm. Psychol. 110 (4), 585–599. https://doi.org/10.1037//0021-843X.110.4.585.

Bruce, J.M., Arnett, P., 2009. Clinical correlates of generalized worry in multiple sclerosis. J. Clin. Exp. Neuropsychol. 31 (6), 698–705. https://doi.org/10.1080/13803390802484789.

Butler, E., Matcham, F., Chalder, T., 2016. A systematic review of anxiety amongst people with multiple sclerosis. Mult. Scler. Relat. Disord. 10, 145–168.

Cole, P.M., Martin, S.E., Dennis, T.A., 2004. Emotion regulation as a scientific construct: methodological challenges and directions for child development research. Child Dev. 317–333.

Cole, P.M., Bendezu, J.J., Ram, N., Chow, S.M., 2017. Dynamical systems modeling of early childhood self-regulation. Emotion 17 (4), 684–699.

Costello, A.B., Osborne, J.W., 2005. Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis. Pract. Assess. Res. Eval. 10 (7).

Dahl, O.P., Stordal, E., Lydersen, S., Midgard, R., 2009. Anxiety and depression in multiple sclerosis. A comparative population-based study in Nord-Trondelag County, Norway. Mult. Scler. 15, 1495–1501.

Demeyer, I., De Lissnyder, E., Koster, E.H., De Raedt, R., 2012. Rumination mediates the relationship between impaired cognitive control for emotional information and depressive symptoms: a prospective study in remitted depressed adults. Behav. Res. Ther. 50 (5), 292–297.

Dennison, L., Moss-Morris, R., Chalder, T., 2009. A review of psychological correlates of adjustment in patients with multiple sclerosis. Clin. Psychol. Rev. 29 (2), 141–153. https://doi.org/10.1016/j.cpr.2008.12.001.

Diamond, B.J., Johnson, S.K., Kaufman, M., Graves, L., 2008. Relationships between information processing, depression, fatigue, and cognition in multiple sclerosis. Arch. Clin. Neuropsychol. 23, 189–199.

Diener, E., Emmons, R.A., Larsen, R.J., Griffin, S., 1985. The satisfaction with life scale. J. Pers. Assess. 49 (1), 71.

Fernandez, K.C., Jazaieri, H., Gross, J.J., 2016. Emotion regulation: a transdiagnostic perspective on a new RDoC domain. Cogn. Ther. Res. 40 (3), 426–440. https://doi.org/10.1007/s10608-016-9772-2.

Fernandez-Jimenz, E., Arnett, P.A., 2015. Impact of neurological impairment, depression, cognitive function and coping on quality of life of people with multiple sclerosis: a relative importance analysis. Mult. Scler. J. 21 (11), 1468–1472.

Gay, M.-C., Bungener, C., Thomas, S., Vrignaud, P., Thomas, P.W., Baker, R., ... Montreuil, M., 2017. Anxiety, emotional processing and depression in people with multiple sclerosis. BMC Neurol. 17 (43).

Göksel Karatepe, A., Kaya, T., Günaydn, R., Demirhan, A., Çe, P., Gedizlioğlu, M., 2011. Quality of life in patients with multiple sclerosis: the impact of depression, fatigue, and disability. Int. J. Rehabil. Res. 34 (4), 290–298. https://doi.org/10.1097/MRR.0b013e32834ad479.

Gold, S.M., Irwin, M.R., 2009. Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. Immunol. Allergy Clin. 29 (2), 309–320.

Gratz, K.L., Roemer, L., 2004. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J. Psychopathol. Behav. Assess. 26 (1), 41–54.

Gross, J.J., 1998. The emerging field of emotion regulation: an integrative review. Rev. Gen. Psychol. 2 (3), 271.

Gross, J.J., 2015. Emotion regulation: current status and future prospects. Psychol. Inquiry 26 (1), 1–26. https://doi.org/10.1080/1047840X.2014.940781.

Gross, J.J., John, O.P., 2003. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J. Pers. Soc. Psychol. 85 (2), 348–362. https://doi.org/10.1037/0022-3514.85.2.348.

Hayes, A.F., 2017. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. Guilford Publications.

Hayter, A.L., Salkovskis, P.M., Silber, E., Morris, R.G., 2016. The impact of health anxiety in patients with relapsing remitting multiple sclerosis: misperception, misattribution and quality of life. Br. J. Clin. Psychol. 55 (4), 371–386. https://doi.org/10.1111/bjc.12106.

Hoang, H., Laursen, B., Stenager, E.N., Stenager, E., 2016. Psychiatric co-morbidity in multiple sclerosis: the risk of depression and anxiety before and after MS diagnosis. Mult. Scler. J. 22 (3), 347–353.

Janssens, A.C., Buljevac, D., van Doorn, P.V., van der Meche, F.G., Polman, C.H., Passchier, J., Hintzen, R.Q., 2006. Prediction of anxiety and distress following diagnosis of multiple sclerosis: a two-year longitudinal study. Mult. Scler. J. 12 (6), 794–801.

Joormann, J., Gotlib, I.H., 2010. Emotion regulation in depression: relation to cognitive inhibition. Cogn. Emot. 24 (2), 281–298.

Koch, M.W., Patten, S., Berzins, S., Zhornitsky, S., Greenfield, J., Wall, W., Metz, L.M., 2015. Depression in multiple sclerosis: a long-term longitudinal study. Mult. Scler. J. 21 (1), 76–82. https://doi.org/10.1177/1352458514536086.

Korostil, M., Feinstein, A., 2007. Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult. Scler. J. 13 (1), 67–72.

Kring, A.M., Sloan, D.M., 2009. Emotion Regulation and Psychopathology: A Transdiagnostic Approach to Etiology and Treatment. Guilford Press.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11) 1444–1444. https://doi.org/10.1212/WNL.33.11.1444.

Mansell, W., Harvey, A.G., Watkins, E.R., Shafran, R., 2008. Cognitive behavioral processes across psychological disorders: a review of the utility and validity of the transdiagnostic approach. Int. J. Cogn. 1 (3), 181–191.

Marrie, et al., 2013. Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. BMC Neurol. 13 (1), 13–16.

Marrie, R.A., Reingold, S., Cohen, J., Stuve, O., Trojano, M., Sorensen, P.S., …, Reider, N., 2015. The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult. Scler. 21 (3), 305–317. https://doi.org/10.1177/1352458514564487.

Michl, L.C., McLaughlin, K.A., Shepherd, K., Nolen-Hoeksema, S., 2013. Rumination as a mechanism linking stressful life events to symptoms of depression and anxiety: longitudinal evidence in early adolescents and adults. J. Abnorm. Psychol. 122 (2), 339–352.

Mineka, S., Watson, D., Clarck, L.A., 1998. Comorbidity of anxiety and unipolar mood disorders. Annu. Rev. Psychol. 49 (1), 377–412. https://doi.org/10.1146/annurev.psych.49.1.377.

Muris, P., Roelofs, J., Rassin, E., Franken, I., Mayer, B., 2005. Mediating effects of rumination and worry on the links between neuroticism, anxiety and depression. Pers. Individ. Differ. 39 (6), 1105–1111.

National Multiple Sclerosis Society, 2011. Who Gets MS? Retrieved from. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx.

Nolen-Hoeksema, S., 2000. The Role of rumination in depressive disorders and mixed anxiety/depressive symptoms. J. Abnorm. Psychol. 109 (3), 504–511.

Patten, S.B., Beck, C.A., Williams, J.V.A., 2003. Major depression in multiple sclerosis: a population-based perspective. Neurology 61 (11), 1524–1527. https://doi.org/10.1212/01.WNL.0000095964.34294.B4.

Pham, T., Jetté, N., Bulloch, A.G.M., Burton, J.M., Wiebe, S., Patten, S.B., 2018. The prevalence of anxiety and associated factors in persons with multiple sclerosis. Mult. Scler. Relat. Disord. 19, 35–39.

Phillips, L.H., Saldias, A., McCarrey, A., Henry, J.D., Scott, C., Summers, F., Whyte, M., 2009. Attentional lapses, emotional regulation and quality of life in multiple sclerosis. Br. J. Clin. Psychol. 48 (1), 101–106.

Phillips, L.H., Henry, J.D., Nouzova, E., Cooper, C., Radlak, B., Summers, F., 2014. Difficulties with emotion regulation in multiple sclerosis: links to executive function, mood, and quality of life. J. Clin. Exp. Neuropsychol. 36 (8), 831–842. https://doi.org/10.1080/13803395.2014.946891.

Prakash, R.S., Snook, E.M., Lewis, J.M., Motl, R.W., Kramer, A.F., 2008. Cognitive impairments in relapsing-remitting multiple sclerosis: a meta-analysis. Mult. Scler. 14 (9), 1250–1261. https://doi.org/10.1177/1352458508095004.

Preacher, K.J., Hayes, A.F., 2004. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav. Res. Methods Instrum. Comput. 36 (4), 717–731.

Sarisoy, G., Terzi, M., Gumus, K., Pazvantoglu, O., 2013. Psychiatric symptoms in patients with multiple sclerosis. Gen. Hosp. Psychiatry 35 (2), 134–140.

Schirda, B., Nicholas, J.A., Prakash, R.S., 2015. Examining trait mindfulness, emotion dysregulation, and quality of life in multiple sclerosis. Health Psychol. 34 (11), 1107–1115. https://doi.org/10.1037/hea0000215.

Segerstrom, S.C., Tsao, J., Alden, L., Craske, M., 2000. Worry and rumination: repetitive thought as a concomitant and predictor of negative mood. Cogn. Ther. Res. 24 (6), 671–688.

Treadaway, K., Cutter, G., Salter, A., Lynch, S., Simsarian, J., Corboy, J., Schaeffer, L., 2009. Factors that influence adherence with disease-modifying therapy in MS. J. Neurol. 256 (4), 568–576. https://doi.org/10.1007/s00415-009-0096-y.

WHOQOL Group, 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol. Med. 28 (3), 551–558.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67 (6), 361–370.