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Neurovegetative Symptoms in Patients with Multiple Sclerosis: Fatigue, not Depression

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Abstract

Elucidating the relationship between fatigue and depression in multiple sclerosis (MS) patients is complicated by ambiguity regarding how these two constructs should be delineated. Neurovegetative symptoms of depression may reflect depression in MS patients, as they do in non-neurological populations; instead these items may measure disease-related fatigue; or disease-related fatigue and depression may reflect the same syndrome in MS patients. The present study sought to evaluate these possibilities by characterizing the underlying factor structure of self-report items designed to measure fatigue and depression symptoms. Questionnaires designed to measure fatigue and depression were administered to 174 MS patients and 84 healthy controls, and these items were subject to factor analysis. Results suggest that neurovegetative symptoms are poor indicators of depression in MS patients. Neurovegetative depression items were removed from the final model due to poor psychometric properties, or they loaded on Fatigue or Sleep Disturbance factors. The correlation between latent factors Depression and Fatigue was large (.47), but does not indicate that these phenomena are manifestations of the same construct. Hence, the results of this study support the notion that vegetative symptoms of depression do not reflect depression in MS patients, but instead measure symptoms of fatigue and sleep disturbance. (*JINS*, 2011, *17*, 46–55)

Keywords: Demyelinating diseases, Neurodegenerative diseases, Diagnosis, Symptoms, Mood disorders, Factor analysis

INTRODUCTION

Depression is common in patients with multiple sclerosis (MS). Lifetime prevalence of major depressive disorder following MS diagnosis is approximately 50% (Joffe, Lippert, Gray, Sawa, & Horvath, 1987), with point-prevalence rates between 15 and 20% (Patten, Beck, Williams, Barbui, & Metz, 2003). Fatigue is also prevalent in MS patients, with up to 88% complaining of significant fatigue and 28% reporting it as their most troubling symptom (Krupp, Alovarez, LaRocca, & Scheinberg, 1988). Findings relating fatigue and depression in MS have been mixed, but generally more rigorous studies have reported positive associations (Arnett, Barwick, & Beeney, 2008; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Flachenecker et al., 2002; Krupp et al., 1988; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989; Mohr, Hart, & Goldberg, 2003; Moller, Wiedemann, Rohde, Backmund, & Sonntag, 1994; Schwartz, Coulthard-Morris, & Zeng, 1996; Voss, Arnett, Higginson, Randolph, Campos, & Dyck, 2002). Elucidating the relationship between fatigue and depression in patients with MS has important clinical and theoretical implications, not only because of the prevalence of these conditions, but also in light of evidence suggesting that both phenomena significantly impact overall quality of life (Amato, Ponziani, Rossi, Liedl, Stefanile, & Rossi, 2001; Janardhan & Bakshi, 2002). However, this endeavor has been complicated by conceptual and methodological ambiguity regarding how these two constructs should be delineated.

Many investigators have recognized theoretical and pragmatic challenges related to assessing depression in individuals with MS, namely, MS disease symptoms may overlap with neurovegetative symptoms of depression. Examples of neurovegetative symptoms include fatigue, trouble concentrating, and psychomotor slowing. It is readily obvious that self-report items designed to assess neurovegetative symptoms of depression appear similar to items comprising disease-related fatigue measures. What remains unclear, however, is the nature of this methodological and conceptual overlap. Specifically, are fatigue and depression manifestations of the same phenomena in MS patients? Are they distinct but related constructs? Or rather, are they distinct and unrelated constructs that demonstrate an artifactual relationship due to measurement limitations?

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At the heart of this issue is ambiguity regarding neurovegetative depression symptoms and their validity as indices of depression in MS patients.

Commonly used measures of depression (such as the Beck Depression Inventory; BDI; Beck & Steer, 1987) have been validated in non-neurological populations. Although research demonstrates that neurovegetative symptoms are good indicators of depression in otherwise healthy individuals, Beck and colleagues acknowledge that these symptoms may have a different relationship to depression in medical and elderly populations (Beck, Steer, & Carbin, 1988). Research supports the notion that vegetative depression items may reflect MS symptoms and not depression. For example, Nyenhius, Rao, Zajecka, Luchetta, Bernardin, and Garron (1995) found that, although there was little difference between MS patients' and non-MS patients' endorsement of mood symptoms, vegetative depression items accounted for group differences in overall depression scores. Furthermore, Beeney and Arnett (2008) examined the relationships between reliable-change in three depressive symptom domains (mood, evaluative, and vegetative) over a 3-year period (Beeney & Arnett, 2008). They found that, whereas reliable changes in mood and evaluative symptoms were correlated, change in vegetative symptoms was statistically unrelated to changes in the other depression symptom domains, suggesting that a common process underlies mood and evaluative, but not vegetative, depression symptoms.

In contrast to these findings, others have concluded that vegetative depression symptoms do indeed measure depression in MS patients. For example, Aikens and colleagues reported that vegetative symptoms of depression were not elevated in MS patients, and were unrelated to MS disease parameters (Aikens et al., 1999). Furthermore, Moran and Mohr found that Cognitive Behavior Therapy (CBT) for depressed MS patients resulted in a reduction of all BDI items, including those related to neurovegetative depression symptoms (Moran & Mohr, 2005).

MS-related fatigue, has also been challenging to characterize. A consensus conference on MS-related fatigue defined it as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). The most common method for assessing fatigue is self-report, which has some inherent limitations. Self-report measures may be vulnerable to affective bias at the point of data collection (Krupp & Christodoulou, 2001). Additionally, some self-report measures define fatigue narrowly, focusing primarily on physical or motoric fatigue, whereas others define fatigue broadly, including items related to cognitive and socio-emotional functioning (Fisk et al., 1994).

In light of the conceptual and methodological overlap between depression symptoms and MS-related fatigue symptoms, three hypotheses regarding the status of vegetative depression symptoms remain plausible. First, vegetative symptoms of depression may, in fact, reflect depression in MS patients just as they do in non-neurological populations. Alternatively, items designed to capture vegetative depression symptoms may instead measure disease-related fatigue in MS patients. Finally, it is possible that disease-related fatigue and depression are manifestations of the same syndrome in MS patients.

The present study sought to evaluate these three possibilities by using factor analysis to uncover the underlying factor structure of self-report items from fatigue and depression measures. If vegetative depression items do measure depression in MS patients, factor analysis should reveal that these items load on the same latent factor as mood and evaluative items. Alternatively, if these items measure MS-related fatigue, they would load on a fatigue factor, along with items from fatigue scales. Finally, if fatigue and depression are manifestations of a single syndrome in MS patients, fatigue and depression items should load on a single factor. As a comparison, the structure of these measures in healthy controls is also explored.

METHODS

Participants

MS group

The MS sample consists of 174 individuals recruited to participate in one of two similar studies at two sites: Washington State University (WSU) and The Pennsylvania State University (PSU). Participants were recruited from neurologists and a local MS society in both locations. All MS participants had definite or probable MS, and were initially diagnosed by board-certified neurologists according to the criteria of Poser et al. (1983). Participants' diagnoses were subsequently updated in accord with McDonald et al. (McDonald et al., 2001) criteria and all met criteria for MS based on this new system, except for two participants who had "possible MS." One of these participants was subsequently diagnosed with definite MS 3 years later at a longitudinal follow-up research visit; the other was not retested.

Exclusionary criteria included history of substance abuse, nervous system disorder other than MS, severe motor or visual impairment that may interfere with testing, premorbid history of a learning disability, and severe physical or neurological impairment that would interfere with evaluation at the testing site.

Controls

Eighty-four neurologically healthy community-based controls were recruited by asking MS participants to recommend a friend, and by posting advertisements in public places and via the university newswires. An attempt was made to match controls with MS participants on demographic features (i.e., age, education, and gender) as closely as possible. The same relevant inclusionary criteria used with the MS patients were used.

Procedure

Informed consent was obtained at the initial session. Testing sessions consisted of administration of measures assessing cognitive, physical, and emotional functioning, delivered by

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Table 1. Characteristics of the sample

	MS group $N = 174$				Control group $N = 84$	
	M	(*SD*)			*M*	(*SD*)
Age	47	(8.63)			46.4	(11.20)
Education	14.5	(2.17)			15.2	(2.44)
Diagnosis duration	9.2	(7.11)				
Symptom duration	14.7	(9.36)				
EDSS	4.6	(1.52)				
	Raw scores		T-scores†		Raw scores	
	M	(*SD*)	*M*	(*SD*)	*M*	(*SD*)
CMDI Total**	76	(20.8)	57.8	(12.8)	63.2	(16.3)
Mood*	21.9	(8.3)	53.8	(11.8)	19.3	(7.0)
Evaluative**	19.1	(7.2)	55.6	(15.6)	16.5	(4.6)
Vegetative**	35.3	(9.7)	59.2	(11.5)	27.5	(8.5)
FIS**	64	(32.4)	74.3	(17.3)	18.5	(18.7)
FSS**	48.6	(13.4)	69.3	(11.9)	26.9	(11.3)
% Female	81%				74%	
% Caucasian	90%				98%	
% Depression history	50%				30%	
Course type						
Relapsing Remitting	70%					
Secondary Progressive	22%					
Primary Progressive	6%					
Progressive Relapsing	2%					

*Group differences are significant at alpha = .05.
**Group difference are significant at alpha = .01.
†T-scores are calculated using the control group as a reference.
EDSS = Expandied Disability Status Scale; CMDI = Chicago Multiscale Depression Inventory; FIS = Fatigue Impact Scale; FSS = Fatigue Severity Scale. Age, Education, Diagnosis, and Symptom duration are in years. Depression History is defined as depression symptoms for which the participant either sought treatment, or considered seeking treatment.

graduate students trained by a licensed psychologist and clinical neuropsychologist. Participants were paid $75 for participation. Those in the MS group were provided with feedback and given a written clinical report. Data were obtained in compliance with the standards of the WSU and PSU Institutional Review Boards. See Table 1 for sample characteristics.

Measures

Depression. Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995)—The CMDI is a self-report questionnaire containing three 14-item subscales assessing Vegetative, Mood, and Evaluative symptoms of depression. The CMDI is well-suited for the present study because it was designed for use in medical populations, and it includes an adequate number of items assessing each domain of symptoms.

Depression history. Participants were asked if they had a history of depression for which they sought treatment, or considered seeking treatment.

Fatigue. The Fatigue Severity Scale (FSS; Krupp et al., 1988)—The FSS is one of the most widely used fatigue scales. It principally measures the impact of fatigue on functioning (Krupp et al., 1988). The developers of the FSS report high internal consistency and good test–retest reliability (Krupp et al., 1989). The FSS has been shown to be sensitive to change over time and in response to treatment, and is able to distinguish patients with different diagnoses (Krupp et al., 1989; Pepper, Krupp, Friedberg, Doscher, & Coyle, 1993).

The Fatigue Impact Scale (FIS; Fisk et al., 1994)—The FIS is a 40-item self-report measure designed to assess the effects of fatigue on quality of life in cognitive, physical, and psychosocial domains. The initial validation study of this measure included participants with chronic fatigue syndrome (CFS), MS, and hypertension. This study reported good internal consistency for the three subscales ($> .87$ for each scale). Discriminant function analysis correctly classified 80.0% of the CFS group and 78.1% of the MS group (Fisk et al., 1994).

These two fatigue scales have been chosen because they are well-validated commonly used scales representing two alternative perspectives on fatigue measurement—the FSS is unidimensional and assumes fatigue is a unitary construct; the FIS, rather, assesses fatigue multi-dimensionally. Both scales have been selected to assure that fatigue is assessed validly, while allowing for the possibilities that fatigue may be multidimensional, and its sub-domains may share different relationships with depression symptoms.

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Approach to exploratory and confirmatory factor analyses

The factor structure of the data was examined in a three-step process. All analyses were carried out using LISREL (version 8.80; Joreskog & Sorbom, 2006).

Step 1: Exploratory and confirmatory analyses of individual instruments. To assess the accuracy of the putative factor structure of the CMDI, FSS, and FIS, item-level exploratory factor analyses (EFAs) were carried out on each of the instruments separately. These analyses were conducted by building nested models of increasing numbers of factors and using χ^2 difference tests to assess improvements in model fit. Goodness of fit was also assessed *via* the following alternative fit indices: the comparative fit index (CFI), the non-normed fit index (NNFI), and the standardized root mean square residual (SRMR).[1]

A factor solution was accepted when the addition of factors ceased to significantly improve fit, or when a given solution presented an excellent model fit. For each instrument, the factor solution was then subjected to an Oblimin rotation. The rotated solution was then inspected at an item-by-item level. Items were discarded for meeting the following criteria: failing to demonstrate a standardized loading of $\geq .40$ on any factor; cross-loading at $\geq .30$ on more than one factor; or loading on what was ruled to be a spurious factor. The thresholds for establishing latent indicators and cross-loadings were set at .40 and .30, respectively, to be maximally conservative about the integrity of the latent factor content. After the removal of poorly loaded, cross-loaded, and outlying items, a confirmatory factor analysis (CFA) was run for each instrument independently.

Step 2: Item-level CFA across all instruments. After confirming the item-level factor structure of each instrument independently, an item-level CFA was conducted across the CMDI, FSS, and FIS collectively.

Step 3: Scale-level CFA across all instruments. After confirming the appropriate item loadings for each factor, items were aggregated into their corresponding factors to create scale scores. A scale-level CFA analysis was then conducted.

RESULTS

MS Patients

Step 1, CMDI

The 42 items of the CMDI were first fit to a single factor model, χ^2 (819) = 3589.30, $p < .001$. A second factor was added, χ^2 (778) = 2318.91, $p < .001$ (χ^2_{diff} (41) = 1270.39; $p < .001$), followed by a third, χ^2 (738) = 2030.06, $p < .001$ (χ^2_{diff} (40)=288.85; $p < .001$), fourth χ^2 (699) = 1663.18, $p < .001$ (χ^2_{diff} (39) = 366.88; $p < .001$), and fifth χ^2 (661) = 1663.18, $p < .001$ (χ^2_{diff} (38) = 317.06; $p < .001$). The five-factor exploratory solution provided an excellent fit to the data, *CFI* = .96, *NNFI* = .95, *SRMR* = .048. Therefore, no further factors were added.

The five-factor solution for the CMDI was then subjected to an Oblimin rotation. Inspection of the semantic content for each factor revealed that the first factor contained items related to mood, the third factor sleep disturbance, and the fifth factor fatigue. Both the second and fourth factors contained evaluative statements. The second factor was indicated by autonomous evaluative items ("unworthy," "inferior," "worthless") and the fourth factor by sociotropic evaluative statements ("despised," "hated," "criticized"). The five factors were thus labeled Mood, Autonomous-Evaluative, Sleep Disturbance, Sociotropic-Evaluative, and Fatigue. As noted above, items were removed if they failed to demonstrate loadings $\geq .40$ or loaded at $\geq .30$ on multiple factors. In all, four items were removed from the CMDI—"unable to pay attention," "punished," "poor appetite," and "uninterested in sex" failed to load $\geq .40$ on any factors. No items exhibited loadings $\geq .30$ on multiple factors.

A five-factor CFA was conducted for the remaining 38 items of the CMDI. This model provided a good fit to the data, χ^2 (655) = 1184.90, $p < .001$, *CFI* = .97, *NNFI* = .96, *SRMR* = .066.

Step 1, FIS

The 40 items of the FIS were first fit to a single factor model, χ^2 (740) = 4478.75, $p < .001$. A second factor was then added, χ^2 (701) = 1760.32, $p < .001$ (χ^2_{diff} (39) = 2718.43; $p < .001$). The two-factor solution provided an excellent fit to the data, *CFI* = .97, *NNFI* = .96, *SRMR* = .054. Therefore, no further factors were added.

The two-factor solution was then subjected to an Oblimin rotation. Inspection of the semantic content for each factor revealed that factor 1 reflected cognitive fatigue and factor 2 physical fatigue, two of the three putative factors of the FIS. In all, five items were removed from the FIS. Items "less able to deal with emotional issues," "unable to provide as much emotional support to my family," and "minor difficulties seem like major difficulties" exhibited loadings $\geq .30$ on both factors; and "few social contacts outside the home" and "engage in less sexual activity" failed to load $\geq .40$ on either factor.

A two-factor CFA was conducted for the remaining 35 items of the FIS. This model provided a good fit to the data, *CFI* = .97, *NNFI* = .96, *SRMR* = .080.

Step 1, FSS

The nine items of the FSS were first fit to a single factor model, χ^2 (27) = 87.58, $p < .001$. A second factor was then added, χ^2 (19) = 35.07, $p = .015$ (χ^2_{diff} (8) = 52.10, $p < .001$). The two-factor solution provided an excellent fit to the data,

[1] The χ^2 statistic can reflect poor model fit due to sample size and large correlations within the data. The CFI, in contrast to the χ^2, benefits from large correlations within the data (which are assumed *a priori* to exist within the present data). The NNFI corrects for the number of parameters in the model. CFI and NNFI reflect good model fit at values of .95 or greater. The SRMR benefits from larger sample sizes and represents the difference between the observed and predicted covariance. A value of zero reflects a perfect fit, and values less than .08 reflect a good model fit.

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Table 2. Correlations between latent factors for item-level CFA across all instruments—MS group

	Mood	Auto-Eval	Sleep Dist	Socio-Eval	PhysFatigue	CogFatigue
Mood	1.00					
Auto-Eval	0.76	1.00				
Sleep Dist	0.35	0.20	1.00			
Socio-Eval	0.84	0.75	0.34	1.00		
PhysFatigue	0.37	0.35	0.38	0.31	1.00	
CogFatigue	0.32	0.32	0.43	0.30	0.65	1.00

Auto-Eval = autonomous-evaluative; Sleep Dist = sleep disturbance; Socio-Eval = sociotropic-evaluative; PhysFatigue = physical fatigue; CogFatigue = cognitive fatigue.

CFI = .99, *NNFI* = .99, *SRMR* = .022. Therefore, no further factors were added.

The two-factor solution for the FSS was then subjected to an Oblimin rotation. Rotation revealed that the second factor was indicated by "exercise brings on fatigue" alone and that this item exhibited a zero loading on the first factor. Therefore, this item was discarded and a one-factor solution, reflecting fatigue was retained.

A one-factor CFA was conducted for the remaining eight items of the FSS. This model provided an excellent fit to the data, *CFI* = .99, *NNFI* = .99, *SRMR* = .026.

Step 2, item-level CFA across all instruments

The remaining 38 CMDI items, 35 FIS items, and 8 FSS items were fit to a six-factor CFA, wherein the latent factors were considered to be Mood, Autonomous-Evaluative, Sleep Disturbance, Sociotropic-Evaluative, Fatigue, and Cognitive Fatigue. This model provided an acceptable fit to the data, χ^2 (3144) = 7379.35, $p < .001$, *CFI* = .94, *NNFI* = .94, *SRMR* = .090, however, modifications indices suggested points of significant model strain at CMDI items 21 (*MI* = 48.38) and 28 (*MI* = 60.02). These items, "Unable to Concentrate," and "Forgetful" were initially indicators of the latent factor Fatigue. Loadings on this factor were fixed to zero, and these items were allowed to load on the latent factor Cognitive Fatigue. Because the items comprising the Fatigue factor now all reflected physical symptoms, this factor was re-labeled Physical Fatigue. These modifications provided a significant improvement in model fit, (χ^2_{change} = 150.4; CFI_{change} = .01; $SRMR_{change}$ = .04). Fit indices demonstrated that this model provided an acceptable fit to the data, χ^2 (3144) = 7228.95, $p < .001$, *CFI* = .95, *NNFI* = .94, *SRMR* = .086. Table 2 displays the correlations between the six latent factors of the item-level CFA.

Step 3, scale-level CFA across all instruments

Finally, the individual items were aggregated to create scale scores. Items from the CMDI, FIS, and FSS were distributed into their respective Mood, Autonomous-Evaluative, Sociotropic-Evaluative, Sleep-Disturbance, Physical Fatigue, and Cognitive Fatigue scales. Mood, Autonomous-Evaluative, and Sociotropic-Evaluative were indicators for the latent factor Depression; Physical Fatigue and Cognitive Fatigue were indicators for the latent factor Fatigue; and Sleep Disturbance was the sole indicator for the latent Factor Sleep Disturbance (λ was fixed to 1.00 and ε was fixed to 0). This model provided an excellent fit to the data, χ^2 (7) = 11.80, $p = .11$, *CFI* = .99, *NNFI* = .98, *SRMR* = .029. Figure 1 depicts the final scale-level CFA model.

Controls

Control data were subjected to exploratory and confirmatory factor analysis as detailed above. For brevity, results are summarized to emphasize points of structural similarity and difference. Consistent with results for the MS sample, exploratory factor analyses of the control data revealed five- and two-factor solutions for the CMDI and FSS, respectively, whereas the FIS revealed a four-factor structure.

Step 1, CMDI

Consistent with structure in the MS sample, latent factors for Mood, Autonomous-Evaluative, Sociotropic-Evaluative, and Fatigue were found within the control group. However, oblique rotation of these data revealed points of contrast with the MS sample findings. First, a latent factor for Sleep Disturbance was not indicated; these items were either eliminated ("easily awakened") or contained within the latent Fatigue factor (e.g., "fitful sleep," "trouble falling asleep"). Second, a separate Cognitive Fatigue factor was indicated by "unable to pay attention" and "unable to concentrate." The factor structure for the CMDI within the control group thus contained latent factors for Mood, Autonomous-Evaluative, Sociotropic-Evaluative, Fatigue, and Cognitive Fatigue. In all, 13 items were removed from the CMDI.[2]

Step 1, FIS

A four-factor solution was found for the Controls' FIS data, Physical Fatigue and Cognitive Fatigue, Social Fatigue, and Mood. Social Fatigue is a putative factor within the FIS that

[2] CMDI Items "easily awakened," "punished," "poor appetite," "miserable," and "uninterested in sex" failed to load ≥.40 on any factors. Additionally, 8 items exhibited loadings ≥.30 on multiple factors; these were items "forgetful," "dreary," "grim," "weak," "gloomy," "forgotten," "somber," and "useless."

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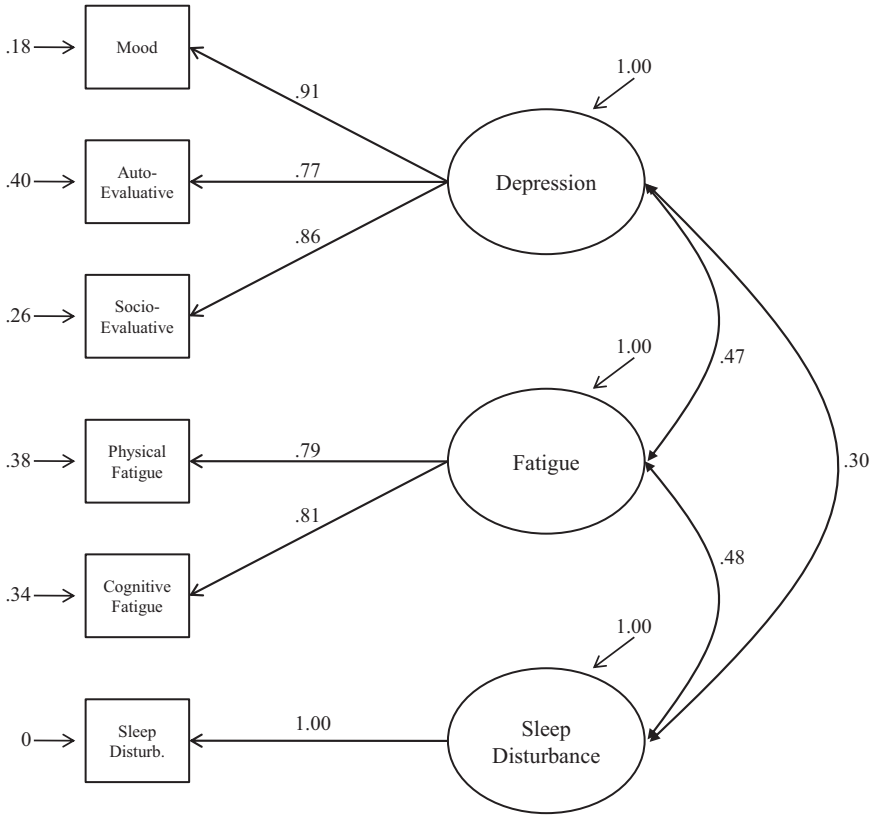

Fig. 1. Final Scale-level confirmatory factor analysis (CFA) model for the multiple sclerosis (MS) group. Standardized path estimates shown. Fit indices: χ^2 (7) = 11.80, p = .11, CFI = .99, NNFI = .98, SRMR = .029.

was not found within the MS sample. The fourth factor was indicated by "more moody" and "more irritable and easily angered." In all, 14 items were removed from the FIS.[3]

Step 1, FSS

Oblique rotation of the FSS data revealed an identical solution to MS counterparts.

Step 2, item-level CFA across all instruments

The remaining 29 CMDI items, 26 FIS items, and 8 FSS items were fit to a six-factor CFA, with latent factors Mood, Autonomous-Evaluative, Sociotropic-Evaluative, Physical Fatigue, Cognitive Fatigue, and Social Fatigue. This model provided a relatively poor fit to the data, χ^2 (1814) = 3220.50, $p < .001$, *CFI* = .88, *NNFI* = .88, *SRMR* = .10; however, it was structurally informative as all items loaded at >.40 on their putative factors and modification indices did not indicate misspecified items.

Step 3, scale-level CFA across all instruments

Finally, the individual items were aggregated to create scale scores. Items from the CMDI, FIS, and FSS were distributed into their respective Mood, Autonomous-Evaluative, Sociotropic-Evaluative, Physical Fatigue, Cognitive Fatigue, and Social Fatigue scales. Mood, Autonomous-Evaluative, and Sociotropic-Evaluative were indicators for the latent factor Depression. Given the specification of multiple indicators for both Physical Fatigue and Cognitive Fatigue across the FIS, CMDI, and FSS, a hierarchical factor structure was created for Fatigue wherein the Physical Fatigue scales from the CMDI, FIS, and FSS indicated a latent Physical Fatigue factor and the Cognitive Fatigue scales from the CMDI and FIS indicated a latent Cognitive Fatigue factor. The FIS Social Fatigue scale was the lone indicator of the latent Social Fatigue factor (thus, λ was fixed to 1.00 and ε was fixed to 0). The three latent factors were then allowed to indicate a higher-order Fatigue factor. This model provided an excellent fit to the data, χ^2 (33) = 44.72, p = .08, *CFI* = .97, *NNFI* = .97, *SRMR* = .062. Figure 2 depicts the final scale-level CFA model.

Factor Scores

Using the factor structure derived from the MS group, factor scores were created by summing the items that comprise each factor: Depression, Fatigue, and Sleep Disturbance. Multivariate analysis of variance models were run examining

[3] Six FIS items were removed for failing to load >.40 on any factor: "difficulties planning activities due to fatigue," "more clumsy and uncoordinated," "less motivated if requiring physical effort," "avoid situations that are stressful," and "worry how I look to other people." Eight FIS items that were removed for loading >.03 on multiple factors: "more isolated from social contact," "cannot think clearly," "rely on others to help or do things for me," "less motivated to engage in social activity," "fatigue limits my ability to travel," "difficult to make decisions," "avoid situations that are stressful," and "slowed down in my thinking."

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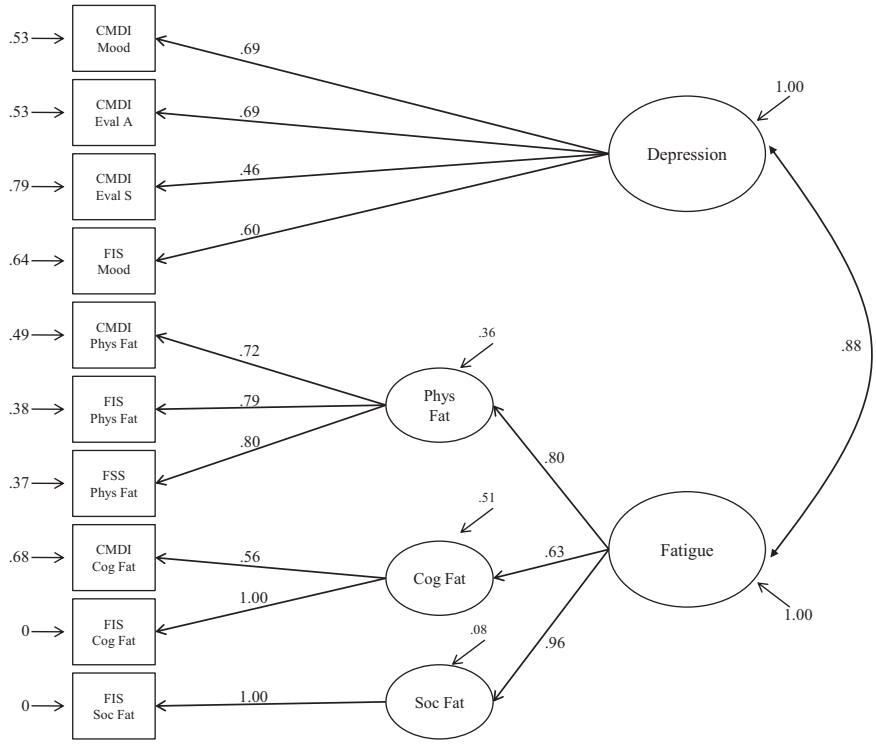

Fig. 2. Final Scale-level confirmatory factor analysis (CFA) model for control group. CMDI Mood, Mood items from the Chicago Multiscale Depression Inventory; CMDI Eval A, Auto-Evaluative items from the CMDI; CMDI Eval S, Socio-Evaluative items from the CMDI; FIS Mood, Mood items from Fatigue Impact Scale; CMDI PhysFat, Physical Fatigue items from the CMDI; FSS PhysFat, Physical Fatigue items from the Fatigue Severity Scale; CMDI CogFat, Cognitive Fatigue items from CMDI; FIS CogFat, Cognitive Fatigue items from the FIS; FIS SocFat, Social Fatigue items from the FIS. Standardized path estimates shown. Fit indices: χ^2 (33) = 44.72, p = .08, CFI = .97, NNFI = .97, SRMR = .062.

group differences in these three factor scores, comparing groups defined by patient status (MS *vs.* Controls) and Depression History. The MS group exhibited significantly higher scores on both Depression and Fatigue, but not on Sleep Disturbance. In the MS group, participants who endorsed a history of depression scored higher on the Depression factor than those with no depression history. In Controls, those with a history of depression scored higher than their never-depressed counterparts on both the Fatigue and Depression factors (see Table 3).

In the MS patient group, bivariate Pearson correlations were calculated for each factor score with a measure of MS-related disability—EDSS score. Fatigue was the only factor score significantly correlated with EDSS (r = .44; p < .001). Sleep Disturbance and Depression were not significantly correlated with EDSS (r = .10, p = .21; and r = .14, p = .06, respectively).

Table 3. Multivariate analysis of variance analyses: effect sizes for between group comparisons (partial η^2)

	Patient status: MS vs. Controls	Depression Hx: Pos vs. Neg	
	Complete sample	MS	Controls
Depression	0.04 *p* < *.005*	0.14 *p* < *.001*	0.20 *p* < *.001*
Fatigue	0.40 *p* < *.001*	0.03 *ns*	0.16 *p* < *.001*
Sleep Disturbance	0.00 *ns*	0.02 *ns*	0.04 *ns*

Criterion for significance set at α = .01. Depression Hx = depression history—defined as depression symptoms for which the participant either sought treatment, or considered seeking treatment.

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DISCUSSION

This study sought to evaluate the status of vegetative depression symptoms as indices of depression in MS patients. Vegetative depression symptoms may be valid indices of depression in MS patients; these symptoms may be related to other MS disease sequelae, like fatigue; or depression and fatigue could be symptoms of the same neurobehavioral syndrome in this patient group. To explore these possibilities, factor analysis was used to elucidate the underlying structure of self-report items designed to measure fatigue and depression symptoms in MS patients and neurologically healthy controls.

Factor analysis revealed a three-factor structure in the MS group—with Depression, Fatigue, and Sleep Disturbance constituting three related, but separable constructs. The Control group analysis revealed a hierarchical two-factor structure—with Fatigue and Depression as two highly related ($\psi = .88$) constructs.[4] These results suggest that self-report measures of fatigue and depression assess qualitatively different phenomena in MS patients *versus* healthy controls. In Controls, physical lassitude, cognitive fatigue, and sleep disturbance are highly related to depressed mood and depressogenic cognitions. In this group, this co-occurrence of symptoms likely reflects depression as it has been defined by the DSM-IV—as a syndrome that is characterized by depressed mood, anhedonia, and neurovegetative symptoms.

In the MS group depressed mood and neurovegetative symptoms (i.e., fatigue and sleep disturbance) constitute distinct conditions that may be related, but are not sequelae of the same syndrome. Neurovegetative items were either removed from the final MS model due to poor psychometric properties or loaded on Fatigue or Sleep Disturbance factors, suggesting that these items measure fatigue and sleep disturbance, not depression. At the latent level, fatigue and depression share a .47 correlation—large according to Cohen's classification, yet short of what is expected of factors indicating the same higher-order construct. This pattern of results suggests that fatigue and depression are distinct, but related constructs. Depression measures that include neurovegetative symptoms may lead to elevated estimates of depression in MS samples, and artifactually inflated relationships between depression and fatigue.

Secondary analysis of factor scores also supports the notion that neurovegetative symptoms are related to disease-mediated fatigue and not depression. Depression history was associated with fatigue in control participants, but not MS participants. Furthermore, in MS patients, Fatigue scores, but not Depression or Sleep Disturbance scores, were significantly correlated with a measure of MS-related disability. It should be noted that disease status had a significant, though small, effect on Depression Factor score (4% of the variance)—suggesting that MS patients experience more mood and evaluative depression—perhaps the true manifestation of depression in this population—than Controls.

These findings are inconsistent with conclusions that have been drawn from treatment research demonstrating CBT-related improvements in all depressive symptoms domains, including neurovegetative (Moran & Mohr, 2005). However, these seemingly divergent findings need not be irreconcilable. It is possible that CBT teaches coping skills that buffer the impact of fatigue symptoms. Furthermore, covariation of mood, evaluative, and neurovegetative symptoms of depression in treatment studies may be a consequence of affectively biased symptom reporting (Krupp & Christodoulou, 2001). Research has demonstrated that formerly depressed individuals are not significantly different from never-depressed individuals in demonstration of affective biases (Gotlib & Cane, 1987). Hence, negative response bias pre-treatment may not manifest after a successful treatment, so neurovegetative symptoms may appear to remit for artifactual reasons.

The results of the present factor analysis revealed properties of the examined measures that warrant discussion. First, in the MS group FIS analysis suggests a two-factor structure, despite the purported three-factor structure of the instrument. Psychosocial fatigue items loaded on Cognitive and Physical Fatigue latent factors, suggesting that physical and cognitive fatigue may underlie fatigue-related difficulties in socio-emotional functioning. Cognitive and physical fatigue have been discussed extensively in the MS literature. Cognitive fatigue has been defined as a decline in cognitive performance during sustained cognitive activity (Schwid, Covington, Segal, & Goodman, 2002). The Physical Fatigue factor in the final model was comprised of items related to motoric fatigue and lassitude—physical experiences that may be most consistent with lay conceptualizations of fatigue (Freal, Kraft, & Coryell, 1984).

Both group analyses yielded two Evaluative factors from the CMDI—one related to negative evaluations of the individual (Autonomous-Evaluative), and one related to negative evaluations of how the individual is regarded by others (Sociotropic-Evaluative). This self/other distinction is consistent with Beck's theory of depression, which posits that evaluative beliefs are related to personality (Beck, 1991). Although this bifurcation of the Evaluative scale was unexpected, it is consistent with prior theory, and supports the notion that interaction between personality and cognition may be applicable to depression in MS patients, as it is in depressed individuals without neurological disorders.

Another unanticipated finding was that sleep disturbance emerged as dissociable from fatigue. The correlation between Fatigue and Sleep Disturbance in the final model was .48, a large correlation according to Cohen's classification. This relationship is consistent with prior research. One recent study demonstrated that MS patients with and without fatigue demonstrate evidence of sleep disturbance, however, elevated sleep-disturbance was related to self-reported fatigue (Kaynak et al., 2006). These data show that sleep disturbance in MS occurs with and without subjective experiences of fatigue.

[4] The notion that Fatigue and Depression are poorly differentiated constructs in the Control group is also supported by the fact that, in total, 27 items were removed from the FIS and CMDI during the analysis due to *a priori* criteria for removal: either poor factor loadings ($< .40$ on any factor) or high cross-loadings ($> .30$ on two factors). As a comparison, in the MS sample, only 9 total items from the CMDI and FIS were removed according to the same criteria.

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However, elevated disturbed sleep in fatigued patients suggests that sleep disturbance may contribute to fatigue in MS, as suggested in other work (Strober & Arnett, 2005). The magnitude of the correlation between latent factors Sleep Disturbance and Fatigue in our final model suggests that these symptoms are related, but distinct phenomena in MS.

There are some limitations of the present study that bear noting. This study is exploratory in nature, and provides a data-driven perspective on the status of vegetative-depression items as indicators of depression in MS patients. Our reported factor structure should be considered tentative until it is confirmed in an independent sample. Some have argued that the sample size for factor analysis should be at least 200 (Cattell, 1978; Guilford, 1954; Lee, Poon, & Bentler, 1992). However, recent empirically based work suggests that appropriate sample size and sample size to parameter ratios are not universal, but vary considerably from one study to another (MacCallum, Widaman, Zhang, & Hong, 1999). It is unlikely that sample size is problematic in this study—MacCallum and colleagues (1999) have presented evidence suggesting that sample size is not problematic when communalities are large, as they were in the present study.[5]

Another possible limitation of the present study is the choice of measures. Others have argued that vegetative depression symptoms may be related to physical disability in patients with MS (Nyenhuis et al., 1998). For the purpose of the factor analyses, we included fatigue instruments because of the phenomenological similarities between fatigue and vegetative depression symptoms, and the prevalence and clinical significance of fatigue in MS. It is possible that vegetative depression items measure fatigue, along with other MS-related symptoms that were not assessed in the present study—for example, trouble with ambulation or cognitive dysfunction. Future research could address this topic. Finally, the present-study used self-report measures of fatigue and depression, which have inherent limitations that have been discussed previously. Clinician ratings or performance-based measures of these constructs may suggest different conclusions. Finally, the lack of one or more patient-control groups hinders conclusions unique to MS. Neurovegetative symptoms of depression may be associated with fatigue and not depression in other chronic illness populations as well.

Although our results suggest that neurovegetative symptoms are poor indicators of depression in MS patients, these symptoms are diagnostically appealing because they may be observed objectively, and hence, are less sensitive to biases in self-report. Future work should attempt to determine if these symptoms have any incremental diagnostic value. Examining specific neurovegetative symptoms, symptom thresholds, or symptom profiles that are less sensitive to MS disease pathology may provide useful guidelines for clinical interpretation of this information.

The results of the present study contribute the understanding of depression assessment in MS in several ways. These findings add to an expanding literature suggesting that neurovegetative depression symptoms are poor indicators of depression in this patient population (Beeney & Arnett, 2008; Nyenhuis et al., 1995). This has important implications for research and clinical practice. Researchers studying depression in MS patients should select measures with caution. Standard measures like the BDI may not be appropriate, and may lead to inflated estimates of depression prevalence. Furthermore, these results suggest that mood and evaluative depression symptoms should be weighted more heavily than vegetative depression symptoms when assessing MS-related depression in clinical settings, as these symptoms appear to be more specific indicators of depression. The differential diagnosis between depression and fatigue in MS patients is critical. Both of these sequelae are prevalent in MS patients, and there are efficacious treatments for both conditions (Mohr & Goodkin, 1999; Rammohan, Rosenberg, Lynn, Blumenfeld, Pollak, & Nagaraja, 2002). Correctly distinguishing between conditions could mean improving a patient's quality of life.

[5] Average communalities for each instrument in the MS sample were .55, .55, and .67 for the CMDI, FIS, and FSS respectively.

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