MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Characterizing the phenotype of multiple sclerosis–associated depression in comparison with idiopathic major depression

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Multiple Sclerosis Journal

2016, Vol. 22(11) 1476–1484

DOI: 10.1177/1352458515622826

Abstract

Background: Depression is a common co-morbidity in patients with multiple sclerosis (MS). While somatic symptoms of MS correlate with depression levels, it is unclear whether the clinical presentation of MS-associated depression differs from patients with "idiopathic" major depressive disorder (MDD).

Objective: To compare the clinical phenotype of depression among MS and idiopathic MDD patients.

Methods: Mean relative contribution of individual Beck Depression Inventory-II (BDI-II) items was evaluated among $n = 139$ patients with relapsing-remitting MS and $n = 85$ MDD patients without somatic illness. Next, comparisons were repeated in $n = 38$ MS with clinically relevant depressive symptoms (BDI-II > 19) and $n = 38$ MDD patients matched for sex, age, and depression severity. Finally, the underlying construct of depression was compared across groups using confirmatory factor analysis (CFA).

Results: Comparisons on a whole-group level produced the expected differences along somatic/non-somatic symptoms. However, when appropriately controlling for depression severity, age, and sex, only four items contributed differentially to BDI-II total scores in MS versus MDD. CFA suggested that the underlying depression construct is essentially identical in both groups.

Conclusion: The clinical phenotype of "idiopathic" MDD and MS-associated depression appears similar when adequately examined. The relevance of these findings for psychotherapeutic approaches for MS-associated depression should be explored in future studies.

Keywords: Depression, multiple sclerosis

Date received: 15 September 2015; revised: 24 November 2015; accepted: 26 November 2015

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Introduction

Psychiatric and neurological disorders are often interrelated as illustrated by the high prevalence of depressive syndromes in patients with stroke, Parkinson's disease, or multiple sclerosis (MS).[1,2] As a case in point, major depressive disorder (MDD) is the most common co-morbidity in MS with a lifetime prevalence between 36% and 54%[3,4] and a point prevalence of 23.7% (95% confidence interval = 17.4–30.0).[5] Depression in MS is of immediate clinical concern as it is associated with cognitive dysfunction, low treatment adherence, increased risk of self-harm (see Feinstein et al.[6] for review) and is one of the major determinants of patients' quality of life.[7] Up to two-third of the MS patients meeting diagnostic criteria for MDD do not receive adequate psychiatric care,[8] which represents a severe unmet medical need.

One reason for insufficient treatment of co-morbid MDD may be the clinical challenge to separate MS-related somatic complaints, such as fatigue,[9,10] from overlapping somatic symptoms of depression.[11–13] Misinterpretation of MS-related complaints as depression may lead to unnecessary medication, while failure to detect an underlying depressive disorder may prevent patients from receiving adequate care.

There is evidence to suggest that MS-related complaints such as fatigue may be differentially associated with vegetative aspects of depression[14] and current

diagnostic recommendations have pointed out that MS symptoms may confound assessment of depression in these patients.[4,15] However, these statements are largely based on correlative findings and only a few studies to date have directly compared the clinical phenotype in MS patients and patients with "idiopathic" MDD without somatic illness.[16–19] Most[16–18] but not all[19] of them reported that the relative contribution of vegetative/somatic items to depression scores was larger in MS compared to MDD. However, in all of the samples, more severe depression was observed in the MDD samples, and the only study to statistically control for depression severity no longer found evidence for a relative overrepresentation of somatic symptoms in MS.[19] Therefore, any difference described in previous studies might better be explained by group differences in depression severity. In line with this notion, a more recent study in MS patients suggested that somatic item contribution on the Beck Depression Inventory-II (BDI-II) scaled with depression severity.[20] Thus, it remains to date unknown if depressive symptomatology in the context of MS has a different clinical presentation and is distinct from "idiopathic" depression without underlying medical illness.

There are several studies that have evaluated the usefulness of questionnaires as screening instruments for depression and their accuracy in identifying patients with clinical depression when compared to a structured interview (e.g. Strober and Arnett,[21] Benedict et al.,[22] and Honarmand and Feinstein[23]). These previous results support reliability and validity of self-report questionnaires for measuring depression in MS. In this study, we aimed to expand these studies conceptually by directly comparing the clinical phenotype and symptom composition of MS-associated and "idiopathic" depression using a multi-step statistical analysis.

Materials and methods

Sample

A total of 139 patients with established diagnosis of relapsing-remitting MS according to the current McDonald criteria 2010 revisions[24] were recruited from the outpatient clinic of the NeuroCure Clinical Research Center, Charité—Universitätsmedizin Berlin. All MS patients underwent neurological examination, and physical disability was assessed using the Expanded Disability Status Scale (EDSS).[25] Exclusion criteria included progressive subtypes of MS, significant medical co-morbidity, and unstable drug regimen.

A total of 85 patients with a confirmed diagnosis of MDD (idiopathic MDD) according to the International Classification of Diseases—10th Revision (ICD-10) criteria were recruited from the Department of Psychiatry and Psychotherapy at Campus Charité Mitte. All idiopathic MDD patients had long-standing, confirmed diagnoses as patients of the department's in- and outpatient clinic. In both groups, patients with neurologic (other than MS), significant psychiatric (other than MDD) or medical co-morbidity were excluded. Personality or anxiety disorders were permitted in the MDD cohort. Current antidepressant medication was noted where available and included all drugs with antidepressant effects, regardless of chemical/pharmacological class.

All procedures were approved by the internal ethics review board of the Charité—Universitätsmedizin (Campus Charité Mitte), and the study was conducted in conformity with the 1954 Declaration of Helsinki in its currently applicable version. All patients provided written informed consent prior to enrollment.

Depression assessment

Depression severity was assessed using the BDI-II,[26] a common self-report measure of depression that has been validated in a wide range of conditions, including MS.[4,27] The BDI-II covers core dimensions of depression by asking patients to endorse 21 statements on a scale from 0 to 3 based on their experiences in the past 2 weeks. The total BDI-II score is calculated as the sum of overall items. Total scores above 19 indicate clinically significant depression in accordance with the literature[26] and for the remainder of the manuscript in MS patients will be referred to as "MS-associated depression."

Data analysis

Data were analyzed with IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). Categorical variables were compared using Pearson's χ^2 and Fisher's exact tests. Independent-samples *t*-tests and univariate analysis of variance (ANOVA) were used for continuous measures.

In order to assess the impact of somatic items on the total BDI-II scores, mean item contribution (i.e. each patient's individual BDI-II item score divided by their total BDI-II score) was analyzed. For mathematical reasons (division by 0), patients with a BDI-II score of 0 ($n = 5$) were excluded from this analysis. We conducted multivariate analysis of variance (MANOVA) with Pillai's trace statistics followed by planned post

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Table 1. Clinical characteristics of MS and MDD patients.

	MS ($n=139$)	MDD ($n=85$)	p-value[a]
Age (years; mean ± SD (range))	43.7 ± 10.7 (24–65)	44.0 ± 13.4 (21–79)	0.579
Female patients (%)	101 (72.7%)	47 (55.3%)	0.009
Years since diagnosis[b] (years; mean ± SD (range))	12.3 ± 11.6 (0–36)	–	–
EDSS[c] (median, range)	3.0 (0–6)	–	–
BDI-II (mean ± SD)	15.1 ± 8.9	33.6 ± 11.0	<0.001
BDI-II < 13	57 (41%)	0 (0%)	
BDI-II = 13–19	44 (32%)	12 (14.1%)	
BDI-II = 20–28	25 (18%)	19 (22.4%)	
BDI-II > 28	13 (9%)	54 (63.5%)	

MS: multiple sclerosis; MDD: major depressive disorder; SD: standard deviation; EDSS: Expanded Disability Status Scale; BDI-II: Beck Depression Inventory-II.
[a]Independent-samples t-test for continuous and Pearson's χ^2/Fisher's exact tests for categorical variables.
[b]$n=123$.
[c]$n=115$ patients.

hoc comparisons adjusted for multiple testing (Bonferroni). For the matched-sample approach, we used a predefined, fully automated algorithm (package optmatch, version 0.9.3) as implemented in R (version 3.1.3; http://www.r-project.org) to match MS patients with depression and MDD patients for sex, age, and BDI-II scores.[28]

To compare underlying depression structure between the MS and MDD group, we conducted confirmatory factor analysis (CFA) in IBM SPSS Amos 22 (IBM Corporation) using maximum likelihood estimation and inspection of χ^2 values ($p \geqslant 0.05$ indicating good fit), comparative fit index (CFI; $\geqslant 0.95$ indicating good fit), and root mean square error of approximation (RMSEA; $\leqslant 0.05$ indicating good fit) in line with established guidelines.[29] To compare models, χ^2 test of homogeneity was calculated.

Results

Relative contribution of individual items to the BDI-II total score

Demographic and clinical characteristics are given in Table 1. A MANOVA of relative item contribution showed a significant main effect of group ($F(20, 198)=6.661$, $p<0.01$) indicating that BDI-II items showed differential contributions to the BDI-II total score between the MS and the MDD group. Planned post hoc tests adjusted for multiple comparisons revealed significant group differences in 13 of the 21 BDI-II items (Figure 1(a)). As expected, numerous items likely related to MS symptomatology such as loss of energy, sleep problems, irritability, difficulty concentrating, and fatigue contributed more to MS-associated depression. In contrast, relative item contribution to the total score was higher for items capturing sadness, pessimism, anhedonia, self-dislike, suicide, crying, worthlessness, and loss of interest in "idiopathic" MDD.

This finding appears to support the hypothesis that depression scores in MS are dominated by symptom items that are likely contaminated by frequent MS-related symptoms such as fatigue and cognitive impairment. However, as was the case in similar comparisons in previous work,[16,18] MDD patients exhibited significantly higher levels of depression overall (BDI-II total score: MDD 33.6 ± 11.0 vs MS 15.1 ± 8.9; $p<0.001$). Moreover, there were significant group differences in sex distribution (see Table 1). Thus, it is possible that the single-item differences observed here and in previous studies might be artifacts of overall group differences in depression severity and/or demographic factors.

Matched group comparisons

In order to circumvent these potential confounds, we individually matched depressed MS patients (BDI-II > 19, $n=38$) with 38 idiopathic MDD patients for sex, age, and depression severity (BDI-II total score) using a fully automated algorithm. Consequently, these subgroups did not differ significantly in BDI-II scores (MS = 26.4 ± 6.5, MDD = 27.6 ± 8.9; $t_{74}=0.633$, $p=0.529$), age (MS = 44.4 ± 9.5 years, MDD = 46.6 ± 11.7 years; $t_{74}=0.882$, $p=0.381$), or sex (9 male and 29 female in each group).

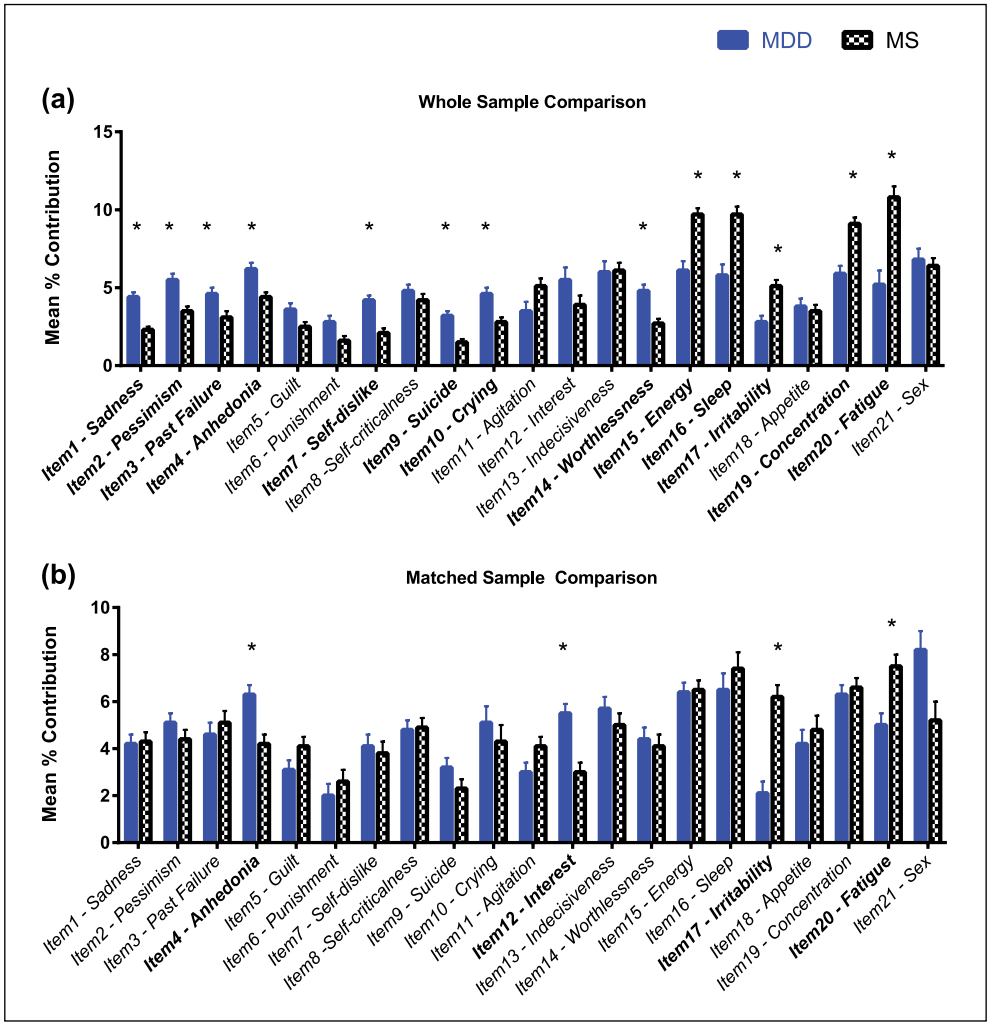

Figure 1. Group differences on single BDI-II items in the (a) whole-sample versus (b) matched-sample approach.
Significant differences ($p < 0.05$, Bonferroni-corrected) are indicated by * and bold *x*-axis label.

Using this approach, multivariate group differences in relative BDI-II item contribution remained significant ($F(21, 54) = 3.267$, $p < 0.01$). However, planned post hoc tests revealed that most of the single-item differences identified in the whole-sample approach disappeared. In the matched-sample analysis, four items showed differential relative contribution in MS (irritability and fatigue) versus idiopathic MDD (anhedonia and loss of interest) (Figure 1(b)). Importantly, inspection of effect sizes (Table 2) showed that loss of significant group differences in relative contribution of the other nine items was not simply a result of lower statistical power in the subgroup analysis. Rather, the data indicate that adequate matching for depression severity accentuates effect sizes of single-item group differences by increasing the differences observed on the items anhedonia (item 4), loss of interest (item 12), irritability (item 17), and fatigue (item 20) but strongly decreasing group differences in the other items.

CFA

The results presented above suggest that even after appropriate control of confounds, there are four items of the BDI-II that show differential influence on depression severity in MS-associated depression (fatigue and irritability) versus "idiopathic" MDD (anhedonia, loss of interest). Thus, we then explored if these differences have an impact on the overall symptom composition of depression ("phenotype") in these two patient populations. To this end, we constructed a CFA model for the latent variable (depression) that included all BDI-II items and compared

Table 2. Effect sizes (ES, Cohen's *d*) for group differences (MDD-MS) on single items.

	Whole sample		Matched sample	
	ES (*d*)	*p*-value	ES (*d*)	*p*-value
Item 1—Sadness	0.744	**<0.001**	−0.02	>0.99
Item 2—Pessimism	0.567	**<0.001**	0.28	>0.99
Item 3—Past failure	0.422	**0.04**	−0.169	>0.99
Item 4—Anhedonia	0.478	**0.01**	0.856	**0.002**
Item 5—Guilt	0.289	0.723	−0.432	>0.99
Item 6—Punishment	0.320	0.391	−0.194	>0.99
Item 7—Self-dislike	0.632	**<0.001**	0.084	>0.99
Item 8—Past failure	0.137	>0.99	−0.049	>0.99
Item 9—Suicide	0.68	**<0.001**	0.385	>0.99
Item 10—Crying	0.44	**0.027**	0.185	>0.99
Item 11—Agitation	−0.295	0.649	−0.386	>0.99
Item 12—Loss of interest	0.211	>0.99	0.94	**<0.001**
Item 13—Indecisiveness	−0.019	>0.99	0.257	>0.99
Item 14—Worthlessness	0.615	**<0.001**	0.114	>0.99
Item 15—Energy	−0.660	**<0.001**	0.044	>0.99
Item 16—Sleep	−0.606	**<0.001**	−0.203	>0.99
Item 17—Irritability	−0.533	**<0.001**	−1.05	**<0.001**
Item 18—Appetite	0.078	>0.99	−0.189	>0.99
Item 19—Concentration	−0.6	**<0.001**	−0.11	>0.99
Item 20—Fatigue	−0.681	**<0.001**	−0.77	**<0.001**
Item 21—Sex	0.070	>0.99	0.607	0.142

MDD: major depressive disorder; MS: multiple sclerosis.
All *p*-values are Bonferroni-corrected, with significant ($p<0.05$) comparisons indicated in bold.

an unconstrained model, where factor loadings were allowed to vary between groups (MS vs MDD), with a model where all loadings were constrained to be equal in MS versus MDD. The unconstrained model provided reasonable fit ($\chi^2_{370}=1.628$, $p<0.01$, CFI=0.867, RMSEA=0.053). Constraining all factor loadings to be equal between groups did not significantly alter the model fit ($\chi^2_{390}=1.615$, $p<0.01$, CFI=0.862, RMSEA=0.053; $\chi^2_{20}=27.451$, $p=0.123$). Standardized regression coefficients are shown in Supplementary Table 1. This analysis indicates that the overall symptom composition and structure of the latent construct depression is similar between MS and "idiopathic" MDD (Figure 2).

Discussion

The results of our study suggest that after adequately adjusting for depression severity, age, and sex, differences between MS-associated and idiopathic MDD are restricted to few BDI-II items. However, these do not appear to have a significant impact on the general phenotype of depression and its syndromal composition.

Previous studies with an earlier version of the BDI yielded heterogeneous results[16–19] and the only other study that directly assessed BDI-II composition in MS patients[20] found no confounding by specific item domains. However, the clinical phenotype of idiopathic and MS-associated depression has not been systematically compared in previous studies. Our investigation now provides robust evidence from multiple statistical approaches that MS-associated and "idiopathic" depression may present with similar clinical phenotypes, at least on a commonly used questionnaire.

In our analyses, we confirmed earlier findings[16] suggesting that when comparing a group of MS patients to patients with MDD, the relative contribution to the BDI total score of items that are likely influenced by frequent MS symptoms such as fatigue and cognitive dysfunction is significantly higher in MS than "idiopathic" MDD. In fact, in our data set, this finding was even more widespread compared to an earlier study by Mohr et al.,[16] showing significant differences in the relative contribution of more than 60% of the BDI-II items. However, it is important to note that

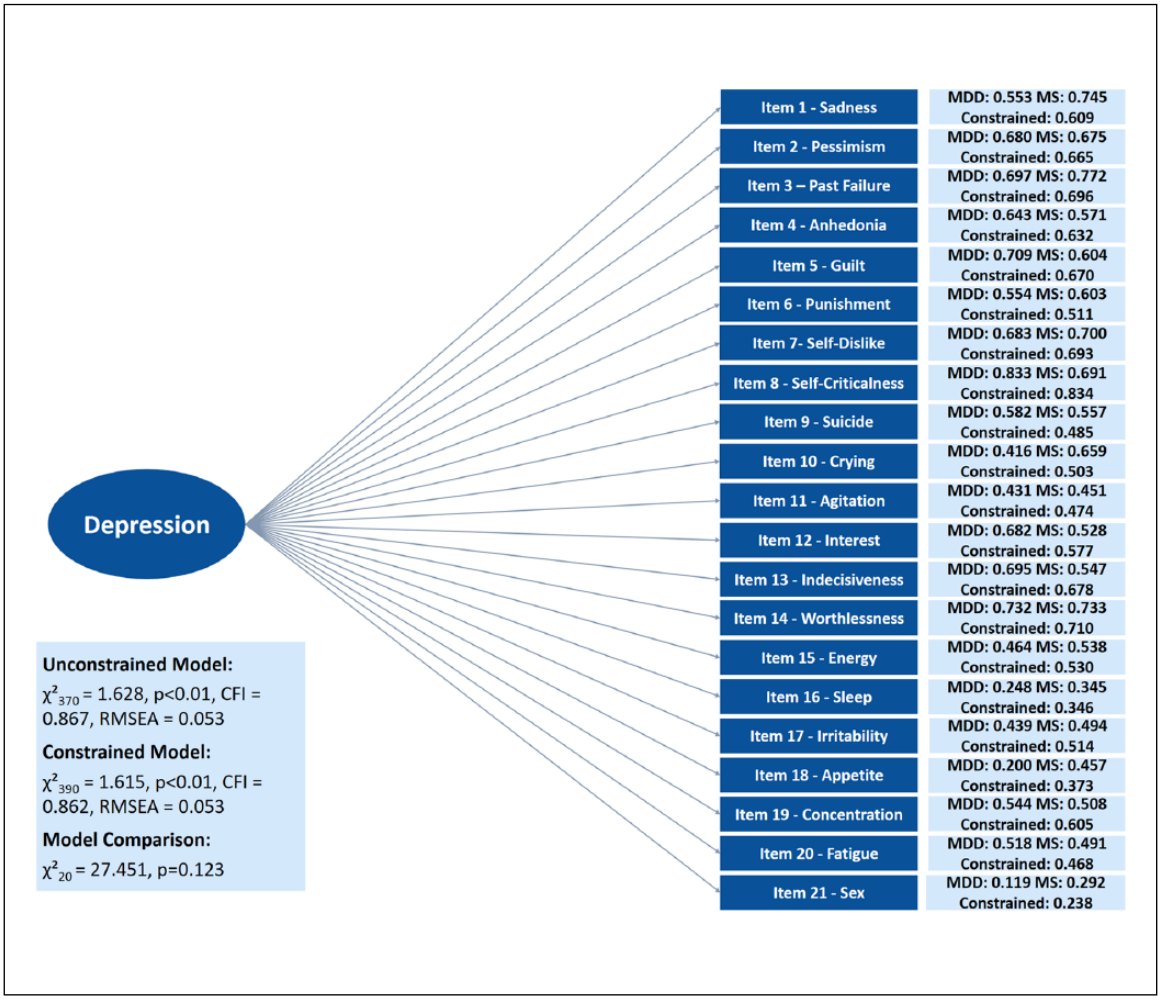

Figure 2. Confirmatory factor analysis of the BDI-II in MS-associated depression versus "idiopathic" major depressive disorder.

such an analysis tends to compare a group of patients that includes non-depressed patients (in the MS samples) and a group where by definition each patient suffers from clinically relevant depression. Indeed, in our sample as well as in previously studied patient groups,[16,18] the MDD group had markedly higher BDI total scores than the MS group. In addition, there were also group differences in sex distribution with more female patients in the MS sample compared to the MDD sample. In other words, any differences observed could simply be a result of comparing mild to severe depression or depression in women versus men.

Thus, in our present analyses, we have employed several statistical approaches to remove the influence of these confounders. First, we compared patients matched individually by an automated algorithm for age, sex, and depression severity (as indicated by the BDI-II total score). This eliminated group differences in the vast majority of BDI-II items. Group differences, however, remained on key items: relative contribution of fatigue and irritability was larger in the MS group, while anhedonia and loss of interest was higher in MDD patients. Taken together, this indicates that—when controlling properly for depression severity—only few items of the BDI-II carry a larger weight in MS-depression compared to "idiopathic" MDD. In addition, while group differences were significant, the magnitude of differences in the relative contribution of these items was quite small. Finally, we conducted a CFA to assess whether the underlying factor structure of depression is similar across groups. The main advantage of CFA is the possibility to assess the composition of a latent construct with single empirical indicator variables, while

controlling for all other indicator variables. This provides information both regarding construct composition as well as the weight of individual items. CFA suggested that BDI-II score construction was similar in MS and MDD patients. Taken together, rather than differing along clear-cut phenotypic lines (such as somatic prominence), our results indicate that depression (as measured by BDI-II) is largely the same construct in MS and "idiopathic" MDD.

Clinical implications

The main clinical concerns of depression in MS are accurate diagnosis and appropriate treatment. With regard to diagnosis, our findings that the "latent construct" of depression is identical in MS-depression and "idiopathic" MDD may explain previous studies that have shown self-report measures of depression developed and validated in the general population are also suitable in MS even if they contain somatic and vegetative items likely affected by MS symptoms such as fatigue and cognitive dysfunction (e.g. Honarmand and Feinstein,[23] Quaranta et al.,[27] Fischer et al.,[30] and Patten et al.[31]). On a conceptual level, our results from the CFA extend the findings from a recent report that neurovegetative symptoms are poor indicators of depression in MS.[32] Moreover, our findings are in line with an empirical exploration of attributional style and learned helplessness in MS-depression, where MS patients more likely listed non-MS-related than MS-related causes of negative events.[33] Our results now integrate such findings into a larger conceptual framework to indicate that while vegetative symptoms are frequently correlated with depression, they have little impact on the underlying construct of depression, which is indistinguishable in depressed patients with or without a neurological disorder such as MS.

Limitations

It is important to consider some of the limitations of our study when interpreting the results. First, our measures of depression rely on a depression self-ratings and are not based on a structured clinical interview. However, the BDI-II cut-off (BDI-II > 19) in our sample yielded a rate of "clinical depression" of 27.3% (38 out of 139), which closely resembles the point prevalence for depression in MS patients reported in 15 previously conducted population-based studies.[5]

While our analysis supports the validity of the BDI-II as a dimensional measure in MS, diagnostic validity was not the focus of this article. Thus, the data presented here do not resolve the problems in the diagnostic evaluation of individual patients posed by the overlap between somatic symptoms and depression. This challenge will likely remain in individual cases, and we endorse the pragmatic view by Feinstein et al.,[6] who recommend to focus on the cardinal features of depression, that is, low mood, anhedonia, and loss of interest in daily activities.

Of note, our analysis of matched MDD and MS patients is limited by the small sample size of 38 patients in each group. However, examination of effect sizes clearly showed that the loss of significant group differences in most of the initially identified items was not simply due to reduced statistical power in this subgroup analysis.

Finally, the MDD and MS group differed in some potentially relevant clinical characteristics. For example, significantly more MDD patients were taking antidepressants than MS patients, which could have introduced a bias. However, as we were most interested in the clinical phenotype of depression, the current level of depression might be more relevant. Also, the percentage of female patients was significantly higher in the MS sample (73%) compared to the MDD sample (55%). However, depression scores did not differ between men and women in either sample, which closely mirrors a recent finding in MS patients.[34] In addition, the influence of sex was removed for the matched group analysis, so that the results reported there will not be affected by the slightly different sex ratios typically observed in MS versus MDD.

Conclusion and outlook

In conclusion, our results from multi-step statistical analyses suggest that adequately controlling for depression severity strongly reduces group differences in relative symptom contribution of depression between MS and MDD. As a result, the symptoms composition and clinical phenotype of MS-associated and idiopathic depression appear very similar. The relevance of these findings for psychotherapeutic approaches should be explored in future studies. Some trials have suggested that "generic" cognitive behavioral therapy (CBT)-based interventions[35] as well as a "generic" version of an Internet-based CBT program[36] may work to some degree in MS. However, adaptations to specific needs and characteristics of MS patients will likely be needed to maximize efficacy. These approaches

should continue to be developed and rigorously evaluated in randomized controlled trials in MS to determine their suitability and effectiveness for this population as well as to determine whether or not symptom composition and clinical phenotype are predictive of treatment response.

Acknowledgements

Alexander U Brandt, Carsten Finke, and Stefan M Gold are equally contributing authors in alphabetical order.

Conflict of interest

H.H., C.F., C.O., and S.M.G. have nothing to disclose. J.B.-S. has received speaking fees and travel grants from Bayer Healthcare, sanofi-aventis/Genzyme, and Teva Pharmaceuticals. R.R. has received a research grant from Aristo Pharma GmbH. T.O. received speaker honorary from TEVA, Germany. M.A. has received grants from Aristo, Servier, and Bristol-Myers Squibb; speaker honoraria from Deutsche Bank, the Johanniter Order, East German Savings Banks Association, Pusch Wahl Legal Lawyers, HRM Forum, Helios Media, Lundbeck, Bristol-Myers Squibb, Boehringer Ingelheim, Servier, Aristo, Viiv, and Gilead; travel grants from the Alfred Herrhausen Society, Lundbeck, and Servier; and has been a consultant to Deutsche Bank, Bristol-Myers Squibb, Aristo, Merz, mytomorrows, and Lundbeck. F.P. has received travel grants, research support, and personal compensation for activities with Alexion, Bayer, MerckSerono, Teva, Sanofi Genzyme, MedImmune, Chugai, BiogenIdec, and Novartis. A.U.B. received consulting fees or speaker honoraria unrelated to this study from Bayer, Biogen, Novartis, Teva, Nexus, and Motognosis.

Funding

H.H. was supported by a NeuroCure Fellowship (Deutsche Forschungsgemeinschaft, EXC257). T.O. and A.U.B. were supported by EXIST-Forschungstransfer (German Federal Ministry for Economic Affairs and Energy, 03EFEBE079). F.P. was supported by the Deutsche Forschungsgemeinschaft (DFG EXC257), the Bundesministerium für Bildung und Forschung (BMBF Competence Network Multiple Sclerosis), and the Guthy Jackson Charitable Foundation. S.M.G. was supported by a Heisenberg Fellowship (Deutsche Forschungsgemeinschaft GO1357/5-1 and 5-2). He currently receives research funding from Deutsche Forschungsgemeinschaft (GO1357/8-1 as part of KFO296), Bundesministerium für Bildung und Forschung (161A130), and the National Multiple Sclerosis Society (RG5225A1 and PR-1412-02262). This research was in part supported by the Deutsche Forschungsgemeinschaft (EXC257 and GO1357/5-2).

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