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Fatigue in Multiple Sclerosis Is Associated With Childhood Adversities

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Fatigue is a common and disabling symptom in patients with Multiple Sclerosis (PwMS). Its pathogenesis, however, is still not fully understood. Potential psychological roots, in particular, have received little attention to date. The present study examined the association of childhood adversities, specific trait characteristics, and MS disease characteristics with fatigue symptoms utilizing path analysis. Five hundred and seventy-one PwMS participated in an online survey. Standardized psychometric tools were applied. The Childhood Trauma Questionnaire (CTQ) served to assess childhood adversities. Trait variables were alexithymia (Toronto Alexithymia Scale; TAS-26) and early maladaptive schemas (Young Schema Questionnaire; YSQ). Current pathology comprised depression (Beck's Depression Inventory FastScreen; BDI-FS) and anxiety symptoms (State-Trait Anxiety Inventory; STAI-state), as well as physical disability (Patient determined Disease Steps; PDDS). The Fatigue Scale for Motor and Cognitive Functions (FSMC) was the primary outcome variable measuring fatigue. PwMS displayed high levels of fatigue and depression (mean FSMC score: 72; mean BDI-II score: 18). The final path model revealed that CTQ emotional neglect and emotional abuse remained as the only significant childhood adversity variables associated with fatigue. There were differential associations for the trait variables and current pathology: TAS-26, the YSQ domain impaired autonomy and performance, as well as all current pathology measures had direct effects on fatigue symptoms, accounting for 28.2% of the FSMC variance. Bayesian estimation also revealed indirect effects from the two CTQ subscales on FSMC. The final model fitted the data well, also after a cross-validation check and after replacing the FSMC with the Chalder Fatigue Questionnaire (CFQ). This study suggests an association psychological factors on fatigue in Multiple Sclerosis. Childhood adversities, as well as specific trait characteristics, seem to be associated with current pathology and fatigue symptoms. The article discusses potential implications and limitations.

Keywords: fatigue, Multiple Sclerosis, childhood adversities, trait characteristics, psychopathology, path model

INTRODUCTION

Fatigue is among the most disabling symptom in patients with multiple sclerosis (PwMS) (1). It affects over 75% of all PwMS (2, 3). Moreover, fatigue is the primary factor for MS-related early retirement (4, 5). Research on the pathogenesis of MS fatigue has identified several (neuro-) biological, immunological, and neurophysiological correlates (1). However, the multifactorial genesis of MS-fatigue remains incompletely understood.

Several studies have suggested that psychological factors might also contribute to MS fatigue, as, for example, indicated by its association with depression (6, 7). Moreover, since behavioral interventions such as Cognitive Behavioral Therapy (CBT) or mindfulness-based approaches are capable of effectively reducing fatigue severity in this PwMS (8), psychological underpinnings appear to modulate aspects of fatigue too.

However, knowledge about the relative contribution of psychological factors to MS fatigue and their functional significance remain limited. Interestingly, evidence from other chronic disorders such as HIV (9, 10), cancer (11, 12), or chronic fatigue syndrome [CFS; (13, 14)] suggests a potential link between fatigue, early life adversities, and traumatic stress. The present exploratory study aimed to interrelate these factors, and assess their relative contribution to fatigue severity in a large sample of PwMS, by conducting an online survey and utilizing a path-analytic approach.

MATERIAL AND METHODS

Participants

Participants were recruited *via* advertisements on the website of the German MS Society (Deutsche Multiple Sklerose Gesellschaft, DMSG) from July 2018 to March 2019. In addition, flyers and newsletters were used to advertise the study at a large rehabilitation center (Kliniken Schmieder Konstanz) and the MS outpatient clinic of the University Medical Center Hamburg-Eppendorf.

Patients were eligible if they had a self-reported diagnosis of MS and if they were at least 18 years old. Access to the Internet was mandatory. Out of a total of 1.490 individuals who registered *via* the website, 608 (41%) completed the study. In order to avoid the imputation of missing data, only complete data sets were included (n = 571). All participants provided full informed consent prior to enrolment. The ethical review board of the University of Konstanz approved the study in June 2018, prior to enrolment of the first participant. The study was conducted following the European data protection regulation (EU-GDPR).

Study Procedure

The flyers in the Kliniken Schmieder Konstanz, the University Medical Center Hamburg-Eppendorf, and the website of the DMSG provided a link to connect directly to the online survey (Unipark survey software, Globalpark AG, Hürth). PwMS provided informed consent online before participation. First, PwMS completed questions related demographic and clinical characteristics {sex, age, MS duration, medication, education, marital status, psychiatric disorders, and the Patient determined Disease Steps [PDDS; (15)] as a measure of disability}. Second, they completed a battery of questionnaires (see below). The duration of the whole survey was approximately 65 min.

Measures

The study utilized two measures of fatigue, the *Fatigue Scale for Motor and Cognitive Functions* (FSMC), and the *Chalder Fatigue Questionnaire* [CFQ, (16)], using the validated German versions (17, 18). The German version of the *Beck Depression Inventory* [*BDI-II*, (19)] served to assess current symptoms of depression. A score of 13 is the cut-off score for as validated for the German version [see (20)] and has also been validated for use in pwMS (21, 22). For the inclusion into the path model, the shortened *BDI-II-FastScreen* was used [*BDI-FS*; (23)]. The BDI-FS omits items covering vegetative and somatic aspects of depression, thus avoiding confounding of the associations between depression and fatigue in the model that could be caused by overlapping items on fatigue and related symptoms. The German version of the *Patient-Determined Disease Steps* [*PDDS*, (15)] served as a measure of disability. The PDDS is a self-report measure which strongly correlates with the neurologist-rated Expanded Disability Status Scale [EDSS, (24)]. To assess alexithymia, the German version of the *Toronto-Alexithymia-Scale-26* [*TAS-26*, (25, 26)] was administered. The German version of the *Childhood Trauma Questionnaire* [CTQ, (27, 28)] is a self-report questionnaire for the assessment of adverse childhood experiences. It is valid for the application in individuals aged 12 years or older. The CTQ has five subscales that were all considered in the present study: 1. *CTQ emotional abuse*; 2. *CTQ physical abuse*; 3. *CTQ sexual abuse*; 4. *CTQ emotional neglect*; and 5. *CTQ physical neglect*. For the assessment of symptoms of anxiety, the present study used the short form of the German *State-Trait Anxiety Inventory* [STAI, (29, 30)], with an emphasis on the current symptoms, assessed with the State Anxiety Scale (*STAI-State).* The *Young Schema-Questionnaire – Short Form* 3 [*YSQ*, (31)] is a measure to assess early maladaptive schemas (EMS), which has been translated and validated in German (32). Young (33) suggest that schemas form domains, which represent the hypothesized developmental origins of the schemas. Each of the domains represents a grouping of developmental needs. Young postulates five domains that were also considered in the present study: 1. *YSQ disconnection and rejection*; 2. *YSQ impaired autonomy and performance*; 3. *YSQ impaired limits*; 4. *YSQ other-directedness*; and 5. *YSQ over-vigilance and inhibition*. Detailed information on the scoring of each measure can be found in **Supplement 3**.

Data Analysis

In a first step, Pearson-correlations between the main variables of interest included in the path analysis served to display the zero-order correlations. According to Cohen (34), correlation coefficients >.10 represent small, >.30 medium, and >.50 large effects. The supplement contains the respective table (**Supplement 1, 2**).

Path analyses calculated in AMOS 25 for Windows served to model the complex relations between 1) childhood adversities, 2)

schema domains and alexithymia, 3) current pathology, and 4) fatigue. All other analyses were carried out with SPSS 25 for Windows. Fatigue, as measured with the FSMC, was the primary dependent variable. All other variables served as predictor variables on the respective levels:

The model followed the hypotheses that childhood precedes the development of a stable personality and that the development of a stable personality precedes current pathology and fatigue symptoms. Therefore, 1. CTQ subscales constituted the first level of the predictor variables, 2. YSQ schema domains and alexithymia the second level, and 3. the current depression and anxiety symptoms, as well as the subjectively reported disability, the third level. Statistical modeling started with the full model and a backward exclusion approach, excluding non-significant paths stepwise. During this procedure, one step also acknowledged the content of the relationship between variables where the identification of a non-significant path was equivocal due to a significant variance overlap between path-coefficients from two CTQ subscales. The fit indices CFI (comparative fit index) and RMSEA (root mean square error of approximation) according to the cut-off scores defined in Hu & Bentler (35) served to estimate the fit of the final model.

First, maximum likelihood estimation was applied. However, multivariate kurtosis and skewness values indicated deviations from multivariate normality [kurtosis = 10.16; c.r. = 7.18; (34)], in particular, due to skewed CTQ distributions. These deviations are critical as violations of multivariate normality may cause an inflation of Chi-Square values (35). The Bollen-Stine bootstrap *p* confirmed that the path model based on Maximum Likelihood estimation did not fit the data adequately ($p = .021$). Therefore, the repeated statistical modeling utilized the backward procedure with a bootstrapping approach. Bootstrapping, with 50.000 bootstrap samples, served to calculate bias-corrected confidence intervals for the path coefficients. Path coefficients that lay within the confidence interval ranging from (SM - 1,96*SE) to (SM + 1,96*SE) were considered as statistically not significant. In the final model, four cases displayed Mahalanobis distances at $p < .001$ fulfilling the criterion of outliers (36). However, the exclusion of these outliers did not have a significant impact on the final model. Thus, maintaining these data in the data set was justified.

Additionally, to support the validity of the final selected model, the model fit was re-estimated by using the second fatigue measure (CFQ) as the dependent variable. Furthermore, a cross-validation approach helped to estimate the robustness of the proposed model by randomly splitting the sample into two halves. Model fits were re-estimated for the split sub-samples. Finally, Bayesian estimation served to calculate the indirect effects of childhood adversities on fatigue symptoms. The Markov Chain Monte Carlo (MCMC) method implemented in AMOS was chosen. This Monte Carlo technique utilizes a random number generator to draw samples, serving to estimate the posterior distribution of parameters in the model. Ninety-five percent confidence intervals were chosen to determine statistical significance. The level of significance was alpha <.05.

RESULTS

Sample Characteristics **Table 1** provides an overview of the sample characteristics. Means (*SD*) represent the primary estimates unless otherwise specified.

The sample had a distribution of clinical characteristics reasonably typical for an MS outpatient sample with a female to male ratio of 3.3 to 1 and approximately 70% RRMS patients. However, depression scores were higher than what is typical for this population (65.5% above the clinical cut-off of ≥13 on the BDI-II for at least mild depressive symptoms).

Path Model

Before inclusion in the path model, inter-correlations between the primary outcome variables were calculated. **Supplement 1** displays Pearson correlation coefficients between the fatigue measures and the measures assessing symptom severity. **Supplement 2** contains Pearson correlations between current symptom severity, fatigue, and childhood adversities, as well as schema domains (EMS) and alexithymia.

In contrast to a multiple linear regression analyses that primarily focuses on the relationship between one dependent variable and various predictor variables, a path model has the advantage of combining different simple regression models into one overarching model. **Figure 1** displays the final path model after stepwise removal of non-significant paths in order to improve model fit. By removing non-significant paths from the initial model, only those paths that are meaningful in terms of the prediction of one variable from other variables remain in the final model.

TABLE 1 | Sample characteristics.

	Total (*N* = 571)
age in years (*M/SD*)	43.4 (10.9)
sex (females/males)	438/133
education	
no graduation	2 (.4%)
9 years	39 (6.8%)
10 years	173 (30.3%)
13 years	357 (62.5%)
disease duration in years (*M/SD*)	9.1 (7.6)
PDDS (*M/SD*)	2.4 (1.9)
Disease course *N* (%)	
Clinically isolated syndrome	7 (1.2%)
Relapsing-remitting (RRMS)	392 (68.7%)
Secondary progressive (SPMS)	75 (13.1%)
Primary progressive (PPMS)	52 (9.1%)
Unknown	45 (7.9%)
FSMC (*M/SD*)	72.26 (16.16)
CFQ (*M/SD*)	21.06 (6.08)
BDI-II (*M/SD*)	17.71 (10.39)
BDI-FS (*M/SD*)	4.41 (3.63)
Clinically relevant depressive symptoms (BDI-II 13 or higher) N, %	374 (65.5)

N, number of participants; SD, Standard Deviation; M, mean; CFQ, Chalder Fatigue Questionnaire; FSMC, Fatigue Scale for Motor and Cognitive Functions; BDI-FS, Beck Depression Inventory II FastScreen; BDI-II, Beck Depression Inventory II; PDDS, Patient Determined Disease Steps.

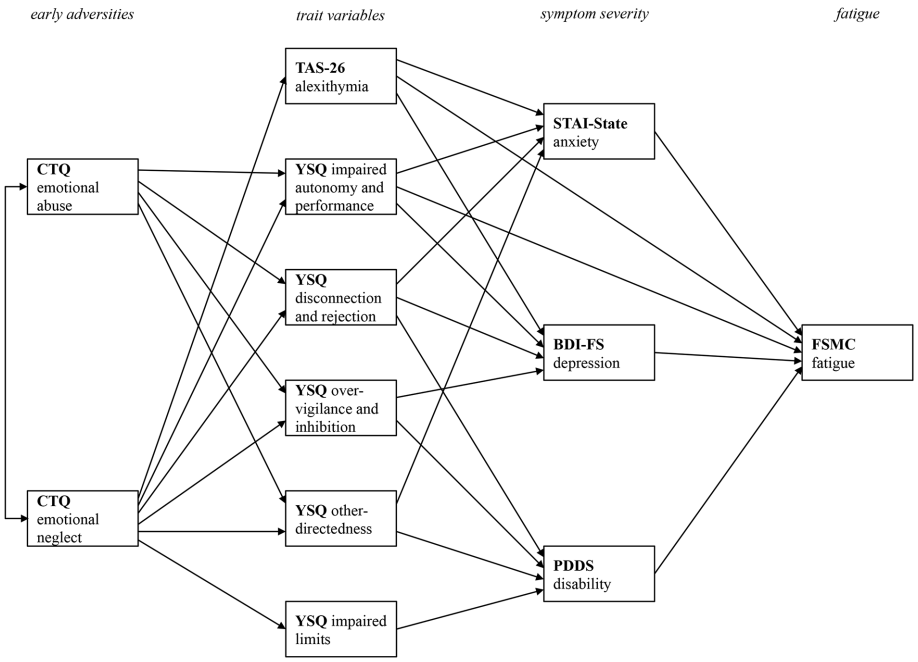

FIGURE 1 | Final path model with all statistically significant paths between the four levels of early adversities, trait variables, current pathology, and fatigue symptoms. CTQ, Childhood Trauma Questionnaire; TAS-26, Toronto Alexithymia Scale 26; YSQ, Young Schema Questionnaire S3; STAI-State, State Trait Anxiety Inventory-State Scale; BDI-FS, Beck Depression Inventory II FastScreen; PDDS, Patient Determined Disease Steps; FSMC, Fatigue Scale for Motor and Cognitive Functions. Only statistically significant paths are printed.

The model fit for the final model was excellent [Chi^2 (20) = 35.94, p = .016, Chi^2/df = 1.80, CFI = 1.00, RMSEA = .04]. To facilitate the presentation of the complex relations between the variables, **Figure 1** only displays the relevant paths without the beta coefficient values. The subsequent figures focus on specific relationships. They also display the bootstrapped 95% confidence intervals.

Figure 2 displays the relation between childhood adversities and trait measures, i.e., the first two levels of the path model. From the five different CTQ scales initially included in the full model, only emotional neglect and emotional abuse remained as significant predictors in the final model. For a better visual representation, **Figure 2** displays the path coefficient from the predictor variables CTQ emotional abuse and CTQ emotional neglect on the PwMSs' trait characteristics, indicated by their EMSs (YSQ) and their level of alexithymia (TAS-26) separately. The results highlight the importance of emotional disturbances in childhood and adolescence. Both CTQ scales significantly predict four of the five YSQ scales (1. YSQ disconnection and rejection; 2. YSQ impaired autonomy and performance; 3. YSQ other-directedness; and 4. YSQ over-vigilance and inhibition) that all remained in the final model. Also, CTQ emotional neglect predicted alexithymia, and the YSQ subscale impaired limits.

For the relation between the trait variables and current symptom severity (**Figure 3**), alexithymia (TAS-26) and the YSQ scales impaired autonomy and performance, disconnection and rejection, as well as over-vigilance and inhibition, predicted depression symptoms. Higher alexithymia scores, as well as higher perceived disconnection and rejection, higher impairments in autonomy and performance, and higher other-directedness predicted more severe anxiety symptoms. PwMS who reported higher levels of disconnection and rejection, as well as impaired limits, also scored higher on the PDDS scale. As indicated by the negative path coefficients, PwMS with lower other-directedness and less over-vigilance and inhibition reported higher disability (PDDS). These results indicate that specific trait characteristics, which in turn are predicted by early life adversities, do have not only a significant impact on the current anxiety and depression severity but are also associated with self-reported disability.

Figure 4 displays all direct significant predictor variables for the prediction of current fatigue severity. Current anxiety and depressive symptom severity directly influence fatigue severity. More severe symptoms of anxiety and depression are associated with higher fatigue scores. PwMS with higher disability also reported more severe fatigue symptoms. As indicated by the direct path from the TAS-26, PwMS with higher scores in alexithymia tend to experience higher fatigue severity. Additionally, PwMS who report impaired autonomy and performance on the respective YSQ-sub-scale also tend to report more fatigue symptoms. Thus, the trait variables TAS-26 and YSQ impaired autonomy and performance, also have a direct impact on fatigue symptoms. Additionally, there were small but significant indirect effects of reported emotional abuse (M = .05, SE <.01) and emotional neglect (M = .11, SE <.01) on fatigue.

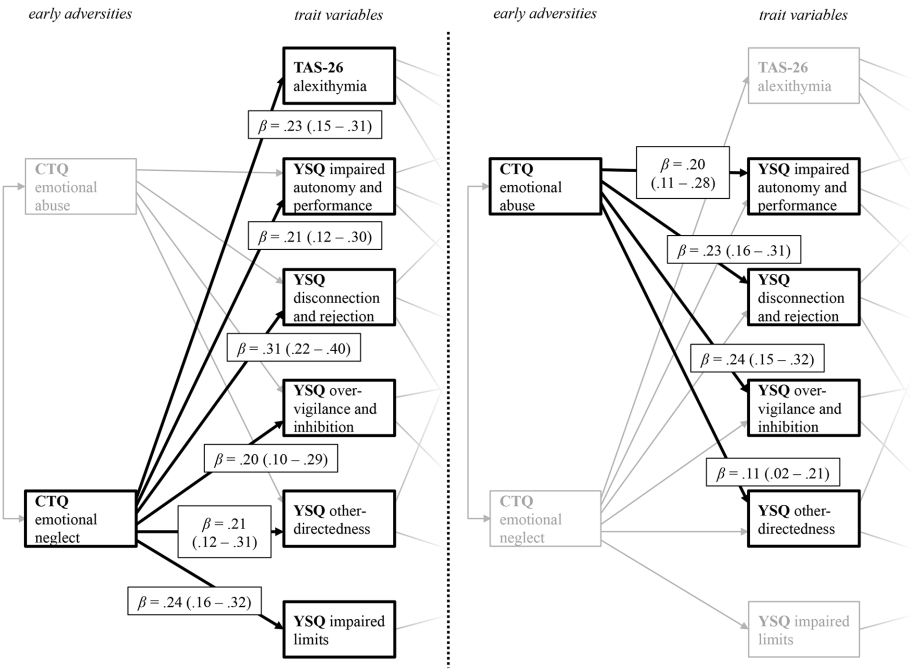

FIGURE 2 | Path coefficients from the predictor variables CTQ emotional neglect (left) and CTQ emotional abuse (right) on the YSQ sub scales and the TAS 26 alexithymia scales. The figure displays the levels of early adversities and trait variables taken from the final path model displayed in **Figure 1**. CTQ, Childhood Trauma Questionnaire; TAS-26, Toronto Alexithymia Scale 26; YSQ, Young Schema Questionnaire S3. For a better visual presentation, the paths from the CTQ subscales *CTQ emotional neglect* (left) and *CTQ emotional abuse* (right) on the trait variables are printed separately, with paths belonging to the other predictor variable respectively being greyed out. Standardized beta coefficients are displayed.

Thus, adverse emotional experiences during childhood also indirectly influence current fatigue symptoms. The path model accounted for 28.2% of the fatigue severity variance.

Validation of the Path Model With a Second Fatigue Measure

The model fit remained excellent after re-calculating the final model with the CFQ instead of the FSMC as a measure for fatigue [Chi^2 (20) = 34.25, p = .024, Chi^2/df = 1.71, CFI = 1.00, RMSEA = .04]. This result supports the validity of the obtained model, as it was possible to replicate it with another fatigue measure.

Cross-Validation Check

As another approach to support the validity of the model, it was re-calculated after splitting the sample into two equally large halves. This method serves to test whether the fit measures remain stable, when a different composition of the sample is chosen, or whether the fit measures are susceptible to one particular selection of participants and not replicable. As for the previous calculations, data fit the hypothesized model in both subsamples [split half 1 (n = 285): Chi^2 (20) = 21.86, p = .348, Chi^2/df = 1.09, CFI = 1.00, RMSEA = .02; split half 2 (n = 286): Chi^2 (20) = 32.78, p = .036, Chi^2/df = 1.64, CFI = .99, RMSEA = .05]. Similar results were observed after replacing the FSMC with the CFQ [split half 1 (n = 285): Chi^2 (20) = 21.84, p = .349, Chi^2/df = 1.09, CFI = 1.00, RMSEA = .02; split half 2 (n = 286): Chi^2 (20) = 30.06, p = .069, Chi^2/df = 1.50, CFI = .99, RMSEA = .04]. Thus, the obtained results support the validity of the final model obtained.

DISCUSSION

The present study aimed to investigate the association of different psychological factors with current fatigue symptoms in MS. In particular, it focused on 1) childhood adversities as measures of early adverse experiences, 2) Alexithymia and EMS according to the Schema-therapeutic model as measures of trait characteristics, 3) anxiety, depression symptoms, as well as disability, and 4) fatigue as the primary outcome variable. Path analysis served to model the complex relations and the relative contributions of these variables to fatigue severity.

Among the five CTQ childhood adversities subscales, only the subscales assessing emotional neglect and abuse remained in the final model, while all other subscales made no significant contribution (physical abuse, sexual abuse, and physical neglect). This finding corroborates and extends a previous cohort study (37), where emotional abuse and emotional neglect showed the largest effect sizes among the different types of childhood trauma in MS compared to healthy controls. Together, this adds to a growing literature from cross-sectional (37, 38) and register-based studies (39) that have indicated a link between childhood adversity, trauma-related disorders, and

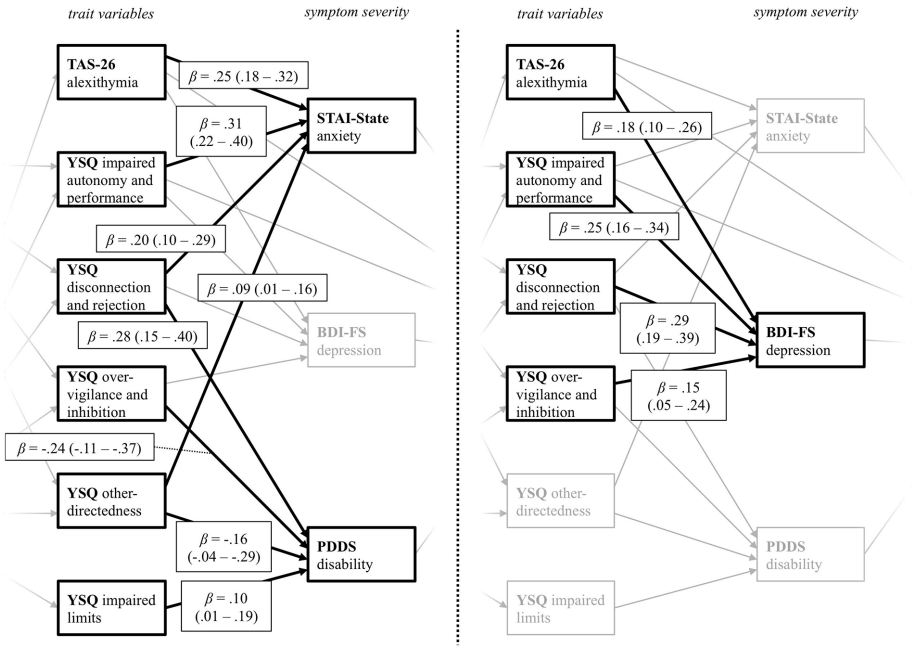

FIGURE 3 | Path coefficients from the YSQ and TAS-26 trait variables on the variables assessing current symptom severity. The figure displays the levels of trait variables and symptom severity taken from the final path model displayed in **Figure 1**. YSQ, Young Schema Questionnaire S3; TAS-26, Toronto Alexithymia Scale 26; STAI-State, State Trait Anxiety Inventory State Scale; BDI-FS, Beck Depression Inventory II FastScreen; PDDS, Patient Determined Disease Steps. For a better visual presentation, the paths from the trait variables on the variables measuring current symptom severity *STAI-State* and *PDDS* (left), as well as the *BDI-FS* (right) are printed separately, with paths belonging to the other predictor variable respectively being greyed out. Standardized beta coefficients are displayed.

autoimmune diseases. While the available data suggest some specificity of emotional vs. physical domains of abuse, the potential causes for this remain unknown. Some of this might be due to statistical power as emotional abuse tends to have a higher reported frequency in MS [e.g. (37)]. It is tempting to speculate that other factors, including possible differential biological substrates of different forms of abuse, could also play a role here and this should be investigated in future research.

Further studies should focus on the comparison between PwMS, patients with other somatic disorders and co-morbid fatigue, as well as healthy controls. This would help to disentangle the specificity of the link between adverse emotional experiences and fatigue as an MS-related or a more general phenomenon. A link between adverse emotional experiences and fatigue has also been reported in other medical conditions, such as CFS or cancer (40, 41).

It should be noted that these findings could at least in part be due to an overlap with comorbid or misdiagnosed depression (14). In the present study, we used the BDI-II-FastScreen to overcome the shortcoming of a symptom overlap (i.e. somatic/vegetative symptoms of depression that may also be impact responses on fatigue questionnaires). Still, the differentiation between the different phenomena requires further study.

While our study was a cross-sectional survey, the assessment of emotional neglect and emotional abuse using the CTQ is a retrospective assessment of experiences during childhood and adolescence. Thus, these experiences will in most or all cases be before MS onset (which only rarely manifests before the age of 18 and typically has an age of onset between 20 and 30 years of age). There are several possibilities that may explain the increased frequencies of adverse childhood experiences reported by MS patients compared to healthy controls in previous studies (37). For example, it is conceivable that MS patients are more likely to recall or report such experiences (a phenomenon known as "effort after meaning"). However, the large population-based by Song et al. (39) used documented diagnoses of stress-related disorders (including PTSD) preceding the MS diagnosis by several years and thus cannot be explained by "effort after meaning". This may suggest that direct or indirect effects of childhood adversity may increase the risk of subsequently developing MS (or other autoimmune diseases). Currently these mechanisms remain unknown but they may include behavioral factors [e.g. altered health behaviors such as diet, exercise, or smoking, the latter of which is a known risk factor for MS, see (42)]. Moreover, there might be biological pathways (e.g. altered stress response system regulation or inflammatory mechanisms) that have been linked to childhood trauma (43) and might also play a role in MS (44). Similarly, these mechanisms could also contribute to MS symptoms such as fatigue. However, at this point, this remains speculative and detailed studies, ideally longitudinal in nature, are required to probe this hypothesis and explore potential behavioral or

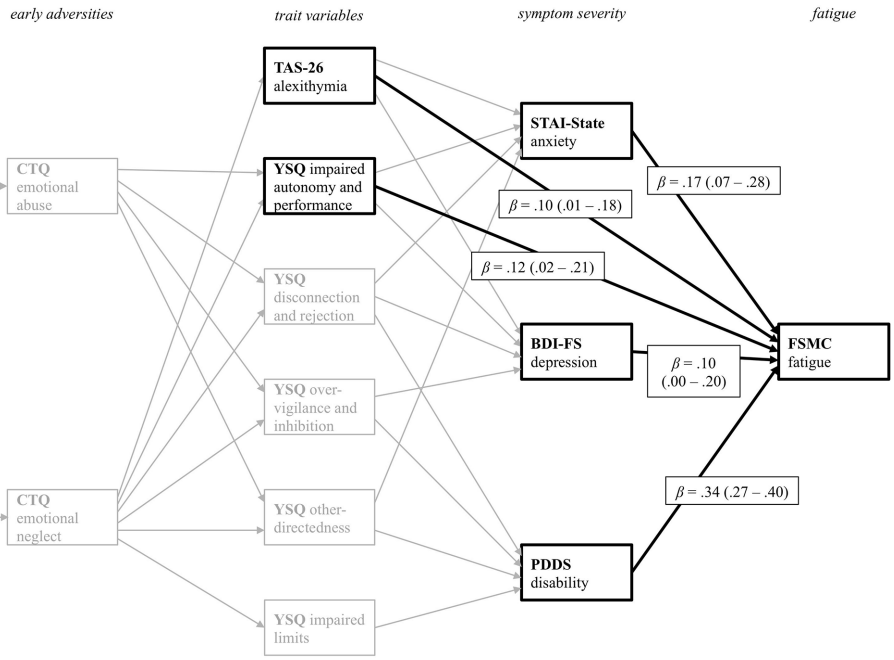

FIGURE 4 | Path coefficients from all variables with direct effect on fatigue symptoms as the primary outcome variable *PDDS*. CTQ, Childhood Trauma Questionnaire; TAS-26, Toronto Alexithymia Scale 26; YSQ, Young Schema Questionnaire S3; STAI-State, State Trait Anxiety Inventory State Scale; BDI-FS, Beck Depression Inventory II FastScreen; PDDS, Patient Determined Disease Steps; FSMC, Fatigue Scale for Motor and Cognitive Functions. For a better visual presentation, only significant direct paths from the various predictor variables on the *FSMC* primary outcome variable are printed in black. Standardized beta coefficients are displayed.

biological mechanisms that might contribute to the association between childhood adversity and MS risk or symptom severity.

Based on the present analysis, the reported childhood adversities may not only be more common in MS than the general population but could indirectly contribute to symptom severity, particularly concerning depression and fatigue. The presented model suggests that these associations could be mediated *via* Early Maladaptive Schemas as measured by the YSQ.

These results are in line with studies in which early adversities predicted the development of EMS in particular in affective disorders (45) and individuals with personality disorders (46). Similarly, research on different psychopathologies, such as affective disorders (47), personality disorders (48), or adult dissociation (49), has reported a relation between emotional abuse/neglect and the development of alexithymia as a trait characteristic. The MS literature also consistently describes moderate associations between symptoms of anxiety, depression as well as disability, and fatigue (50, 51), which the proposed path model from our study confirms. Intriguingly, trait characteristics predicted current self-reported disability, which may reflect an overlap between psychological and somatic phenomena. However, while the associations were statistically significant in this large cohort, the magnitude of the contribution of YSQ and alexithymia to fatigue scores was rather small and a sizeable portion of variability in fatigue severity remained unexplained, suggesting that other factors not included in our model likely contribute to MS-associated fatigue.

Considering the relation between adverse childhood experiences and MS-related fatigue indicated by our data, it is tempting to hypothesize that Schema Therapy could provide a useful taxonomy to understand and link the functional aspect of fatigue to childhood adversities. Schema Therapy provides a trans-diagnostic conceptual and empirically validated framework (32, 51). A central aspect of schema therapy is the concept of EMS, thought to develop in childhood (52). While this might be interesting from a conceptual point of view, the cross-sectional associations between schemas and fatigue alone are not sufficient to claim causality, and no clinical trial to date has explored the potential of schema therapy for neuropsychiatric aspects of MS (including fatigue).

However, further research is required in order to elaborate a profound etiologcal working model on how early life adversities could manifest in MS and contribute to associated symptoms such as fatigue or psychopathology. While Young's Schema Questionnaire assesses EMS, it does not capture the functional or dysfunctional nature of these concepts. Measures, such as the OPD conflict questionnaire (53) or the Schema Mode Inventory (54) could deepen our understanding of the psychosomatic or psychodynamic nature of fatigue. Fatigue could for example constitute a potential defense mechanism according to psychodynamic theories. Moreover, interactions on both the

psychological and the biological level could account for the specific relation between adverse emotional experience and MS-fatigue found in this study and should be targeted by future research strategies.

The major limitation of the present study is that all data were obtained cross-sectionally and are correlational and the path model's hierarchical structure does not necessarily imply a cause-effect relationship between the three levels. Moreover, responses in the CTQ specifically may be prone to recall bias or effort-after-meaning effects.

The present study was web-based and all MS diagnoses and clinical data rely on participants' self-reports A selection bias for the PwMS sample can also not be excluded. The advertisement of the study as a survey on fatigue in MS may explain the high average levels of fatigue in our sample. In a related matter, depression scores were quite high, and the percentage of patients who had depressive symptoms above the clinical cut-off was higher than what is common in MS (55). Structured clinical interviews would have been helpful to validate anxiety and depression symptoms. Bed-ridden patients or patients who do not have access to the internet might also not have participated. Biased sample characteristics could limit the generalizability of the present findings.

Moreover, MS has a genetic component and can cluster in families (56). Although the majority of MS patients do not have first-degree relatives with the disease, it is conceivable that genetic or environmental factors linked to family history of MS can affect childhood experiences. In our study, we did not assess and thus could not explore the effect of parental MS on any of the measures obtained.

Taken together, the present study revealed a path model based on a large sample of PwMS from an online-survey. Among different childhood adversities, only emotional neglect and emotional abuse predicted certain personality traits, current disability, and psychopathology, as well as MS fatigue symptoms. Alexithymia, as well as EMS, play a mediating role in the relation between childhood emotional abuse/neglect and current disability, as well as symptoms of depression and anxiety. Current disability and symptoms of depression and anxiety were, in turn, associated with fatigue symptoms. Thus, the current study not only confirms the well-established relation between psychopathology and fatigue in MS but is -to the best of our knowledge- the first to also establish a link to early adversities and specific trait characteristics. If early abuse and neglect increase the probability for the development of individual personality predispositions and the susceptibility to develop fatigue, this might provide a new perspective on the genesis of MS-fatigue.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available upon request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical review board of the University of Konstanz. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GP, RS, CH, and SG designed the study. GP, CD, and JR were responsible for data collection. GP conducted the statistical analysis and the data pre-processing. All authors interpreted the results and gave critical feedback. GP and SG wrote the manuscript. CD, JR, AR, CH, and RS critically revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00811/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.