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Personality traits in patients with multiple sclerosis: their association with nicotine dependence and polypharmacy

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Abstract

Background: The modifiable risk factor exerting the most substantial influence on the development and disease course of multiple sclerosis (MS) is cigarette smoking. Furthermore, smoking is associated with a higher risk of suffering from one or more comorbidities and potentially contributes to polypharmacy. We aimed to use personality tests to explore health-promoting and harmful patient characteristics.

Objective: To investigate two important factors influencing the course of MS – the degree of smoking dependence and the status of polypharmacy – in association with personality traits.

Design: This is a bicentric, cross-sectional study.

Methods: We collected sociodemographic, clinical and medical data from patients with MS ($n = 375$) at two German neurological clinics. The participants were asked to complete the NEO Five-Factor Inventory (NEO-FFI) and the Temperament and Character Inventory-Revised (TCI-R). Relationships between variables were examined using correlation analyses, and differences between groups were examined using linear models. Current smokers with MS were also asked to complete the Fagerström questionnaire to categorize them into patients with mild, moderate and severe smoking dependence.

Results: In our sample, 67.5% were women, and the mean age was 48.1 years. The patients had a median Expanded Disability Status Scale of 3.0 at a median disease duration of 10 years. Patients with MS with severe smoking dependence had on average a significantly higher neuroticism score in the NEO-FFI compared to those with mild or moderate smoking dependence. Patients with MS and polypharmacy had significantly higher neuroticism scores than those without. In the extraversion scale of the NEO-FFI, patients with MS and polypharmacy had significantly lower scores on average. Significant differences were also found when analysing the TCI-R in patients with MS and heavy smoking dependence, with higher scores for harm avoidance (HA) and lower scores for reward dependence, self-directedness (S-D) and cooperativeness (CO) in various subscales. Polypharmacy in patients with MS was associated with higher scores for HA and self-transcendence. Furthermore, patients with polypharmacy showed lower values than patients without polypharmacy in individual subscales of the dimensions of persistence, S-D and CO.

Conclusion: Using the NEO-FFI, we were able to show that neuroticism is a detrimental trait and extraversion a protective trait in patients with MS in relation to nicotine dependence and polypharmacy. In addition, the evaluation of the TCI-R showed that high HA as well as low S-D and CO scores were more common in patients with MS and nicotine dependence or polypharmacy. With this knowledge, the risk of polypharmacy and smoking can be understood in the context of personality characteristics and targeted treatment and counselling can be provided.

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Introduction

Multiple sclerosis (MS) is the most common chronic immune-mediated neurological disease, affecting 2.8 million people worldwide.[1] It is a complex multifactorial inflammatory disease[2] that leads to demyelination, oligodendrocyte injury, synaptic and axonal loss and reactive gliosis.[3] These processes are neither temporally nor locally limited, making the symptoms of MS very heterogeneous and the course of the disease difficult to predict.[4,5] Current MS definitions differentiate between the clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), which may progress over time to secondary progressive MS (SPMS) with increasing neurologic impairment, and primary progressive MS (PPMS).[6,7] However, these subtypes should be seen as points on a continuum of disease.[2,8]

There is currently no cure for MS, but there are treatments that can reduce the severity of symptoms, prevent relapses and delay disability progression.[9,10] For this purpose, immunomodulatory or immunosuppressive disease-modifying drugs (DMDs) are used.[11] In addition to DMDs, patients with MS require symptomatic medication and medication for concomitant diseases. Patients with late-stage MS often suffer from multiple symptoms, such as gastrointestinal, psychiatric or motor symptoms.[12,13] Psychiatric disorders represent the most common comorbidities in patients with MS,[14] with depression being the most common disorder at roughly 20%.[15] The use of several symptomatic medications in combination with DMDs and comorbidity therapies can quickly lead to polypharmacy in patients with MS.[16–19] Polypharmacy is typically defined as the simultaneous intake of five or more medications.[20] Polypharmacy reduces patients' quality of life and bears the risk of medication errors, adverse drug reactions, lack of adherence to treatment and drug interactions.[18,20] It also increases costs for the healthcare system.[16,21] The estimated prevalence of polypharmacy in patients with MS is between 14% and 76.5%.[22]

Patients with MS smoke tobacco more frequently than the normal population (38.1% vs 29.2%),[23] and more than half of the patients who smoke suffer from comorbidities,[11,24] which often makes polypharmaceutical treatment necessary.[25] Cigarette smoke is a lung irritant that is thought to trigger a pro-inflammatory cascade in the lungs that can cause chronic inflammation and, with prolonged exposure, autoimmunity. Smoking increases the risk of MS by approximately 50%.[26] The free radicals, cyanates and carbon monoxide contained in cigarettes are directly neurotoxic. Therefore, patients with MS who smoke cigarettes have a higher disease activity, a faster rate of brain atrophy and a greater disability burden.[27] Smoking patients with MS are also at risk of developing neutralizing antibodies against the biologics used, which also leads to a poorer prognosis[28] due to adverse effects on the severity and progression of MS.[29,30] Rodgers et al. showed that when smokers quit, the rate of deterioration of motor disability slows to match the rate of motor decline in those who have never smoked.[31] This indicates that smoking cessation is beneficial for people with MS.[31–34]

Smoking and polypharmacy are two important factors in the course of MS. Understanding one's personality could help identify health-promoting and harmful behaviours.[35] The term 'personality' denotes enduring personal characteristics that are expressed in a range of thoughts, feelings and behavioural patterns in different situations.[36] Personality characteristics appear to be particularly important in MS, as 20%–40% of patients with MS exhibit personality changes and disorders.[37] This aberrant personality profile is characterized in the NEO Five-Factor Inventory (NEO-FFI) by low scores for conscientiousness, extraversion and agreeableness and high scores for neuroticism.[38] The NEO-FFI is based on both a robust and differentiated factor model, which according to Borkenau[39] reflects the most important dimensions of meaning underlying the attribution of personality traits based on behavioural

observations. Personality traits can play a decisive role in the acceptance of the illness and adaptive coping mechanisms.[37] Jacot de Alcântara et al. have shown that high neuroticism and openness as well as low conscientiousness and extraversion are associated with poor treatment adherence.[38]

Cloninger has developed a biosocial model of personality based on seven basic dimensions of temperament and character (Temperament and Character Inventory (TCI)),[40,41] The four temperament dimensions are as follows: novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (PS). Temperament refers to automatic emotional reactions to experiences that are stable over time, whereas character refers to self-concept and individual differences in goals and values.[40] The three character dimensions are as follows: self-directedness (S-D), cooperativeness (CO) and self-transcendence (ST). Evidence already exists that there are links between smoking behaviour and TCI scores in the general population.[42,43] Several studies used the TCI to explore the personality traits of people with MS to understand associations between personality characteristics and MS symptoms, disease progression, comorbidities and quality of life.[44–46] However, to date, no study has analysed TCI scores of patients with MS in a large number of cases. More specifically, studies analysing TCI dimensions in patients with MS with regard to smoking dependence and polypharmacy have not yet been published.

In the present study, we evaluated personality traits in a large group of patients with MS. We hypothesized that individual psychological and behavioural patterns are associated with smoking habits and drug utilization, thereby potentially influencing the course of the disease. Our primary objective was therefore to elucidate the relationships between various personality traits and (1) smoking dependence and (2) polypharmacy in MS.

Methods

Study population

Patients were recruited in the Department of Neurology (Neuroimmunology Section) at the Rostock University Medical Centre (Germany) and in the Department of Neurology at the Ecumenical Hainich Hospital Mühlhausen (Germany). Inclusion criteria were age over 18 years and a confirmed diagnosis of a CIS or MS according to the revised McDonald criteria.[47] Data acquisition from outpatients and inpatients was conducted from June 2019 to July 2020. Of the 461 patients who were asked to participate voluntarily, 57 were excluded due to unwillingness, lack of time or poor cognitive state. The remaining 404 patients provided written informed consent prior to inclusion in this cross-sectional study. Finally, 375 patients with a fully completed NEO-FFI assessment were analysed in the present study. Regarding this cohort, sociodemographic, clinical and medication data were acquired. The patients were also asked to complete the revised TCI (TCI-R) and Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and -Depression (HADS-D) questionnaires.

Data collection

We collected sociodemographic data of the patients with MS (sex, age, years of schooling, educational level, employment status, disability pension, current place of residence, partnership, number of children and current smoking status) using patient records, clinical examinations and structured interviews. In addition, we collected medication data, including polypharmacy status, the total number of medications taken, long-term and *pro re nata* (PRN) medications, prescription (Rx) and over-the-counter (OTC) medications, current and previous DMD use as well as symptomatic and comorbid medications of each patient. Furthermore, we gathered clinical data, that is, disease duration, MS course,[6] comorbidities, degree of disability according to Kurtzke's Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Severity Score (MSSS). The EDSS is the standard instrument for assessing the impairment caused by MS through neurological examination.[48] The MSSS is an algorithm that relates the EDSS score to the distribution of disability in patients with comparable disease duration.[49] Polypharmacy was defined as the concurrent consumption of five or more medications, including OTC substances.[19] Comorbidity was defined as any additional disease that developed before or during the course of MS and which is not an obvious complication of MS.[50]

To stratify nicotine consumption among patients with MS who smoke cigarettes, we used the Fagerström Test for nicotine dependence.[51,52]

This questionnaire comprises six questions on smoking habits. The maximum score is 10. Scores of 5 or above indicate a severe dependency, scores of 3 or 4 a moderate dependency and scores below 3 a mild dependency.[53] Based on this, we categorized the patients into four groups: non-smokers and smokers with mild, moderate or severe smoking dependence.

The German version of the validated NEO-FFI questionnaire was used to assess five main personality dimensions (neuroticism, extraversion, openness to experience, agreeableness and conscientiousness) in patients with MS with and without polypharmacy and different smoking status. The NEO-FFI measures these dimensions by a total of 60 items (12 items for each dimension) on a five-point Likert scale, which ranges from 0 (strong agreement) to 4 (strong disagreement).[54] A cumulative score (ranging from 0 to 48) was calculated for each dimension.[55]

We used the German version of the TCI-R.[56] The patients were asked to complete the questionnaire with 240 items. The questions relate to likes and dislikes, emotional reactions, interests, attitudes, goals and values, which the person answers with yes or no.[57,58] Studies from different countries have shown that the TCI-R is a valid instrument for assessing temperament and character features with adequate internal consistency and test–test reliabilities.

The HADS comprises two distinct subscales, which are scored separately, one that assesses anxiety (with seven items) and one that evaluates depression (also with seven items).[59] The patients were asked to provide a rating on a four-point scale (0–3) for each item, thus enabling each subscale to have a possible score range of 0–21. It has been reported that this screening tool is valid and possesses suitable psychometric properties for the diagnosis of anxiety and depressive symptoms in patients with MS.[60] This is due to the exclusion of somatic symptoms, such as dizziness, headache and sleeping disorders as disease indicators.[61] A classification of the anxiety/depression severity was carried out[62]: we distinguished normal scores ranging from 0 to 7 points, borderline scores ranging from 8 to 10 points and abnormal scores exceeding 10 points.[63,64]

Data analysis

The data from this exploratory study were prepared with IBM SPSS Statistics version 29.0.1.1, and further data analyses were performed in the statistical software environment R version 4.1.2. Numerical data were summarized by means and standard deviations or medians and ranges, depending on whether the data were normally distributed or not. Ordinal and nominal data are reported by numbers and percentages per category. A correlation analysis was performed with 42 variables, of which 17 were categorical and 25 were numerical. For the MS course types, we utilized dummy variables. The Pearson correlation coefficients were computed using pairwise complete data in the case of variables with missing values. As a cut-off for visualizing the more relevant variables, we used $|r| > 0.35$. The score in the personality dimensions were considered individually as an independent variable, while the degree of smoking dependence and the polypharmacy status were regarded as dependent variables. To test for significant differences in NEO-FFI or TCI-R scores between patient groups, we compared the mean values of each group using *F*-tests for linear models. The significance level was set at $\alpha = 0.05$.

Results

Patient cohort

A total of 375 patients were included in this study (Table 1). The proportion of women was 67.5% ($n = 253$). The age of the patients ranged from 19 to 80 years (mean ± standard deviation: 48.1 ± 12.9). On average, the patients attended school for 10.5 ± 1.3 years. About half of them were employed ($n = 179$, 47.7%) and 35.7% ($n = 134$) of the patients received disability pension. The patient cohort was composed of cases with CIS/RRMS ($n = 260$), SPMS ($n = 87$) and PPMS ($n = 28$). The median EDSS score of the patients was 3.0 (range: 0–8.5) at a median disease duration of 10 years (range: 0–52). The patients global MSSS had a median of 4.4 (range: 0.1–9.7). Half of the patients (50.4%) suffered from two or more comorbidities. Within the cohort, 185 patients were under multidrug treatment (49.3%). The average number of drugs taken per patient was 4.9 ± 2.9 (range: 0–16).

Table 1. Overview of the total patient cohort.

Characteristic	*n*	Statistics
Sociodemographic data		
Sex, *n* (%)	375	
Female		253 (67.5)
Male		122 (32.5)
Age (years), mean (±SD; range)	375	48.1 (±12.9; 19-80)
School years, mean (±SD; range)	375	10.5 (±1.3; 8–18)
Educational level, *n* (%)	375	
No training		11 (2.9)
Skilled worker		230 (61.3)
Technical college		67 (17.9)
University		67 (17.9)
Employed, *n* (%)	375	
Yes		179 (47.7)
No		196 (52.3)
Disability retired, *n* (%)	375	
Yes		134 (35.7)
No		241 (64.3)
Place of current residence, *n* (%)	375	
Rural area		147 (39.2)
Small town		57 (15.2)
Middle-size town		70 (18.7)
City		101 (26.9)
Partnership, *n* (%)	375	
Yes		281 (74.9)
No		94 (25.1)
Number of children, *n* (%)	375	
0		104 (27.7)
1		103 (27.5)
2		142 (37.9)
⩾3		26 (6.9)
Smoking, *n* (%)	371	
Yes		110 (29.6)
No		261 (70.4)
Smoking dependence, *n* (%)	102	
Low		41 (40.2)
Moderate		27 (26.5)
Severe		34 (33.3)
Clinical data		
EDSS score, median (range)	375	3.0 (0.0–8.5)
Global MSSS, median (range)	375	4.4 (0.1–9.7)
Disease duration (years), median (range)	375	10 (0–52)
MS course type, *n* (%)	375	
CIS/RRMS		260 (69.3)
SPMS		87 (23.2)
PPMS		28 (7.5)
Number of comorbidities, *n* (%)	375	
0		95 (25.3)
1		91 (24.3)
⩾2		189 (50.4)
Medication data		
Polypharmacy, *n* (%)	375	
Yes		185 (49.3)
No		190 (50.7)
All drugs, mean (±SD; range)	375	4.9 (±2.9; 0–16)
Long-term drugs, mean (±SD; range)	375	4.4 (±2.8; 0–16)
PRN drugs, mean (±SD; range)	375	0.5 (±0.9; 0–6)
Rx drugs, mean (±SD; range)	375	3.9 (±2.7; 0–16)

Table 1. (Continued)

Characteristic	*n*	Statistics
OTC, mean (± SD; range)	375	1.1 (±1.2; 0–6)
DMD, mean (±SD; range)	375	0.8 (±0.4; 0–1)
DMD switches, *n* (%)	375	
0		127 (33.9)
1		115 (30.7)
⩾2		133 (35.5)
Symptomatic drugs, mean (±SD; range)	375	1.9 (±1.9; 0–9)
Comorbidity drugs, mean (±SD; range)	375	2.2 (±2.1; 0–12)
Psychological testing		
NEO-FFI, mean (±SD; range)	375	
Neuroticism		22.3 (±7.2; 0–46)
Extraversion		25.1 (±5.3; 5–46)
Openness		26.6 (±5.1; 10–46)
Agreeableness		28.2 (±6.0; 12–43)
Conscientiousness		31.7 (±5.7; 13–47)
TCI-R, mean (± SD; range)		
Novelty seeking	316	15.1 (±4.7; 0–28)
Harm avoidance	314	18.3 (±6.6; 4–33)
Reward dependence	317	18.3 (±5.2; 4–29)
Persistence	317	19.3 (±5.8; 0–31)
Self-directedness	317	29.6 (±6.6; 8–40)
Cooperativeness	317	27.1 (±4.3; 12–36)
Self-transcendence	317	7.1 (±4.0; 1–20)
HADS-anxiety, *n* (%)	371	
Normal		205 (55.3)
Borderline		103 (27.8)
Abnormal		63 (17.0)
HADS-depression, *n* (%)	370	
Normal		263 (71.1)
Borderline		69 (18.6)
Abnormal		38 (10.3)

CIS, clinically isolated syndrome; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; HADS, Hospital Anxiety and Depression Scale; MSSS, Multiple Sclerosis Severity Score; *n*, number of cases; NEO-FFI, NEO Five-Factor Inventory; OTC, over-the-counter; PPMS, primary progressive multiple sclerosis; PRN, *pro re nata*; RRMS, relapsing-remitting multiple sclerosis; Rx, prescription; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; TCI-R, Temperament and Character Inventory-Revised version.

The majority of the patients ($n=292$, 77.9%) currently received a DMD, and 248 patients (66.1%) had previously discontinued a DMD therapy. Approximately one-third of the cohort were current smokers ($n=110$, 29.6%), of which 102 completed the Fagerström test, which allowed to categorize them into patients with low ($n=41$, 40.2%), moderate ($n=27$, 26.5%) and severe ($n=34$, 33.3%) smoking dependence.

When analysing the NEO-FFI dimensions for the entire cohort ($n=375$), the lowest mean value was found for neuroticism (22.3 ± 7.2), and the highest mean value was found for conscientiousness (31.7 ± 5.7). Regarding the TCI-R, some patients did not complete the test ($n=58$–61). With regard to HADS-A scores, around one in five patients with MS showed an abnormal score ($n=63$, 17.0%), whereas more than half of the patients achieved a normal score ($n=205$, 55.3%). The majority of the patients also had a normal HADS-D score ($n=263$, 71.1%; Table 1).

Relationships between the investigated variables

In the evaluation of the NEO-FFI dimensions, the correlation analysis revealed significant relationships between neuroticism and smoking addiction ($r=0.22$, $p=0.028$) as well as between

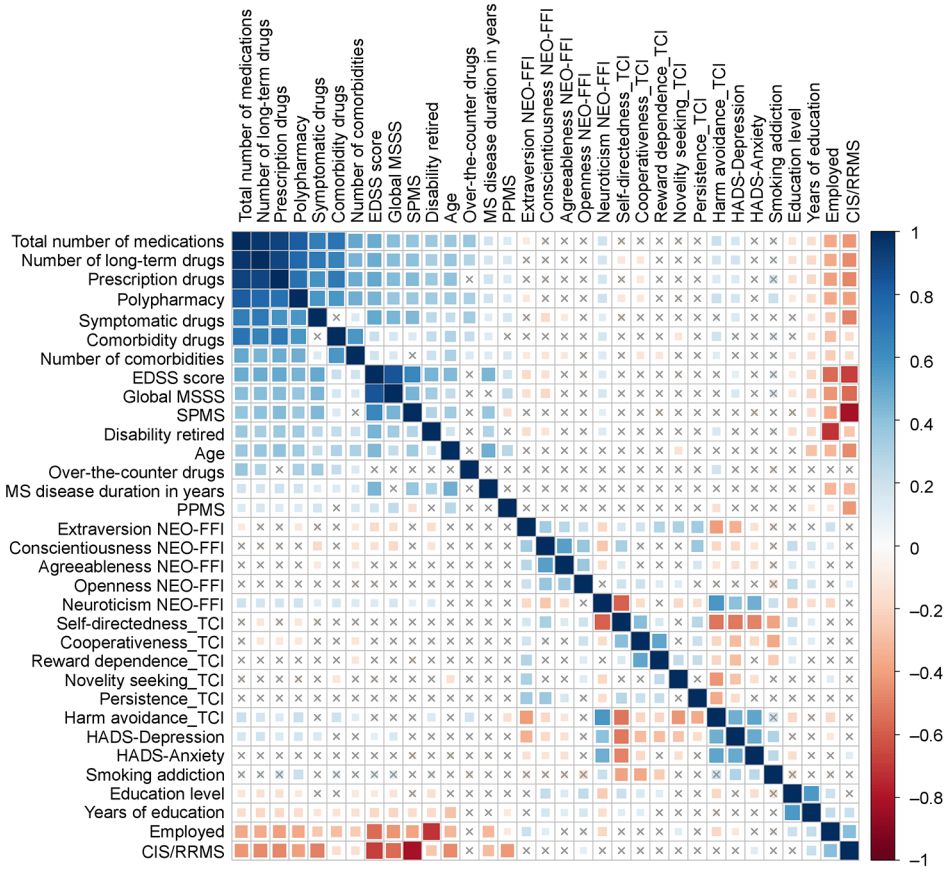

Figure 1. Correlation between sociodemographic, clinical, medication and psychological testing data in patients with multiple sclerosis ($n = 375$). The correlation diagram shows the pairwise association of 33 variables for which there was at least a correlation coefficient of $|r| > 0.35$. The strength and direction of the Pearson correlation coefficient r are indicated by colour: Blue marks a positive correlation and red is a negative one. X indicates p-values $\geqslant 0.05$. The full correlation matrix is provided in Supplemental Table S1.
CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; HADS, Hospital Anxiety and Depression Scale; MSSS, Multiple Sclerosis Severity Score; *n*, number of cases; NEO-FFI, NEO Five-Factor Inventory; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TCI, Temperament and Character Inventory-Revised version.

neuroticism and polypharmacy ($r = 0.19$, $p < 0.001$). Extraversion, on the other hand, was negatively associated with polypharmacy ($r = -0.11$, $p = 0.031$; Figure 1 and Supplemental Table S1).

In the dimensions of the TCI-R, nicotine dependence correlated significantly negatively with RD ($r = -0.25$, $p = 0.019$), S-D ($r = -0.39$, $p < 0.001$) and CO ($r = -0.38$, $p < 0.001$). Polypharmacy was also significantly negatively associated with S-D ($r = -0.12$, $p = 0.031$) and CO ($r = -0.11$, $p = 0.041$) but positively associated with HA ($r = 0.22$, $p < 0.001$).

Further significant correlations indicated that the ratings in the HADS-A and HADS-D scales and the degree of disability EDSS were negatively associated with extraversion and conscientiousness and positively associated with neuroticism. The TCI-R dimensions of HA and CO showed significant associations with HADS-A and HADS-D grades as well as the number of comorbidities (Figure 1 and Supplemental Table S1). The degree of nicotine dependence correlated significantly positively with both HADS-A and HADS-D grades. Patients with polypharmacy more frequently had an abnormal HADS-D score

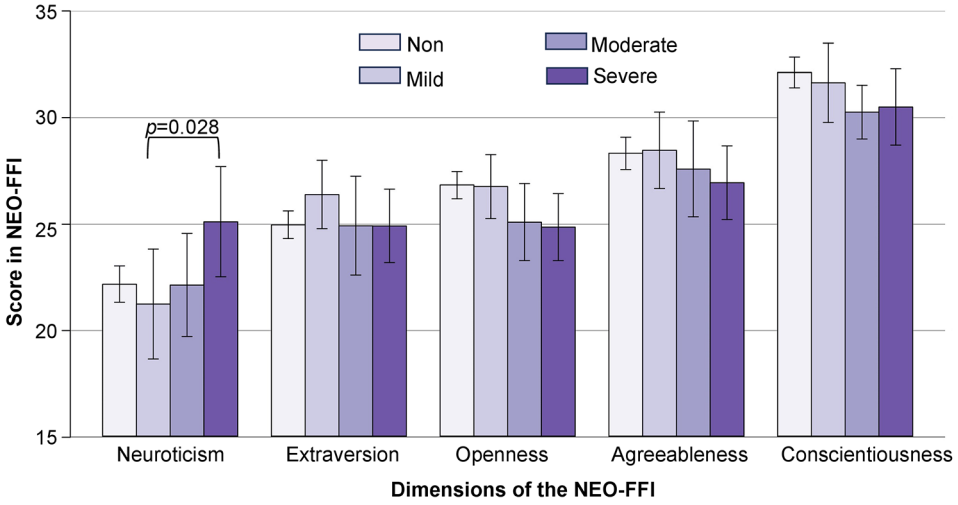

Figure 2. Differences in personality dimensions in the NEO-FFI among patients with multiple sclerosis who were non-smokers and patients with mild, moderate or severe smoking addiction. Shown are the five dimensions of the NEO-FFI and their mean values per group in bars with the corresponding 95% confidence intervals in error bars. We distinguished between non-smoking patients with MS ($n = 261$) and smoking addicts (mild $n = 41$, moderate $n = 27$, severe $n = 34$). We found a significant association between more severe smoking addiction and higher neuroticism scores ($p < 0.028$).
NEO-FFI, NEO Five-Factor Inventory.

compared to patients without polypharmacy (13.7% vs 7.0%).

NEO-FFI personality dimensions in relation to nicotine dependence and polypharmacy in patients with MS

For the 375 patients with MS analysed, we detected a significant difference in the NEO-FFI neuroticism dimension between patients with mild ($n = 41$, mean ± SD: 21.2 ± 8.2), moderate ($n = 27$, mean ± SD: 22.1 ± 6.1) and severe smoking addiction ($n = 34$, mean ± SD: 25.1 ± 7.4; $p = 0.028$; Figure 2). No significant difference was found in the other four dimensions. However, we found nominally higher values on average for non-smokers ($n = 261$) and smokers with mild smoking dependence in the dimensions of openness, agreeableness and conscientiousness compared to smokers with moderate or severe smoking dependence.

When comparing the mean values in the NEO-FFI dimensions between patients with MS with ($n = 185$) and without ($n = 190$) polypharmacy (Figure 3), significant differences were found in the areas of neuroticism (mean ± SD: 23.7 ± 6.9 vs 21.0 ± 7.2, $p < 0.001$) and extraversion (mean ± SD: 24.6 ± 4.8 vs 25.7 ± 5.6, $p = 0.031$). In the dimensions of openness, agreeableness and conscientiousness, slightly higher mean values were found for patients without polypharmacy, but these differences did not reach the significance level.

TCI-R scores in relation to the degree of nicotine dependence and polypharmacy status

In the dimension of HA, significant differences were observed between smokers with moderate/severe versus mild smoking dependence with regard to anticipatory worry ($p < 0.05$) and shyness ($p < 0.05$; Figure 4). Patients with MS with mild nicotine dependence showed lower mean scores in these two subscales than those with moderate or severe dependence. Significant differences between patients with different degrees of nicotine dependence were also evident for RD in the openness to warm communication ($p < 0.05$) and attachment ($p < 0.05$) subscales. Likewise, significant differences regarding helpfulness ($p < 0.05$) and compassion ($p < 0.001$) were found in the CO dimension. Furthermore, smokers with mild, moderate and severe smoking dependence differed significantly in all subscales of the S-D dimension, with patients with MS with

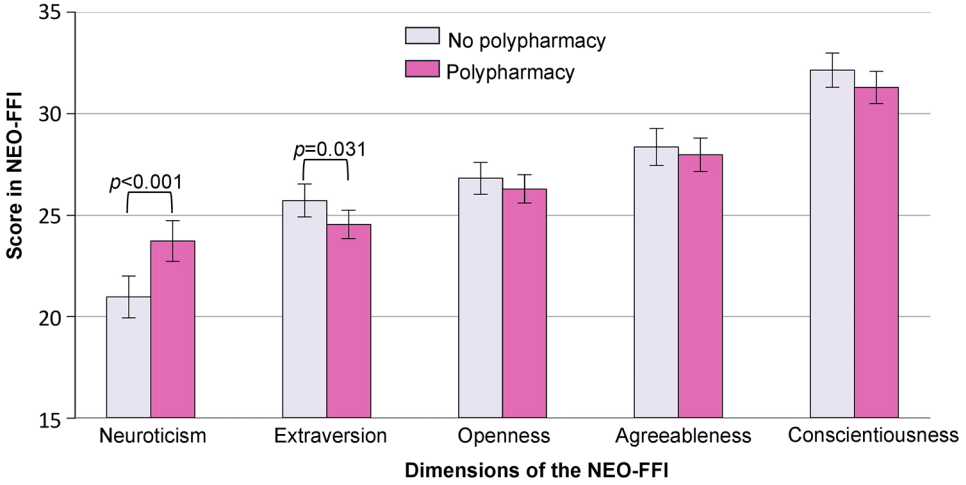

Figure 3. Differences in the NEO-FFI personality dimensions between multiple sclerosis patients with and without polypharmacy. Shown are the five dimensions of the NEO-FFI and the mean values in bars with the corresponding 95% confidence intervals in error bars for patients with MS with ($n = 185$) and without ($n = 190$) polypharmacy. Significant differences were found in the neuroticism ($p < 0.001$) and extraversion ($p = 0.031$) scales.
MS, multiple sclerosis; NEO-FFI, NEO Five-Factor Inventory.

mild smoking dependence having higher mean scores. No statistically significant differences were found in the dimensions of NS, PS and ST.

Regarding the polypharmacy status of patients with MS, no significant differences were found in the dimensions of NS and RD (Figure 5). However, statistically significant differences were evident in the HA dimension for anticipatory worry ($p < 0.01$), fear of uncertainty ($p < 0.05$) and fatigability + asthenia ($p < 0.001$), with higher values observed on average for polypharmaceutically treated patients. There were also higher mean values for patients with MS with polypharmacy in the ST dimension, with statistical significance in the spiritual acceptance subscale ($p < 0.05$). In the scales of the dimensions of PS, S-D and CO, we found differences in the eagerness of effort ($p < 0.05$), resourcefulness ($p < 0.01$), enlightened second nature ($p < 0.05$) and helpfulness ($p < 0.05$), with significantly higher mean values for patients with MS without polypharmacy.

Discussion

Smoking is one of the biggest risk factors for the development of MS[30] and is also associated with increased disease severity.[27] Polypharmaceutical treatment is more often necessary in patients with MS who smoke due to the higher rate of comorbidities in these patients.[30] We aimed to use the NEO-FFI and the TCI-R to identify personality traits that are positively or negatively associated with nicotine dependence and polypharmacy in patients with MS.

We found that NEO-FFI neuroticism scores were on average significantly higher in patients with MS and severe smoking dependence and in patients with MS and polypharmacy. Our data therefore suggest that the results of previous studies on smoking and personality traits in the general population also apply to the group of patients with MS.[65,66] The neuroticism dimension describes how a person deals with negative emotions. People with higher neuroticism scores are more likely to lose their mental balance due to stress and quickly feel overwhelmed. They are also more likely to have unrealistic expectations and poor control over their needs.[67] In addition, we found a significantly lower mean score for extraversion in patients with polypharmacy. Extraversion refers to the extent to which a person seeks stimulation/excitement and can be described as optimistic, cheerful, sociable and self-confident.[67] Lower levels of extraversion and higher levels of neuroticism have a negative influence on cognitive domains, mood and psychological well-being[36] and were described as characterizing individuals with

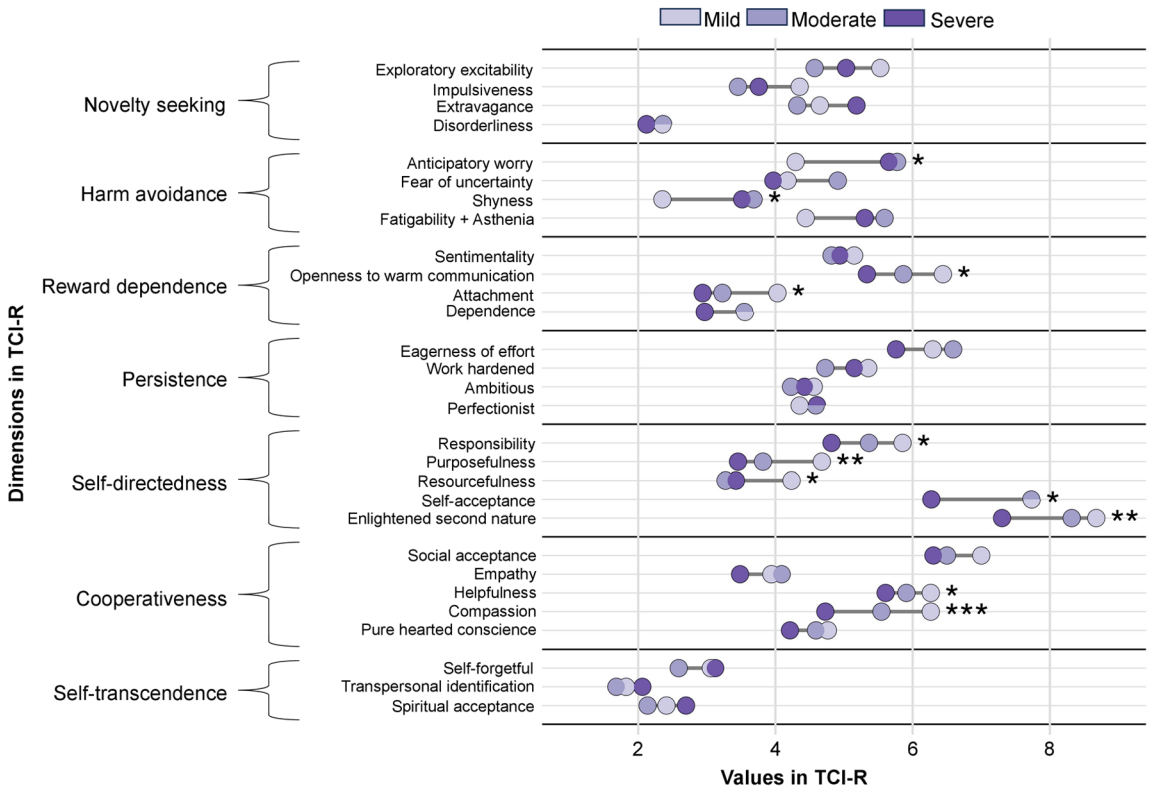

Figure 4. Differences in TCI-R personality dimensions among patients with multiple sclerosis who had a mild, moderate or severe smoking addiction. The average scores in the TCI-R subdimensions are shown for the different patient groups in this dumbbell plot. The coloured dots mark the mean values per group. Significant differences could be found in four of the seven dimensions (harm avoidance, reward dependence, self-directedness and cooperativeness). ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
TCI-R, Temperament and Character Inventory-Revised version.

so-called Type D Personality by Strober.[68] The latter study showed that Type D Personality is also a significant factor for negative outcomes of patients with MS.[68] High levels of neuroticism in MS can be understood as emotional instability[69] and are associated with cognitive deficits, particularly executive function, and cortical atrophy.[70] Both MS as an unpredictable, changing stressor and emotional instability as a personal vulnerability can lead to increased helplessness. In terms of poor self-management, this can lead to poor disease coping and compliance[37,71,72] with the development of depression.[73] We identified positive personality characteristics for non-smokers and patients without polypharmacy, as reflected in relatively high values in the dimensions of openness and conscientiousness. Both characteristics have been associated with a roughly 30% lower risk of an MS diagnosis within 7 years.[74] Overall, the tendency to want to build interpersonal relationships (extraversion), to use an active imagination (openness), to inspire trust in others (agreeableness) and to take responsibility (conscientiousness) seems to improve one's self-esteem and the environment, and thus to strive for meaning in life.[75] In the treatment of chronically ill patients with MS, these characteristics also support adaptive functions.[75,76] Schwartz et al. therefore considered the NEO-FFI as a valid and reliable supportive item for clinicians to assess personality changes, personality functioning and dispositional risks for poor prognosis in MS.[77] With our data, we were able to complement the current body of research that considers neuroticism as a detrimental and extraversion as a protective factor for health.[36–38,78,79] The NEO-FFI is available to clinicians as a valid test instrument.

We applied the TCI-R questionnaire to explore the relationships of personality traits to nicotine dependence and polypharmacy in patients with MS. The psychobiological model of the TCI

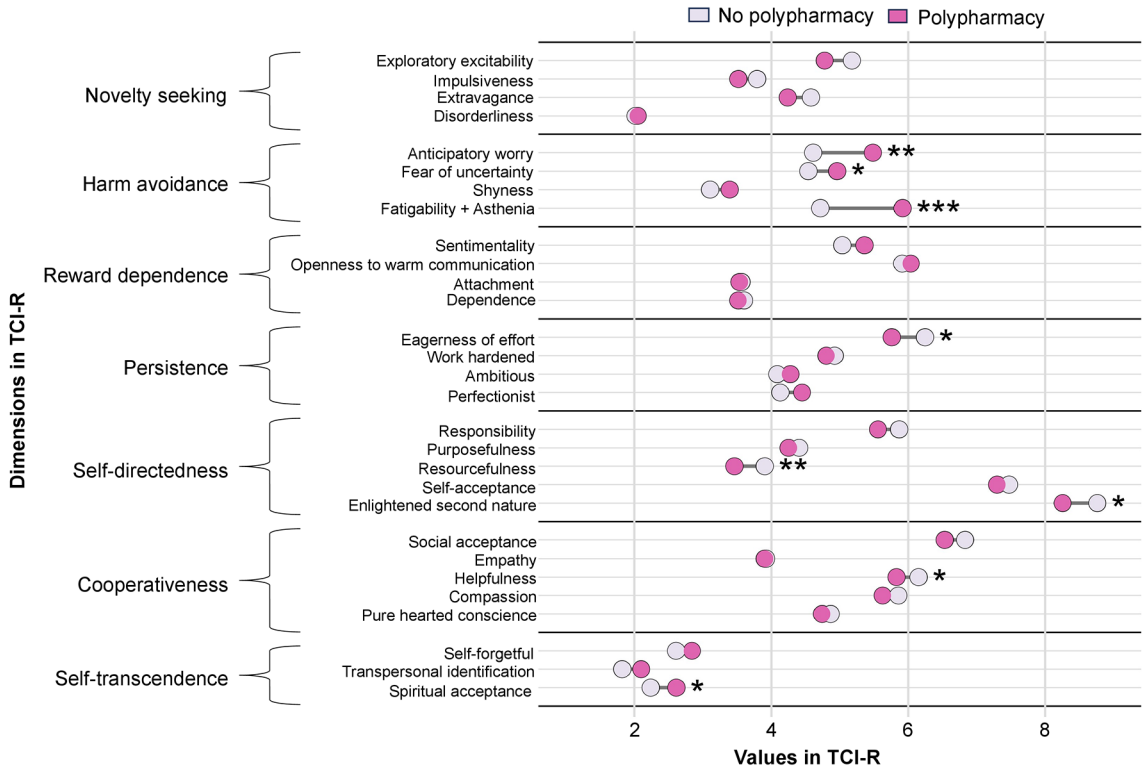

Figure 5. Differences in the TCI-R personality dimensions between multiple sclerosis patients with and without polypharmacy. The average scores in the TCI-R subdimensions are shown for the different patient groups in this dumbbell plot. The coloured dots depict the mean values per group. Significant differences could be found in five of the seven dimensions (harm avoidance, reward dependence, self-directedness, cooperativeness and self-transcendence). ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
TCI-R, Temperament and Character Inventory-Revised version.

considers individual differences in behaviour. Temperament and character are in constant bidirectional interaction to maximize adaptation to the changing environment.[80] Our analysis of the TCI-R data revealed that patients with MS who are more dependent on smoking tend to exhibit behavioural inhibition (high HA) with simultaneous behavioural rigidity (low RD). They were also found to be less able to adjust their goals (low S-D) and to be less socially tolerant (low CO). Gazioglu et al. showed that patients with MS have higher levels of HA and lower levels of S-D than matched healthy controls.[81] High HA scores and low S-D scores may predict MS-related fatigue.[46] Etter et al. reported in agreement with our data that there is a link between smoking and high HA and low S-D scores in the general population.[42] A study conducted among alcohol, cannabis, cocaine, benzodiazepine and hallucinogen users showed the same result when analysing TCI dimensions in addicts.[82] In another study of German smokers, a significant association was found between smoking status and NS in the TCI.[83] Gurpegui et al. demonstrated an association between NS, which is thought to be associated with low basal dopaminergic activity, and nicotine use, which enhances dopaminergic neurotransmission.[84] Reduced dopamine levels are known to occur in patients with MS.[85] A study on associations between TCI and acute tobacco withdrawal showed that people with high HA and NS levels develop stronger withdrawal effects, which may be explained, among other things, by the fact that smokers can react to certain stressful situations only with limited reward during abstinence and thus experience greater stress and frustration.[86] Smoking, in turn, is associated with stress relief.[86] In addition, HA subscales are positively associated with the availability of nicotinic acetylcholine receptors across different brain regions, meaning that a biological determinant of personality has been demonstrated.[87] A

meta-analysis of associations between TCI and psychobiological theories showed a link between low S-D and high NS scores in relation to substance use disorder.[88] The data from Bishry et al. further showed that there is a positive correlation between NS, PS, CO and the motivation to quit smoking.[89] Because of this, one should consider the personality profile of the smoker when developing intervention strategies for smoking cessation. Neuropsychological functions must also be considered.[43]

To our knowledge, there is no previous study in which the TCI dimensions have been compared between patients with and without polypharmacy. Our data showed that polypharmaceutically treated patients with MS are typically inhibited in their behaviour (high HA) and are less eager in making an effort (low PS). They are also more likely to have difficulties in adjusting their goals (low S-D). Our data thus indicated that both smoking-dependent and polypharmaceutically treated patients with MS tend to have high HA and low S-D levels. Our data thus suggest that both smoking-dependent and polypharmacologically treated MS patients tend to have high HA and low S-D values. Correlations between the Five-Factor model and temperament have already been investigated, with HA values found to correlate negatively with extraversion.[90] The patients had also higher HADS-A and HADS-D scores than the respective comparison group. Our correlation analysis further demonstrated a positive association between high HA scores and abnormal HADS-A as well as HADS-D scores, while S-D scores showed a negative association with both HADS scores. These findings are important as depressive symptoms can have significant consequences for individuals with MS, including a worsening of their condition, a reduction in their health-related quality of life, and an increased risk of suicide. It is therefore crucial to recognize the presence of a depressive disorder in MS and to understand the factors that can influence depression.[45,91–93]

A limitation of this work is that we were only able to analyse differences and associations within a non-representational sample of the MS cohort as we did not include a control group. In addition, we used self-report instruments, which we limited to two theories of personality measurement. Our study design was cross-sectional. A longitudinal analysis to make comparisons over time would be useful, as would be the investigation of a larger number of cases. Particularly in view of the fact that MS is a disease that extends over several decades, the extent to which targeted smoking cessation interventions are effective in patients with MS with different personality characteristics could be an objective. It remains to be discussed to what extent a high neuroticism score can be seen as an indicator of individual stress and resulting secondary illnesses such as depression, which may make polypharmacy necessary. The same applies to the association between polypharmacy and HA. Investigating the underlying causal relationships could be part of a further analysis. In addition, the extent to which smoking as a substance dependence affects the prescription of medications for MS treatment that have a dependency potential, for example, benzodiazepines or cannabis, could be a focus of investigation.

Conclusion

To conclude, in our investigation of NEO-FFI personality traits in patients with MS, we were able to show that higher neuroticism and lower extraversion scores were associated with polypharmacy and that neuroticism was also related to smoking addiction. In addition, by analysing the TCI-R, we were able to show that patients with MS with severe smoking dependence and polypharmacy were characterized by high levels of HA and low levels of S-D and CO. The data indicate that there are patients who, due to their personality structure, tend to smoke and are treated polypharmaceutically, which may have implications for clinical practice. With this in mind, patients should not only be informed about the already known harmful effects of smoking on the course of the disease but individual stress factors and supportive behaviours should also be explored and included in the treatment concept.

Declarations

Ethics approval and consent to participate

The study was conducted with approval from the ethics committees of the University of Rostock and of the Physicians' Chamber of Thuringia (permit number A 2019-0048) and in compliance

with the principles of the Declaration of Helsinki, the Good Clinical Practice Guidelines and the European General Data Protection Regulation. All participants provided a written informed consent for study participation.

Consent for publication
Not applicable.

Author contributions
Janina Meißner: Conceptualization; Formal analysis; Investigation; Project administration; Writing – original draft.

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Silvan Elias Langhorst: Writing – review & editing.

Pegah Mashhadiakbar: Writing – review & editing.

Barbara Streckenbach: Writing – review & editing.

Katja Burian: Writing – review & editing.

Julia Baldt: Writing – review & editing.

Felicita Heidler: Writing – review & editing.

Jörg Richter: Writing – review & editing.

Uwe Klaus Zettl: Conceptualization; Project administration; Validation; Writing – review & editing.

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Availability of data and materials
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