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Multiple sclerosis twin study reveals distinct genetic, disease-specific, and psychometric impact on coping with critical life events

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ABSTRACT

Background: Critical life events challenge our competence to develop coping strategies. In people with multiple sclerosis (MS), the impact of genetics, disease-specific, and psychometric factors on coping strategies have not been explored to date.

Methods: In a unique cohort of 56 monozygotic twins discordant for MS, we applied comprehensive psychometric and clinical testing to measure factors influencing the psychosocial impact (including stressors and coping strategies) of a critical life event, exemplified by the COVID-19 pandemic (measured by the COVID-19 Pandemic Mental Health Questionnaire, CoPaQ). CoPaQ results were compared to an independent age- and sex-matched control cohort. We applied factor analysis, structural equation modeling, hypothesis testing, and regression models.

Results: We detected no differences in the perception of 14 CoPaQ subscales between MS and non-MS co-twins. However, compared to the independent control group, MS co-twins valued 5/14 CoPaQ subscales differently. Strong perception of pandemic-related stressors in MS co-twins was accompanied by higher HADS-Anxiety (ρ = 0.69, Hospital Anxiety and Depression Scale), HADS-Depression (ρ = 0.57), BDI-II (ρ = 0.74, Beck Depression Inventory), and MSIS-29-psychological scores (ρ = 0.58, Multiple Sclerosis Impact Scale 29). In a generalized linear mixed model, individuals who perceived pandemic-related stressors as more burdensome relied on inner resources, with a notable dependency on twinship.

Discussion: Using a unique twin approach, our study suggests that coping with critical life events is mainly driven by the genetic background. However, in people with MS, coping and the perception of stressors is further confounded by psychometric and disease-related factors.

1. Introduction

Multiple sclerosis (MS) is the most common autoimmune inflammatory disease of the central nervous system. It predominantly affects younger individuals, with a clinical course that remains largely unpredictable, often resulting in significant impairment of daily living. This encompasses not only physical dysfunctions but has also a significant impact on psychological and social integrity, emotional balance, self-satisfaction, sense of competency, self-efficacy, and social interactions [1]. Therefore, the ability to cope with health-related stressors emerges as a crucial psychological skill to either mitigate the exacerbation or prevent a secondary reinforcement of both physical and mental dysfunctions.

Coping is a strategy to react to critical life events, existential crises or health threats and involves behavioral and cognitive strategies to maintain physical and mental integrity [1]. It was originally conceptualized by Lazarus in 1966 and defined by Lazarus and Folkman as "constantly changing cognitive and behavioral efforts to manage external and/or internal demands that are appraised as taxing or exceeding the resources of a person" [2]. Coping is process-oriented rather than trait-based with the goal to overcome stressors directly (*problem-focused coping*, PFC) or to regulate emotions that result from the individual's exposure towards stressors (*emotion-focused coping*, EFC) (Biggs et al., 2017; Lazarus & Folkman, 1984). Emotion-focused coping

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utilizes blaming others, self-blame, emotion containment or passive resignation [4]. It is controversially discussed if EFC enhances anxiety and depression [5,6] or fosters psychological well-being [7].

Only little is known how people with MS (pwMS) cope with critical life events. Recent studies reported that acceptance, active coping, planning, and positive reinterpretation were the coping strategies used most [8]. However, coping strategies were shown to be associated with clinical and demographic characteristics. Seeking of emotional social support and focus on and venting of emotions were strategies more often applied by women. Individuals with a higher degree of disability who were unemployed used behavioral and mental disengagement more frequently.

The COVID-19 pandemic can be considered as a critical life event for many individuals, imposing significant burden on personal health, social connections, and economic stability. Because of individual preexisting health conditions, the perception of the COIVD-19 pandemic as a critical life event may differ significantly across individuals. Likewise, individuals may adapt differently to these critical life events. Thus, the COVID-19 pandemic can be seen as a standardized stressor which at the same time similarly challenged coping strategies of people. Little is known how people with preexisting medical conditions, such as MS, perceive and cope with additional critical life events. Likewise, the impact of genetic background and disease-specific characteristics on how individuals cope with critical life events remains enigmatic.

In this study, we aimed to evaluate how pwMS perceive and cope with additional health threats (i.e. the COVID-19 pandemic). For that purpose, we made use of the MS TWIN STUDY, a unique cohort of monozygotic twins discordant for MS, to achieve an ideally matched case-control study that, most importantly, controls for genetic variation between two samples. Moreover, since most twins were raised within the same environment, it controls for external confounders which might have influenced coping strategies during adolescence. Within this setup, we measured the perception of COVID-19-related stressors and coping strategies and dissected the role of genetics, disease-specific as well as psychometric and demographic characteristics.

2. Methods

2.1. Study population and clinical and demographic data

The MS TWIN STUDY is comprised of monozygotic twin pairs discordant for MS (MS twin cohort). All twin pairs (MS co-twin and non-MS co-twin) were recruited and followed up by the outpatient clinic at the Institute of Clinical Neuroimmunology at LMU University Hospital in Munich. Diagnosis was based on the revised McDonald criteria (2017) and verified by reviewing medical documentation. After recruitment, both twins were longitudinally followed up. All study participants gave their informed consent for study participation, the study was approved by the local ethics committee. Demographic and clinical routine data was recorded through regular study visits. For this study, diagnosis, disease duration (time interval in years from year of diagnosis to 2020), sex and age were extracted from medical and study records. The EDSS value closest to the time of sending the questionnaire was extracted for analysis. The progression index (PI) was calculated as the quotient of the EDSS divided by the time difference between the time of diagnosis and the date when the EDSS was documented. Only EDSS scores which were obtained within a time frame of two years around the time of sending the questionnaire were included in this analysis. We compared our MS twin cohort to an independent control cohort comprised of age- and sex-matched cases [9].

2.2. Instrument modification and application

We applied a modified version of the self-report COVID-19 Pandemic Mental Health Questionnaire (CoPaQ), originally developed by Rek et al. (Supplement Table 1) [9]. In addition to the CoPaQ, we used the Hospital Anxiety and Depression Scale (HADS-Anxiety, HADS-Depression), Beck Depression Inventory (BDI-II), and Multiple Sclerosis Impact Scale 29 (MSIS-29) to psychometrically assess the study participants. The survey was paper-based, and participants received questionnaires by mail during the COVID-19 pandemic from 07/2020 on. The last questionnaire was returned in 08/2021. Overall, 166 questionnaires were sent out to 83 twin pairs.

2.3. Data analysis

Raw data was screened for missing data. Items with more than 10 % missing values or participants who answered less than 90 % of the items were excluded from further analyses. Furthermore, an exclusion criterion for this study was an incomplete CoPaQ by either twin. To identify relevant latent factors and reconstruct the original factor structure of the instrument, we conducted an exploratory factor analysis with varimax rotation. Items with factor loadings <0.5, those that loaded as the only item on a factor or did not fit plausibly within the context of other items loading on the same factor were excluded from the model. Subsequently, min-max scaled sum values for each subscale were calculated from raw Likert scale values. Internal (subscale) consistency was estimated by *Cronbach's* α. Structural equation modeling (SEM) was conducted with semopy using default parameters [11]. Wishart loglikelihood was used to assess the fit of the covariance structure of the model. Raw questionnaire data as well as clinical and demographic data was considered as (non-parametric) ordinal data. To estimate central tendencies and statistical dispersion, median values (Md) and interquartile ranges (IQR, 25th to 75th percentile) were calculated. To assess differences between subcohorts, we calculated *Cliff's* Δ to estimate the effect size. Rank-based statistical testing was applied to test the null hypothesis whether values from individuals from two subgroups were similar (MS twin subgroup versus non-MS twin subgroup, Mann–Whitney U test, MWU) or to test for consistent intra-twin pair differences and differences between MS co-twins and their age- and sex-matched control subject (paired analysis, Wilcoxon signed-rank test). To test the relationship between two variables, Spearman's correlation coefficient was calculated. The relationship between subscales was assessed by generalized linear mixed models based on a Poisson distribution. Twinship and gender were set as random effects to control for twin- and gender-specific variation.

3. Results

3.1. Demographic features of the MS twin cohort

122 CoPaQs were returned in total (response rate: 0.73). 56 twin pairs (112 individuals) met the inclusion criterion of complete CoPaQ data for MS and non-MS co-twin and were subjected to further analyses (MS twin cohort). The median age was 44 years (IQR = 35–53 years, min-max = 25–74 years) as of 2020. Most individuals were female (n = 84, 75 %). The most frequent diagnosis was relapsing-remitting multiple sclerosis (RRMS, n = 44), 10 individuals were affected with secondary-progressive multiple sclerosis (SPMS), one patient each was diagnosed with clinically isolated syndrome (CIS) or primary-progressive multiple sclerosis (PPMS). The median disease duration as of 2020 was 12 years (IQR = 7.5–19.3 years, min-max = 1–44 years, n = 56), the median EDSS value was 2.0 (IQR = 1.5–2.5, min-max = 0–4.5, n = 25). The median progression index (PI) was 0.18 (IQR = 0.12–0.29, min-max = 0–2.14, n = 25).

3.2. Perception of the psychosocial impact of the COVID-19 pandemic

We measured the perception of the COVID-19 pandemic as a critical life event in MS and non-MS co-twins with an adapted version of the self-report COVID-19 Pandemic Mental Health Questionnaire (CoPaQ) developed by Rek et al. [9]. The original factor structure (according to Rek et al., 2021) was partially reproduced through exploratory factor

Table 1
CoPaQ items.

Latent factor	Stem	Cronbach's α	Item	Factor loading
Political restrictions	How necessary and sensible do you consider the following behaviors since the COVID-19 pandemic? Political measures, such as:	0.90	temporary closures of playgrounds	0.80
			temporary border closures to Germany	0.78
			temporary curfews	0.76
			temporary closures of kindergartens, schools, and universities	0.72
			temporary closure of bars, pubs, theaters, cinemas, etc.	0.69
Anxiety buying	How necessary and sensible do you consider the following behaviors since the COVID-19 pandemic? Stockpiling consumer goods (panic buying), such as	0.93	toilet paper	0.87
			groceries (vegetables, lentils, rice, pasta...)	0.76
			water (20 l per person)	0.86
			soap, dishwashing detergent, cleaning supplies, laundry detergent, etc.	0.82
			cash	0.86
Solidarity behavior	How necessary and sensible do you consider the following behaviors since the COVID-19 pandemic? Solidarity behavior, such as	0.83	supporting people experiencing existential hardship due to the current situation	0.84
			supporting people who belong to the risk group, e.g. actively going shopping or passively staying at home	0.76
			offering help to close friends and family members	0.83
			engaging in neighborhood assistance	0.57
Hygiene measures	How necessary and sensible do you consider the following behaviors since the COVID-19 pandemic?	0.78	thorough handwashing (at least 30 s long)	0.77
			increasing disinfection of hands and objects	0.69
			regular handwashing	0.83
			maintaining at least 1.5 m distance from other people	0.64
			not touching mouth, eyes, or nose with hands	0.56
Stressor pandemic	Due to the COVID-19 pandemic, during the lockdown, I have felt stressed or burdened by	0.84	quarantine.	0.73
			curfews.	0.74
			fear of what the future holds or that I won't be able to cope with everything.	0.62
			the current pandemic.	0.63
			a confined living space.	0.75
			financial worries.	0.53
Stressor work		0.70	uncertainties about my job, training position, studies, or school.	0.59
Stressor childcare		0.86	childcare.	0.77
			taking over school teaching.	0.84
Political trust	Since the COVID-19 pandemic, during the lockdown, I have	0.88	felt that the political leadership is advocating for me.	0.72
			perceived democracy as an effective form of government.	0.77
			felt that public institutions (e.g. police, judiciary) are reliable.	0.71
			perceived politicians as trustworthy.	0.65
Contamination anxiety	How do you currently assess the risk posed by the COVID-19 pandemic? I am concerned that	0.83	I will infect myself with COVID-19.	0.76
			I will infect other persons with COVID-19.	0.76
			Persons close to me will become infected with COVID-19.	0.81
Social distancing	How necessary and sensible do you consider the following behaviors since the COVID-19 pandemic? Reducing social contacts, such as	0.62	moving your work to home office	0.72
			avoiding physical contact (e.g. shaking hands or hugs) when greeting or saying goodbye to other people	0.56
Inner resources		0.57	focused on my inner strengths, resources, abilities, and talents.	0.52
			changed my attitudes about what is truly important in life.	0.53
Daytime structure	Since the COVID-19 pandemic, during the lockdown, I have	0.78	integrated sports and exercise into my daily life.	0.54
			maintained a regular daily structure.	0.84
			planned the day as accurately as possible.	0.64
Conspiracy beliefs		0.87	considered the possibility that this infection is intended to deliberately reduce the world's population due to insufficient resources for everyone.	0.75
			considered the possibility that	0.82

(*continued on next page*)

Table 1 (*continued*)

Latent factor	Stem	Cronbach's α	Item	Factor loading
			what is happening here is the result of a combat and competition strategy between different world superpowers.	
			considered the possibility that there is a connection between the events and the production and testing of biological weapons.	0.80
			considered the possibility that there are alternative or secret explanations for the current events.	0.78
			there is more solidarity and cohesion in our society.	0.83
Social cohesion	Since the COVID-19 pandemic, during the lockdown, I have felt that	0.80	I am an important part of our society or community.	0.52
			our nation is coming closer together.	0.78

analysis: Out of a total of 69 items, 16 were excluded due to inadequate factor loadings (<0.5), and an additional 4 were excluded after manual selection. The remaining 49 items loaded onto a total of 14 latent factors/subscales (explained variance: 57 %, CFI: 0.75, RMSEA: 0.08, Table 1). *Cronbach's α* (estimated for each subscale) was between 0.57 and 0.93. Stressor-associated items loaded onto three individual factors which encompassed childcare-, work-, or pandemic-related aspects. Structural equation modeling (SEM) was performed to assess the relationships between the stressor-associated and coping-associated latent variables (Fig. 1). SEM revealed that stressor and coping subscales were not associated with each other, indicating that work-related, childcare-related, and pandemic-related stressors were distinctly perceived from the coping strategies relying on internal resources and structuring daily routines.

Overall, MS and non-MS co-twins most valued *hygiene measures*, followed by *solidarity behavior* and *social distancing*. *Childcare-related*, *conspiracy beliefs*, and *anxiety buying* were the least appreciated items. We did not detect any difference between the perception of the psychosocial impact of the COVID-19 pandemic between MS and non-MS co-twins (Table 2).

3.3. Comparison of the MS twin cohort with an independent age- and sex-matched cohort

To address the question if the similar perception of the psychosocial impact of the COVID-19 pandemic between MS and non-MS co-twins was related to their shared genetic background, we compared the MS twin cohort with an independent age- and sex-matched control cohort (cf. [9]). MS co-twins and the independent control cohort perceived 5/14 subscales differently: Individuals in the independent control cohort less appreciated *hygiene measures* (*Cliff's* $\Delta = 0.35$, $p = 2.11 \times 10^{-3}$) and

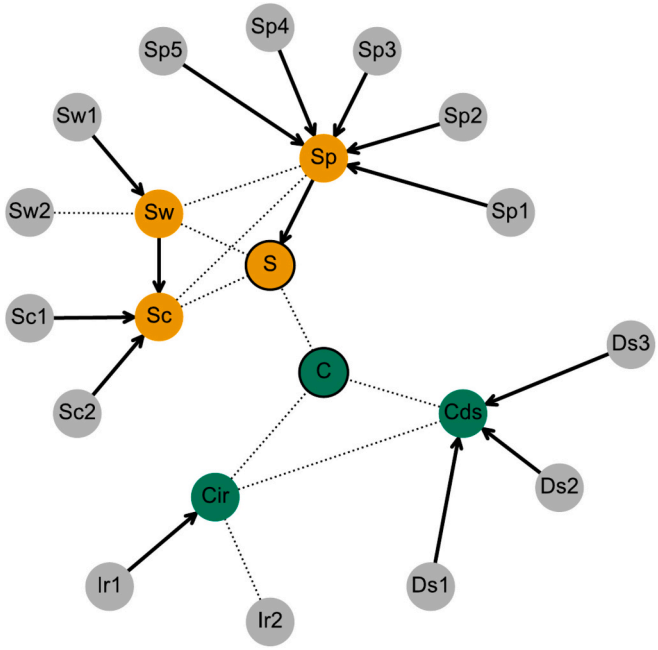

Fig. 1. Relationship between stressors and coping. Structural equation modeling illustrating the hypothetical relationship between stressor- and coping associated variables. Grey nodes indicate measured variables (Sp1 to Sp5: pandemic-related stressors, Sp1: "current pandemic", Sp2: "confined living space", Sp3: "quarantine", Sp4: "curfews", Sp5: "fear of what the future holds or that I won't be able to cope with everything"; Sw1 and Sw2: work-related stressors, Sw1: "financial worries", "uncertainties about my job, training position, studies, or school"; Sc1 and Sc2: childcare-related stressors, Sc1: "childcare", Sc2: "taking over school teaching"; stem for all stressor items: "Due to the COVID-19 pandemic, during the lockdown, I have felt stressed or burdened by"; Ir1 and Ir2: coping through focusing on inner resources, Ir1: "focused on my inner strengths, resources, abilities, and talents", Ir2: "changed my attitudes about what is truly important in life"; Ds1 to Ds3: coping through maintaining a daily structure, Ds1: "maintained a regular daily structure", Ds2: "planned the day as accurately as possible", Ds3: "integrated sports and exercise into my daily life"; stem for all coping items: "Since the COVID-19 pandemic, during the lockdown, I have"). Latent variables (after explorative factor analysis) are shown as orange (stressors, Sp: pandemic-related stressors, Sw: work-related stressors, Sc: childcare-related stressor) and green (coping, Cir: coping through inner resources, Cds: coping through maintaining a daily structure) nodes. Nodes with black edge (S and C) indicate the perception of stressors (orange) and coping mechanisms (green). Significant ($p \leq 0.05$) interactions or projections are indicated as solid edges (arrows), non-significant interactions ($p > 0.05$) as dotted edges (lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

social cohesion (*Cliff's* $\Delta = 0.25$, $p = 0.02$) and felt less *contamination anxiety* (*Cliff's* $\Delta = 0.28$, $p = 6.63 \times 10^{-3}$). In contrast, they perceived *pandemic-* (*Cliff's* $\Delta = -0.27$, $p = 1.38 \times 10^{-3}$) and *work-related stressors* (*Cliff's* $\Delta = -0.32$, $p = 5.00 \times 10^{-5}$, Wilcoxon signed-rank test) as more burdensome (Fig. 2, Table 2).

3.4. Psychometric and disease-specific characteristics of the MS-twin cohort

Ultimately, since we did not detect any differences within twin pairs, we aimed to understand how psychometric and disease-specific variables were associated with the perception of stressors and coping strategies. Thus, we first assessed signs of anxiety and affective disorders in our MS twin cohort using the Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory (BDI-II). Furthermore, we evaluated how disease-related mental and physical alterations were perceived with the Multiple Sclerosis Impact Scale 29 (MSIS-29).

Table 2
Perception of the psychosocial impact of the COVID-19 pandemic of the MS twin cohort and an independent age- and sex-matched control cohort ($n = 112$).

Subscale	Cumulative subscale Likert score (Median [IQR])				*P* value (Wilcoxon signed-rank test)		Cliff's Δ (MS co-twin vs control)
	All	MS co-twins	Non-MS co-twins	Control	MS vs non-MS co-twin	MS co-twin vs control	
Hygiene measures	0.95 [0.85–1.0]	0.95 [0.9–1.0]	0.95 [0.8–1.0]	0.88 [0.71–0.96]	0.49	2.11×10^{-3}	0.35
Solidarity behavior	0.94 [0.75–1.0]	0.91 [0.75–1.0]	0.94 [0.75–1.0]	0.85 [0.71–0.9]	0.69	0.15	0.2
Social distancing	0.75 [0.5–1.0]	0.75 [0.5–1.0]	0.75 [0.5–0.88]	0.68 [0.4–0.9]	0.13	0.11	0.16
Political restrictions	0.65 [0.45–0.81]	0.6 [0.45–0.85]	0.65 [0.45–0.8]	0.52 [0.3–0.8]	0.49	0.12	0.14
Daytime structure	0.58 [0.417–0.83]	0.58 [0.42–0.83]	0.58 [0.48–0.83]	0.58 [0.33–0.75]	0.96	0.33	0.13
Political trust	0.62 [0.438–0.75]	0.62 [0.44–0.75]	0.56 [0.38–0.77]	0.55 [0.26–0.75]	0.99	0.24	0.11
Social cohesion	0.5 [0.333–0.67]	0.5 [0.4–0.6]	0.5 [0.31–0.69]	0.42 [0.17–0.58]	0.75	0.02	0.25
Contamination anxiety	0.5 [0.25–0.75]	0.5 [0.33–0.75]	0.5 [0.25–0.75]	0.38 [0.25–0.5]	0.7	6.63×10^{-3}	0.28
Inner resources	0.5 [0.25–0.75]	0.5 [0.25–0.75]	0.5 [0.25–0.62]	0.5 [0.28–0.62]	0.64	0.48	0.09
Stressor pandemic	0.2 [0.05–0.36]	0.18 [0.05–0.4]	0.2 [0.05–0.35]	0.25 [0.15–0.5]	0.8	1.38×10^{-3}	−0.27
Stressor work	0.0 [0.0–0.25]	0.0 [0.0–0.25]	0.0 [0.0–0.16]	0.25 [0.0–0.75]	0.52	5.00×10^{-5}	−0.32
Anxiety buying	0.0 [0.0–0.25]	0.0 [0.0–0.26]	0.0 [0.0–0.21]	0.18 [0.01–0.4]	0.08	0.09	−0.24
Conspiracy beliefs	0.0 [0.0–0.19]	0.0 [0.0–0.14]	0.0 [0.0–0.19]	0.08 [0.0–0.2]	0.93	0.28	−0.11
Stressor childcare	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.03]	0.0 [0.0–0.0]	0.13	0.43	−0.06

Overall, we observed low BDI-II and HADS scores (Table 3). Most participants showed no signs of depression (Supplement Table 2). However, MS co-twins scored slightly higher in all three instruments (Fig. 3, Table 3). The MSIS-29 subscale, which assesses the perception of physical impairment in the context of MS (MSIS-29-physical), could discriminate best between MS and non-MS co-twins, both on a group level as well as in-between co-twins (*Cliff's* $\Delta = 0.36$, $p = 2.77 \times 10^{-6}$, Wilcoxon signed-rank test, $p = 5.6 \times 10^{-6}$, Mann-Whitney U test). Moreover, higher MSIS-29-physical scores correlated with higher EDSS scores ($\rho = 0.61$, $p = 1.15 \times 10^{-3}$) and longer disease duration ($\rho = 0.33$, $p = 1.27 \times 10^{-2}$, Spearman correlation, p for H_0: $\rho \neq 0$, Fig. 3).

Cognitive alterations and fatigue are frequent symptoms in pwMS and not solely attributed to depression. These symptoms are partially captured by the BDI-II. Thus, we analyzed BDI-II items separately. Overall, only six items were perceived differently between the MS co-twins and non-MS co-twins subcohorts (*loss of pleasure*, *indecisiveness*, *loss of energy*, *difficulty of concentration*, *fatigue*, *libido loss*, Supplement Table 3). Among them, the items *fatigue* and *loss of energy* showed the highest differences between the MS and non-MS co-twins subcohort (*Cliff's* $\Delta = 0.30$ and 0.31), whereas the difference between the MS and non-MS co-twins subcohorts among the other items was marginally.

3.5. Perception of stressors and coping strategies

Our previous analyses showed that stressors were perceived differently between MS co-twins and individuals of the independent control group, however, no differences were observed between the MS and non-MS co-twins. Thus, we next tested the hypothesis that MS co-twins perceive (COVID-19-associated) stressors, reflected by the subscales *stressor (work)*, *stressor (childcare)*, and *stressor (pandemic)*, and their respective coping strategies, reflected by the subscales *inner resources* and *daytime structure*, independently of disease-specific, psychometric, and demographic characteristics. Hierarchical cluster analysis of the correlation matrix revealed separation of psychometrical (BDI-II, HADS-Anxiety, HADS-Depression, and MSIS-29-psychological) and disease-specific as well as demographic characteristics (EDSS score, MSIS-29-physical, progression index, age, and disease duration) in terms of their correlation with the perception of stressors and coping strategies (Fig. 4). Overall, MS co-twins with higher HADS-Anxiety ($\rho = 0.69$, $p = 4.33 \times 10^{-9}$), HADS-Depression ($\rho = 0.57$, $p = 4.0 \times 10^{-6}$), BDI-II ($\rho = 0.74$, $p = 1.06 \times 10^{-10}$), and MSIS-29-psychological scores ($\rho = 0.58$, $p = 3.0 \times 10^{-6}$) tended to perceive *stressors (pandemic)* as more burdensome (Spearman correlation, p for H_0: $\rho \neq 0$). In contrast, higher scores in the HADS-Depression ($\rho = -0.39$, $p = 3.0 \times 10^{-3}$), MSIS-29-psychological ($\rho = -0.29$, $p = 3.0 \times 10^{-2}$), MSIS-29-physical instruments ($\rho = -0.43$, $p = 1.0 \times 10^{-3}$), and higher EDSS values ($\rho = -0.40$, $p = 5.0 \times 10^{-2}$) were associated with a lower appreciation of the coping subscale *daytime structures*. Older participants perceived pandemic-related stressors as less burdensome ($\rho = -0.46$, $p = 4.29 \times 10^{-4}$). There was no correlation between the perception of *inner resources* and psychometric or MS-specific or demographic characteristics.

To test within twin-pair-specific variation in coping strategies and the perception of stressors, we employed generalized linear mixed models with twinship as a random effect (Table 4). Our findings revealed that individuals who perceived *pandemic stressors* as more burdensome tended to place a higher value on *inner resources* as a coping strategy, while no effect was observed for maintaining a *daytime structure*. Importantly, the random effect of twinship in this model accounted for a substantial portion of the variance, overshadowing the contribution of fixed effects.

4. Discussion

Critical life events may be experienced differently between individuals [12]. In our approach, the COVID-19 pandemic could be seen as a unique critical life event to which everybody, including pwMS, have been unwillingly and similarly exposed. Our aim was to understand how pwMS perceive critical life events and how this perception is influenced by the genetic background and psychometric and disease-specific factors. With an adapted version of the COVID-19 Pandemic Mental Health Questionnaire (CoPaQ) we measured the perception of the psychosocial impact of the COVID-19 pandemic in a twin setting of the MS twin cohort, comprised of monozygotic twins discordant for MS which enabled us to gain unique insights into the genetic basis of coping in pwMS. After resolving the underlying factor structure of the instrument we could measure 14 different subscales, including 3 subscales which captured the perception of stressors and 2 subscales which reflected the perception of coping strategies. Structural equation modeling showed that the stressor and coping subscales were not associated with each other. Thus, a distinct perception of work-related, childcare-related, and pandemic-related stressors, as well as coping strategies relying on internal resources and structuring daily routines, can be assumed.

How is coping with additional health threats, such as the COVID-19 pandemic, shaped in people with chronic diseases? We hypothesized that MS co-twins, who have delt with a critical life event (being diagnosed with MS) and, thus, health threat before, would adapt differently

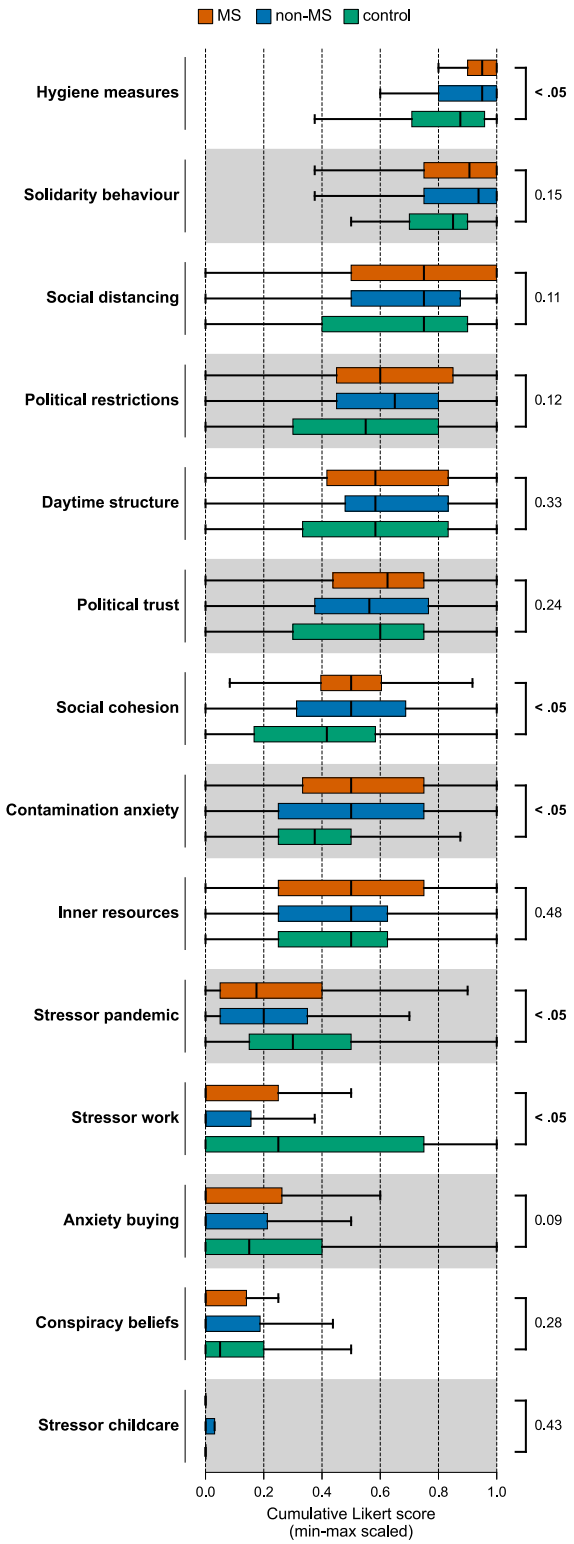

Fig. 2. Perception of the psychosocial impact of the COVID-19 pandemic. Min-max scaled cumulative subscale Likert scale values from the self-report COVID-19 Pandemic Mental Health Questionnaire (CoPaQ), originally developed by [9]. Vertical lines indicate median values, boxes span from the 25th to 75th quantile, whiskers show minimum and maximum values. Subgroups (MS co-twins, non-MS co-twins, and subjects from the age- and sex-matched control group) are color-coded. *P* values from Wilcoxon signed-rank test (MS co-twin versus non-MS co-twin) are shown on the right ($n = 56$ subjects per subgroup).

to an additional critical (health-threatening) life event, such as the COVID-19 pandemic. However, with our representative MS cohort with 56 twin pairs discordant for MS, we showed that the perception of the psychosocial impact of the COVID-19 pandemic did not differ between MS and non-MS co-twins. Hence, our findings suggest a strong impact of genetic factors. However, when looking at subscale levels we found that there was no difference in the perception of coping strategies between MS co-twins and individuals from the independent control group, although stressors were perceived differently between these subcohorts. We conclude that even if coping strategies are perceived similarly, the effect of coping strategies on the perception of stressors might be determined by genetic factors, potentially through differently employed coping strategies. We further hypothesized that besides genetic factors additional psychometric and disease-specific factors might play a role in the way someone perceives stressors and coping strategies. Surprisingly, higher scores in psychometric (BDI-II, HADS, MSIS-29) and disease-specific parameters (EDSS score, disease duration, progression index) were not accompanied by altered perception of the coping strategy *inner resources* in MS co-twins. In contrast, MS co-twins who were prone to cognitive and/or affective alterations perceived stressors as more burdensome. Possibly, while both pwMS and healthy controls may employ similar coping strategies, the efficacy of these strategies, as reflected in the perception of stressors, could differ based on their respective medical histories and/or current disease burdens.

Of note, although the perception of the psychosocial impact of the COVID-19 pandemic did not differ between MS and non-MS co-twins, the perception of anxiety and depression (measured by BDI-II and HADS) was consistently pronounced in the MS co-twin cohort compared to the non-MS co-twins subcohort. However, when BDI-II items were analyzed in detail, we observed that items that relate to symptoms which occur frequently in MS (e. g. fatigue) weighed the most. Accordingly, we cannot conclude from the elevated sum scores in the BDI-II that there is increased susceptibility for affective disorders in the MS co-twins subcohort. More precise instruments would be needed to further address this question.

We observed a stronger perception of stressors in individuals with stronger perception of MS-related psychological deficits (in the MSIS-29 psychological) and higher scores in anxiety and depression screening (BDI-II and HADS). Thus, signs of affective disorders, which either developed independently of MS or are a clinical feature of the individual MS patient, can be interpreted as a negative factor in the context of resilience of people with MS to additional health threats.

The question arises as to whether a chronic illness, such as multiple sclerosis, is an influencing factor for resilience to (another/additional) health hazard. In general, resilience reflects the ability to develop an attitude towards a (health) disadvantage, while coping can be interpreted as a toolbox [13]. Resilience can be influenced by risk or protective factors [14]. For MS it was shown that psychological factors such as positive affect and self-efficacy are more reliable predictors for resilience than disease-related factors [15]. This is in line with our finding since monozygotic twins discordant for MS perceived COVID-19-related health threats similarly which implies that being diagnosed with MS (as a disease-related factor) has a negligible impact on (COVID-19) resilience. However, our results can only provide limited insights into the underlying resilience, as our measurement instruments assessed coping mechanisms only and not resilience per se. Furthermore, our participants might be biased by the interplay between MS as an immune-mediated disorder and COVID-19 as an infectious disease, especially since many disease modifying treatments for MS harbor an increased risk of infection. In addition, the non-MS affected co-twin has a better understanding and awareness of the demands of risk groups and hence the acceptance for e.g. hygiene measures is higher. Thus, it is unclear if the assessment of an MS cohort can be interpretated as a *pars pro toto* for any chronic disease, whose impact on the resilience to COVID-19 was tested or if other (pre-existing) medical conditions would lead to different results. It remains to be discussed whether the measured

Table 3
Psychometric testing of the MS twin cohort. Hospital Anxiety and Depression Scale (HADS, with its subscales HADS-Anxiety and HADS-Depression), Beck Depression Inventory (BDI-II), and Multiple Sclerosis Impact Scale 29 (MSIS-29, with its subscales MSIS29-physical and MSIS29-psychological) were used to assess the severity of mood alterations in our MS twin cohort. Median values (Md) for the MS and non-MS co-twins subcohorts with interquartile ranges (IQR, 25th to 75th percentile) are shown. Cliff's delta estimates the effect sizes of the differences between the MS and non-MS co-twins subcohorts. Rank-based statistical testing was used to test the null hypothesis whether individuals from both subcohorts scored similarly (Mann–Whitney U test, MWU) or to test for consistent intra-twin differences (Wilcoxon signed-rank test).

	n	Md_{MS} [IQR]	$Md_{non\text{-}MS}$ [IQR]	Cliff's Δ	$p_{Wilcoxon}$	p_{MWU}
HADS-Anxiety	112	5.0 [2.75–9.0]	4.0 [1.0–6.0]	0.25	6.69×10^{-3}	0.02
HADS-Depression	112	3.0 [1.0–6.0]	2.0 [0.0–4.25]	0.21	0.05	0.05
BDI-II	112	9.0 [4.0–15.25]	4.0 [0.0–9.25]	0.34	2.96×10^{-5}	1.79×10^{-3}
MSIS29-physical	109	33.5 [22.75–46.0]	22.0 [20.0–26.0]	0.36	2.77×10^{-6}	5.60×10^{-6}
MSIS29-psychological	108	17.0 [12.0–23.5]	11.0 [9.0–17.5]	0.21	3.0×10^{-4}	4.09×10^{-4}

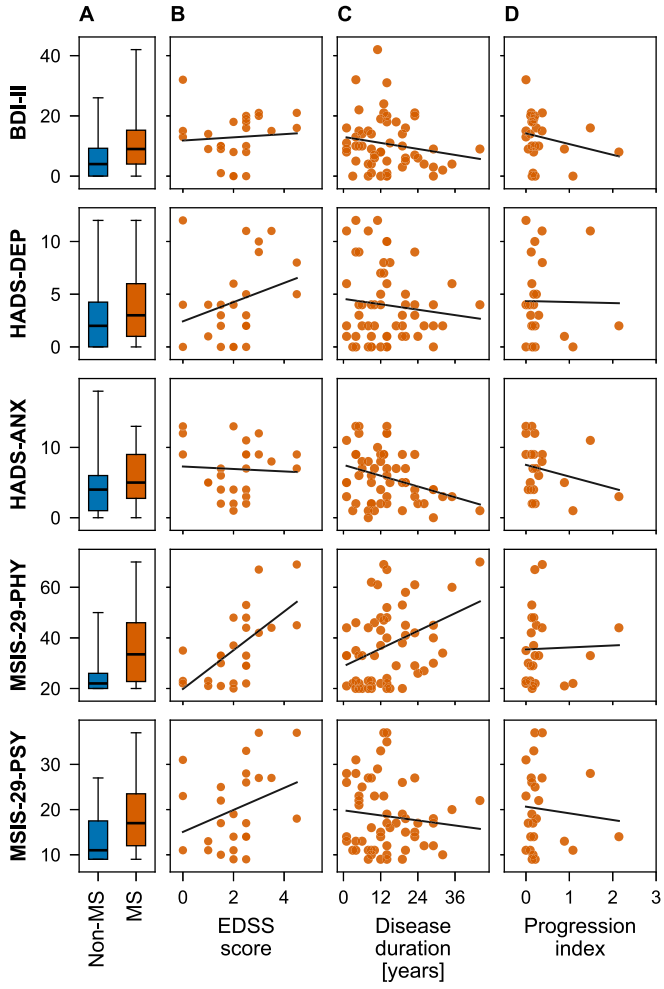

Fig. 3. Sum values of psychometric instruments and correlation between psychometric and MS-specific parameters in the MS co-twin subcohort. Hospital Anxiety and Depression Scale (HADS, with its subscales HADS-Anxiety and HADS-Depression), Beck Depression Inventory (BDI-II), and Multiple Sclerosis Impact Scale 29 (MSIS-29, with its subscales MSIS29-physical and MSIS29-psychological) in the MS co-twin subcohort. Boxplots with median sum values (horizontal lines), interquartile ranges (25th to 75th percentile, boxes), and minimum and maximum values (whiskers, A). Correlation between psychometric and MS-specific parameters (Expanded Disability Status Scale, EDSS, B, disease duration, C, and progression index, D). Lines indicate the polynomial fit (least squares) between two variables.

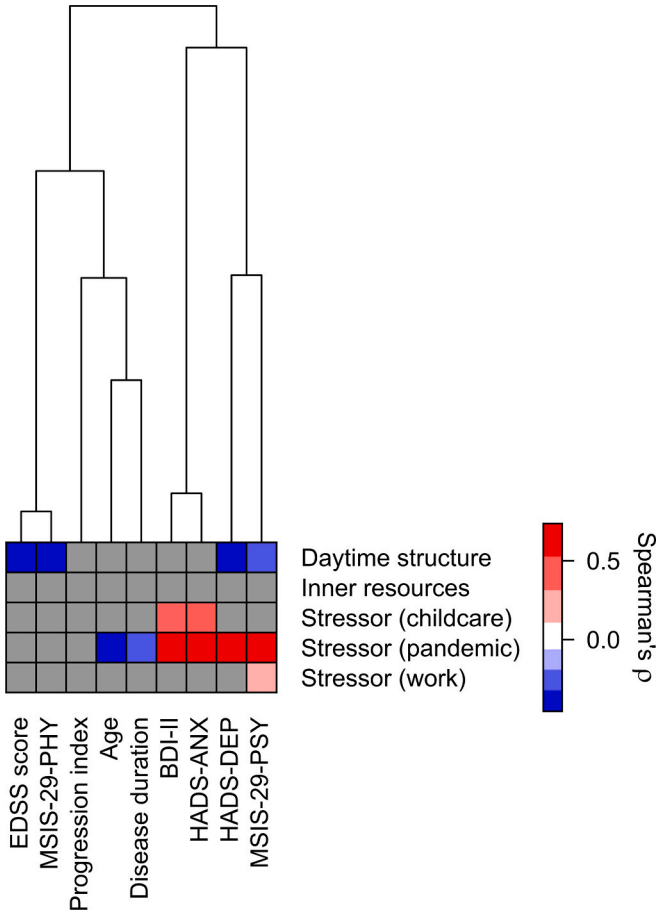

Fig. 4. Correlation between the perception of stressors and coping strategies and psychometric and disease-specific and demographic characteristics in the MS co-twin subcohort. Correlation matrix based on color-coded Spearman correlation coefficients (ρ). Fields with color-coded correlations have low and grey fields high alpha errors probabilities ($p \leq 0.05$ and $p > 0.05$, for H_0: $\rho \neq 0$). Columns were hierarchically clustered according to their Euclidean distances.

stressor - the COVID-19 pandemic - might have been perceived as too mild overall to reveal clear differences within the twin pairs. Differences between the twin pairs might become more apparent if other stressors or stress responses, such as bereavement or received a terminal diagnosis were measured. However, this would have the disadvantage that the stressor might not affect all study participants uniformly, and confounders could arise due to variations in the intensity of the stressor's exposure, which may differ between twin pairs. Furthermore, because of the identical genetic background and since MS and non-MS co-twins grew up in similar environments it remains unclear which factor predominantly imprints resilience. There is evidence that genetic factors would play a more important role in the capacity to deal with stress as compared to a shared environment [16]. However, to address this specific question in the context of MS, a dizygotic MS twin cohort study would be needed.

Table 4
Generalized linear mixed model.

Target variable	Fixed effects			Random effects		R^2		AIC
	Variable	Coefficient [95 % confidence interval]	z value (*p* value)	Variable	Variance (SD)	Marginal	Conditional	
Stressor (pandemic)	Daytime structures Inner resources	−0.19 [−0.87–0.49] 1.39 [0.75–2.05]	−0.56 (0.57) 4.3 (1.99×10^{-5})	Twinship	0.85 (0.92)	0.08	0.78	585.4

This study highlights that the perception of coping and stressor in pwMS is mainly driven by genetic factors and potentially altered by disease-related variables. Further studies will be conducted to precisely elucidate how pwMS deploy coping mechanisms to deal with their health and socioeconomical burden.

CRediT authorship contribution statement

Daniel Engels: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrea Flierl-Hecht:** Project administration, Methodology, Investigation, Data curation, Conceptualization. **Gabriela Shalaginova:** Resources, Project administration, Data curation, Conceptualization. **Stephanie Rek:** Resources, Methodology. **Daniel Keeser:** Resources, Methodology. **Matthias A. Reinhard:** Resources, Methodology. **Frank Padberg:** Supervision, Resources, Methodology. **Tania Kümpfel:** Writing – review & editing, Supervision, Resources, Investigation. **Lisa Ann Gerdes:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

DE received speaker honoraria and/or travel reimbursements from Alexion, Horizon/Amgen, Merck, and Roche, not related to this study.

AFH: none related to this study.

GS: none related to this study.

SR: none related to this study.

DK: none related to this study.

MAR: none related to this study.

FP: none related to this study.

TK has received speaker honoraria and/or personal fees for advisory boards from Novartis Pharma, Roche Pharma, Alexion/Astra Zeneca, Horizon Therapeutics/Amgen, Merck, Chugai Pharma and Biogen. The Institution she works for has received compensation for serving as a member of a steering committee from Roche. TK is a site principal investigator in several randomized clinical trials and her institution has received compensation for clinical trials from Novartis Pharma, Roche Pharma, and Sanofi Genzyme; all outside the present work.

LAG received speaker honoraria and/or personal fees for advisory boards from Roche Pharma, Merck, Sanofi and Biogen. LAG is a site principal and sub investigator in several randomized clinical trials and her institution has received compensation for clinical trials from Novartis Pharma, Roche Pharma, and Sanofi Genzyme; all outside the present work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123381.

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