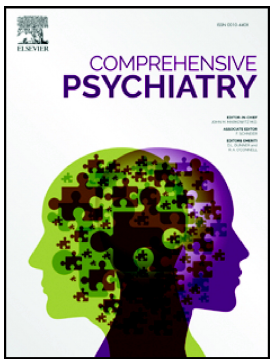

The influence of psychological traits and prior experience on treatment expectations

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The Influence of Psychological Traits and Prior Experience on Treatment Expectations

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ABSTRACT

Background: Placebo and nocebo responses are modulated by the treatment expectations of participants and patients. However, interindividual differences predicting treatment expectations and placebo responses are unclear. In this large-scale pooled analysis, we aim to investigate the influence of psychological traits and prior experiences on treatment expectations.

Methods: This paper analyses data from six different placebo studies (total *n* = 748). In all studies, participants' sociodemographic information, treatment expectations and prior treatment experiences and traits relating to stress, somatization, depression and anxiety, the Big Five and behavioral inhibition and approach tendencies were assessed using the same established questionnaires. Correlation coefficients and structural equation models were calculated to investigate the relationship between trait variables and expectations.

Results: We found small positive correlations between side effect expectations and improvement expectations (*r* = .187), perceived stress (*r* = .154), somatization (*r* = .115), agitation (*r* = .108), anhedonia (*r* = .118), and dysthymia (*r* = .118). In the structural equation model previous experiences emerged as the strongest predictors of improvement (β = 0.32, *p* = .005), worsening (β = -0.24, *p* = .005) and side effect expectations (β = 0.47, *p* = .005). Traits related to positive affect (β = - 0.09; *p* = .007) and negative affect (β = 0.04; *p* = .014) were associated with side effect expectations.

Discussion: This study is the first large analysis to investigate the relationship between traits, prior experiences and treatment expectations. Exploratory analyses indicate that experiences of symptom improvement are associated with improvement and worsening expectations, while previous negative experiences are only related to side effect expectations. Additionally, a proneness to experience negative affect may be a predictor for side effect expectation and thus mediate the occurrence of nocebo responses.

Keywords (max. 6): placebo effects; personality; nocebo effects; treatment experience; side effects; expectancies

1. INTRODUCTION

Prior to starting a medical treatment, patients usually form and hold beliefs about the likelihood of different treatment outcomes. Such beliefs are commonly called treatment expectations [1,2]. Treatment expectations have been found to modulate a large number of treatment effects and are seen as a central mechanism driving beneficial or noxious effects of inert substances (i.e., placebo and nocebo responses) [2–6]. Numerous

studies have demonstrated the effects of patients' treatment expectations on various medical conditions, with a majority of research focusing on pain [5,7–9]. Furthermore, these effects have been shown to extend beyond subjective symptom ratings, as behavioral measures and physiological parameters have also been affected by treatment expectations [5,10–12]. Those findings show the pivotal role of treatment expectations in determining health outcomes after active and inert treatments.

Unsurprisingly, positive treatment expectations have been theoretically and empirically linked to beneficial effects of inert interventions (i.e., to placebo responses) and to enhanced beneficial effects of active substances. Negative treatment expectations and side-effect expectations have been have been associated with noxious effects of inert interventions (i.e., to nocebo responses) and dampened efficacy as well as heightened adverse effects of active treatments [3,8,9,13].

Of note, however, positive and negative expectations should not simply be seen as opposite ends of a spectrum. Patients can have positive and negative expectations about the same treatment, plus separate expectations about the side effects of that treatment, indicating the necessity of separately measuring positive and negative treatment effects as well as side-effect expectations [14].

Treatment expectations themselves are thought to be formed and modulated by various parameters. On the one hand, broad evidence points to the importance of the clinical context in forming treatment expectations (verbal or written information about the treatment, patient-physician-interaction, hidden vs. open application of a substance etc.). On the other hand, various psychological factors (prior treatment experiences, personality traits, stress etc.) seem to influence a person's treatment expectation as well [1,5]. Consequently, treatment expectations can be seen as an intermediary, potentially mediating influence of psychological antecedences and context factors on treatment outcomes [1,2].

While the influence of the clinical setting on patients' treatment expectations and on placebo and nocebo responding is well established, pronounced interindividual differences in placebo and nocebo responding [1,12,15] motivate the search of psychological factors to explain those interindividual differences in treatment expectations beyond setting factors.

The two most investigated factors are a patient's prior treatment experiences and general personality traits. So far, most studies focused on directly linking those variables with treatment outcomes. Less research addressed the potential association to the intermediary construct of treatment expectations [4,8,16]. A strong influence on treatment expectations has been shown for prior treatment experience, using different paradigms, such as sampling previous treatment experiences, associative learning and observational learning procedures [6,17–20]. To our knowledge however, no study has yet tested the differential impact of improvement, worsening and side-effect experiences on improvement, worsening and side-effect expectations, respectively. As mentioned above, this is important to elucidate the interplay between different experiences and expectations.

Regarding personality traits, numerous studies have tried to link broad traits directly to placebo and nocebo responding, and the idea of a person's personality differentiating "placebo responders" from "non-responders" has a long history in the field [15,21]. However, systematic reviews of those studies found only small and inconsistent direct associations between personality traits – such as the Big Five, behavioral activation, behavioral inhibition etc. - and placebo responding [16,22]. In a systematic review of the literature, inconclusive results were reported for potential links between negative affect, neuroticism, trait anxiety and pessimism with nocebo responding [23], in part because included studies were often conducted with few participants and in specialized treatment settings. Beyond classical personality traits and prior treatment experience, there is initial evidence for the role of somatosensory amplification and stress in the development of nocebo responses [23–30]. Surprisingly, however, to our knowledge, no study has yet investigated a possible link between broad personality traits and treatment expectations instead of directly linking traits to placebo or nocebo responding.

To further clarify the differential role played by experience and personality in explaining treatment expectations, we tested the differential effects of positive, negative and side-effect prior treatment experience and personality traits on positive, negative and side-effect treatment expectations. We examined the potential links using a large sample, consisting of heterogeneous participant groups and experimental conditions, testing whether associations hold across contexts. In doing so, we aim to disentangle the differential role played by different experiences and

personality traits in explaining treatment expectations. This could ultimately contribute to individually tailored strategies to maximize placebo and minimizing nocebo responding to optimize overall treatment outcomes [12].

2. METHODS

2.1 Procedure

This paper analyses data across six different studies conducted at three locations (Philipps University Marburg, University Medical Center Hamburg-Eppendorf, University Hospital Essen) between June 8th, 2020 and October 10th, 2022. See Appendix A.1 for an overview over the different projects and ethics approval. All studies were funded by the DFG (422744262) as part of the TRR 289 "Treatment Expectations", conducted in accordance with the Declaration of Helsinki and all participants gave informed consent for their participation in the study.

2.2 Materials

2.2.1 Sociodemographic information

Age in years and self-reported gender identity were recorded during the first study visit of participants.

2.2.2 Treatment expectations

Expectations regarding the treatment applied in each study were recorded with the German version of the generic rating scale for previous treatment experiences, treatment expectations, and treatment effects (G-EEE) [14]. Participants rated on a scale from 0 ("no improvement/worsening/complaints") to 10 ("greatest imaginable improvement/worsening/complaints") how much they expect the treatment to lead to an improvement, a worsening or side effects related to the treatment condition (e.g., "How many complaints/side effects do you expect from the treatment?"). The reported score on each of the three questions was used as the main dependent variables. Additionally, the G-EEE includes questions about previous experiences with the relevant treatment. If previous experience was reported, the same three questions

(improvement, worsening, side effects) were posed to participants with regards to their previous experience. The three resulting variables were used as predictors for a secondary analysis. The G-EEE is a newly developed instrument from our group [14] and studies regarding the reliability and validity of this questionnaire are still ongoing.

2.2.3 Stress

To assess perceived stress in participants, the German version of the perceived stress scale (PSS) was used [31]. The scale contains ten items (e.g., "In the last month, how often have you been upset because of something that happened unexpectedly?") rated on a scale from 0 ("never") to 4 ("very often") resulting in a maximum total score of 40 (Cronbach's $\alpha = .87$).

2.2.4 Somatization

The German version of the somatosensory amplification scale (SSAS) [32] was used to assess the tendency of participants to amplify somatosensory symptoms. The scale contains ten items (e.g., "I hate to be too hot or cold.") answered on a scale of 1 ("not true at all") to 5 ("completely true"), with a resulting total score range of 10-50 (Cronbach's $\alpha = .69$).

2.2.5 Depression and Anxiety

The trait scales of the German version of the state-trait anxiety-depression inventory (STADI) [33] were used to assess trait depression and anxiety in participants. The scale contains 20 items (e.g., "I am happy.") answered on a scale of 1 ("almost never") to 4 ("almost always"). Five subscale scores are calculated based on the sum of the corresponding items: "agitation", "apprehension", "euthymia", "anhedonia" (reverse scoring of "euthymia" items), and "dysthymia". Here we analyzed the four subscales "agitation" (Cronbach's $\alpha = .74$), "apprehension" (Cronbach's $\alpha = .78$), "anhedonia" (Cronbach's $\alpha = .85$), "dysthymia" (Cronbach's $\alpha = .85$).

2.2.6 Big Five

A German version of the 10-item version [34] of the big five personality inventory (BFI-10) [35] was used as an assessment of the personality domains openness (Spearman-Brown coefficient = .80), conscientiousness (Spearman-Brown coefficient = .81), extraversion (Spearman-Brown

coefficient = .88), agreeableness (Spearman-Brown coefficient = .74), neuroticism (Spearman-Brown coefficient = .82). The sum of two items for each personality domain gives a score for the corresponding domain, all five of which are analyzed here.

2.2.7 Behavioral Inhibition System and Behavioral Approach System (BIS/BAS)

To specifically assess BIS/BAS sensitivity, the German version of the behavioral inhibition system and behavioral approach system scales (BIS/BAS) [36] were applied. The scale consists of 24 items (e.g., "How I dress is important to me.") with a 4-point Likert scale (1= very true for me to 4= very false for me). Four subscale scores are reported consisting of the sum of the included items: "Behavioral Inhibition System" (Cronbach's α = .80), "BAS Drive" (Cronbach's α = .77), "BAS Fun Seeking" (Cronbach's α = .56), "BAS Reward Responsiveness" (Cronbach's α = .79). All four subscales are analyzed here.

2.3 Statistical Analysis

Resulting p-values were considered significant with $p < .05$. For significant tests the alpha level was adjusted according to the Benjamini-Hochberg false discovery rate procedure [37] as suggested for structural equation modelling [38] to reduce type 1 error rate. Analyses were conducted in RStudio [39] and JASP [40].

2.3.1 Pre-processing

As the current study aims to summarize effects across a large number of different settings, and treatment expectations are specific to their settings, we z-transformed the three outcome variables (G-EEE improvement; G-EEE worsening; G-EEE side effects) and previous experience variables (G-EEE previous improvement; G-EEE previous worsening; G-EEE previous side effects) within each study. Further, we only included data from participants that had completed all questionnaires leaving us with $n = 667$ ($n_{excluded} = 81$), all of whom were descriptively analyzed.

2.3.2 Factor analysis

We factor analyzed all trait predictor variables (BFI-10 outcomes, BAS/BIS outcomes, STADI outcomes, perceived stress, somatization) for two reasons: First, we hoped to minimize misguided conclusions based on the "jangle" fallacy [41,42] which is an erroneous judgement that two

constructs refer to different phenomena because of different names. Based on a high intercorrelation between trait variables (see Appendix B.1) we see potential for this fallacy in our data. Second, based on the large number of trait parameters we aimed to minimize alpha inflation by reducing the number of included explanatory variables in further analyses. In a first step, we tested whether the data is suitable for a factor analysis, using the Kaiser-Meyer-Olkin (KMO) test. KMO > 0.5 is usually seen as a prerequisite a factor-analyzing data [43]. Given the theoretical grounding of the scales described, we expected a two-factor structure, with one factor representing the common variance of negative affect related traits ('Factor NA', including scales assessing stress, anxiety, neuroticism, behavioral inhibition system) and another factor representing positive-affect related traits ('Factor PA', including extraversion, behavioral approach system and anhedonia (negatively loaded) scales). Parallel analysis and Eigenvalue (Eig. > 1) criterion was used to determine the appropriate number of factors. In accordance, an oblique factor analysis employing oblimin rotation was used for extracting factors.

2.3.3 Participants without experience

Structural equation modelling was selected as the primary method of analysis, as it allows us to account for latent variables, we assumed to be present in our trait predictors. As only a subset of participants reported previous experience with the relevant interventions and complete data on all variables is needed for proper analysis, we decided to split the sample into those without (w/o) previous experience (n = 528) and those with previous experience (n = 139). Separate analyses were conducted in the two samples. To analyze which psychological traits influence treatment expectations, we build a maximum likelihood structural equation model with the three expectation variables (G-EEE improvement; G-EEE worsening; G-EEE side effects) as dependent variables and age (continuous), gender (categorical: male, female, diverse), study (categorical: which specific project the data belong to) and the resulting factors from the EFA as independent variables in the sample w/o experience. The resulting factors were treated as latent variables having a direct influence on the outcomes. Our model was cross-validated using k-fold cross validation. A good fit across k validations would be indicated by a $\chi 2$ to degrees of freedom (df) ratio < than 2 (a ratio between 2 and 3 is acceptable), a Comparative Fit Index (CFI) ≥ 0.95 (0.90–0.94 acceptable), a standardized root mean square residual (SRMR) ≤ 0.05 (0.05–0.10 acceptable), and a

root mean square error of approximation (RMSEA) ≤ 0.05 (0.05–0.10 acceptable) [44]. We also calculated Pearson's regression coefficients between all predictor and outcome variables, with r ≥ |.10| considered small, r ≥ |.30| medium, and r ≥ |.50| large effects [45].

2.3.4 Participants with experience

In the sample of participants with previous experience (*n* = 139) the model was extended by inclusion of three G-EEE items regarding previous experiences as predictors (G-EEE previous improvement; G-EEE previous worsening; G-EEE previous side effects). All other aspects of the analysis remained the same, see Figure 1 for an exemplary SEM model including all parameters.

[INSERT FIGURE 1 HERE]

2.3.5 Analytic considerations

We did consider the suggestion of an alternative analytic method (meta-analysis), however, we stuck to the procedure of SEM for the following reasons: 1) Most importantly, we are not interested in investigating a single effect (e.g., the relationship between improvement experience and improvement expectation) but the association between a number of trait factors and different facets of baseline expectations. Thus, instead of being able to compare one main effect across the six studies we would need to conduct a separate analysis for each trait and the corresponding expectation outcome. This would not be parsimonious, increase the difficulty of interpreting results and would not allow for controlling all other parameters collected. 2) All included studies use the exact same measures and instruments, making one of the major benefits of meta-analysis, assessment across different instruments, unnecessary. 3) Sticking to the SEM procedure also allows for the inclusion of the extracted factors from the factor analysis and provides more confidence that associations are general instead of study-specific effects.

3. RESULTS

3.1 Participants

In total, *n* = 667 participants were included in our analyses, with an average age of 27.89 years (SD = 8.9) and 56.5% female participants, see Table 1 for demographic details. Raw values of improvement expectations ($F(5,677) = 70.1$, $p < .001$), worsening expectations ($F(5,677) = 8.78$, $p < .001$), and side effect expectations ($F(5,677) = 21.9$, $p < .001$) differed significantly across the included projects. Interestingly, improvement expectations were different between all projects (all $p < .05$) except for the two projects involving mood manipulations ($t = 2.04$, $p = .63$). While improvement expectations varied around the middle of the scale (overall mean = 4.73), expectations regarding symptom worsening and treatment side effects were generally low (mean worsening = 0.88, mean side effects = 1.34).

Table 1. Demographic details and expectations across studies.

	A01 (*n* = 173)	**A02 (*n* = 112)**	**A06 (*n* = 106)**	**A07 (*n* = 124)**	**A11 (*n* = 73)**	**A12 (*n* = 79)**	**Total (*n* = 667)**	**Experienced participants (*n* = 139)**	**Participants w/o experience (*n* = 528)**
Mean age in years (SD)	26.09 (4.2) Range: 18.25 – 38.67	25.45 (4.6) Range: 18.50 – 43.67	26.57 (4.2) Range: 19.08 – 34.83	24.58 (4.8) Range: 19.25 – 38.92	25.14 (3.8) Range: 19.58 – 36.17	44.80 (14.4) Range: 20.67 – 73.33	27.89 (8.9), Range: 18.25 – 73.33	33.73 (13.8) Range: 19.58 – 71.75	26.36 (6.3) Range: 18.25 – 73.33
Gender									
Male	*n* = 65	*n* = 39	*n* = 45	*n* = 61	*n* = 26	*n* = 52	*n* = 288	*n* = 68	*n* = 220
Female	*n* = 108	*n* = 72	*n* = 61	*n* = 62	*n* = 47	*n* = 27	*n* = 377	*n* = 71	*n* = 306
Diverse	*n* = 0	*n* = 1	*n* = 0	*n* = 1	*n* = 0	*n* = 0	*n* = 2	*n* = 0	*n* = 2
Raw improvement expectations (SD)	4.27 (2.7)	5.89 (2.1)	3.29 (2.7)	2.68 (2.1)	6.15 (2.0)	7.94 (2.0)	4.73 (2.9)	6.73 (2.4)	4.20 (2.8)

Raw worsening expectations (SD)	1.47 (2.1)	0.54 (1.4)	0.34 (0.8)	1.00 (1.6)	0.79 (1.8)	0.67 (1.4)	0.88 (1.7)	0.76 (1.7)	0.91 (1.7)
Raw side effect expectations (SD)	1.13 (1.6)	2.38 (1.8)	0.37 (0.9)	1.06 (1.4)	1.25 (2.1)	2.18 (1.7)	1.34 (1.7)	1.70 (2.1)	1.24 (1.6)

3.2 Correlation between expectations and trait variables

In the complete sample, z-transformed improvement expectations (henceforth all expectation values refer to the z-transformed values) were positively associated with side effect expectations (r = .187, p < .001), conscientiousness (r = .087, p = .022), and agitation (r = .079, p = .039). Worsening expectations correlated with side effect expectations (r = .419, p < .001), reward sensitivity (r = - .088, p = .022), and perceived stress (r = .09, p = .019). Side effect expectations were associated with neuroticism (r = .083, p = .030), perceived stress (r = .154, p < .001), somatization (r = .115, p < .001), agitation (r = .108, p = .005), apprehension (r = .094, p = .014), anhedonia (r = .118, p = .002), and dysthymia (r = .118, p = .002). Additionally, each trait predictor correlated significantly with at least seven other trait predictors (see Appendix B.1 for an overview over all correlations between variables), supporting the notion of multicollinearity between predictors and indicating the need for a reduction through factor analysis.

3.3 Factor analysis

Based on high levels of multicollinearity (see above) we included all trait predictors in the factor analysis. The KMO-test showed a good suitability for factor analysis in the data (MSA =.81). As expected, both parallel analysis and Eigenvalue criterion indicated a two-factor solution. The two extracted factors are only slightly correlated (r = -.21), have well-interpretable factor loadings and explain almost half of the variance within the trait scales (cumulative explained variance = .36), see Table 2 for details on factor loadings and explained variance. Except for the BFI-10 openness and tolerance subscales all trait factors loaded on the two extracted factors.

Table 2. Factor loadings (> 0.2) and explained variance.

Scales	Factor NA	Factor PA	h^2
PSS total score	.57	- .26	.46
SSAS score	.31	.22	.12
BFI-10 Neuroticism	.77		.57
BFI-10 Extraversion	- .20	.32	.17
BFI-10 Conscientiousness		.37	.14
BFI-10 Openness			.03
BFI-10 Tolerance			.06
BIS Score	.74		.53
BAS Drive		.70	.49
BAS Fun		.36	.15
BAS Reward		.67	.43
STADI Apprehension	.75		.58
STADI Agitation	.79		.60
STADI Anhedonia	.48	- .49	.56
STADI Dysthymia	.58	- .3[illegible]	.54
Explained variance	.23	.13	**Σ** .36

3.4 Trait variables as predictors of treatment expectations

Cross-validation with *k* = 5, across *n* = 528 participants, showed mostly acceptable fit of the model to the data (CFI = 0.72, SRMR = 0.09, RMSEA = 0.10, $\chi 2$/df = 5.02). None of the trait predictors were significant after alpha-level adjustment, see Table 3 for a complete overview.

Table 3. Coefficients for the single predictors on the three expectation outcomes.

	Estimate (SE)	Z-Value	*p* - value	$\alpha_{Benjamini\text{-}Hochberg}$
G-EEE improvement				
Factor NA	0.02 (0.02)	0.88	.379	
Factor PA	0.01 (0.04)	0.13	.898	
BFI-10 Tolerance	0.05 (0.03)	1.73	.083	
BFI-10 Openness	0.00 (0.02)	0.16	.874	
Age	0.00 (0.01)	0.11	.911	
Gender	0.15 (0.09)	1.64	.100	
Study	0.01 (0.03)	0.27	.788	
G-EEE worsening				
Factor NA	0.01 (0.02)	0.50	.618	
Factor PA	- 0.04 (0.04)	- 0.91	.360	
BFI-10 Tolerance	- 0.00 (0.03)	- 0.17	.865	
BFI-10 Openness	0.01 (0.02)	0.41	.679	
Age	0.00 (0.01)	0.14	.89[illegible]	
Gender	- 0.06 (0.09)	- 0.64	.524	
Study	- 0.02 (0.03)	- 0.66	.509	
G-EEE side effects				
Factor NA	0.04 (0.02)	1.98	.048	.014
Factor PA	- 0.09 (0.04)	- 2.09	.036	.007
BFI-10 Tolerance	-0.01 (0.03)	- 0.35	.724	.043
BFI-10 Openness	0.02 (0.02)	0.80	.426	.029

Age	0.00 (0.01)	0.47	.641	.036
Gender	0.10 (0.09)	1.20	.230	.021
Study	- 0.01 (0.03)	- 0.32	.748	.05

Note: *, significant at the .05 level; CFI = 0.72; SRMR = 0.09; RMSEA = 0.10; $\chi 2/df = 6.02$

3.5 Influence of treatment experiences

Cross-validation with k = 3, across n = 139 participants, showed low to acceptable fit of the model to the data (CFI = 0.58, SRMR = 0.14, RMSEA = 0.12, $\chi 2/df = 2.45$). Based on the adjusted alpha level previous experiences of symptom improvement were associated with expected improvement (z = 3.97, $p < .001$)while previous experiences of symptom worsening (z = 2.45, $p = .014$) and side effects (z = 4.96, $p < .001$) were in turn associated with expected side effects. See Table 4 for all coefficients and Figure 2 for a graphical representation of all effects.

Table 4. Coefficients for the single predictors, including previous treatment experiences on the three expectation outcomes.

	Estimate (SE)	**Z-Value**	***p* - value**	**$\alpha_{Benjamini\text{-}Hochberg}$**
G-EEE improvement expectation				
Previous improvement experience	0.32 (0.08)	3.97	< .001*	.005
Previous worsening experience	0.12 (0.09)	1.37	.170	.020
Previous side effect experience	0.06 (0.09)	0.67	.501	.030
Factor NA	0.01 (0.04)	0.12	.905	.050
Factor PA	0.02 (0.04)	0.65	.519	.035
BFI-10 Tolerance	- 0.08 (0.05)	- 1.62	.106	.015
BFI-10 Openness	0.04 (0.18)	0.56	.573	.040
Age	0.02 (0.01)	2.03	.042	.010

Gender	0.06 (0.17)	0.37	.710	.045
Study	- 0.16 (0.18)	- 0.88	.379	.025
G-EEE worsening expectation				
Previous improvement experience	- 0.24 (0.09)	-2.63	.009	.005
Previous worsening experience	0.14 (0.10)	1.43	.153	.020
Previous side effect experience	0.03 (0.10)	0.33	.740	.040
Factor NA	0.00 (0.05)	-0.04	.968	.050
Factor PA	- 0.08 (0.06)	- 1.43	.152	.015
BFI-10 Tolerance	0.01 (0.06)	0.17	.864	.045
BFI-10 Openness	0.08 (0.05)	1.72	.086	.010
Age	- 0.01 (0.01)	- 0.92	.356	.030
Gender	0.08 (0.18)	0.44	.660	.035
Study	0.22 (0.20)	1.13	.260	.025
G-EEE side effect expectation				
Previous improvement experience	- 0.17 (0.09)	1.99	.047	0.020
Previous worsening experience	- 0.23 (0.09)	-2.45	.014*	0.015
Previous side effect experience	0.47 (0.10)	4.96	< .001*	0.005
Factor NA	0.12 (0.05	2.55	.011	0.010
Factor PA	- 0.05 (0.05)	- 0.85	.395	0.030
BFI-10 Tolerance	0.04 (0.06)	1.51	.131	0.025
BFI-10 Openness	0.07 (0.04)	0.68	.498	0.035
Age	- 0.00 (0.01)	- 0.51	.611	0.045

Gender	0.11 (0.18)	0.64	.526	0.040
Study	0.01 (0.19)	0.05	.964	0.050

Note: CFI = 0.59, SRMR = 0.13, RMSEA = 0.12, $\chi 2/df = 3.00$; * significant after alpha-level adjustment

[INSERT FIGURE 2 HERE]

4. DISCUSSION

In this study, we assessed the effects of prior treatment experience, broad personality traits as well as tolerance and openness distinctly on treatment expectations. Based on conservative estimates we did not find an association between trait factors and treatment expectations, although we found small and significant correlations between negative trait factors (perceived stress, somatization, agitation, dysthymia) and side effect expectations. In contrast to these overall negligible effects of personality traits, we found large effects of prior treatment experiences. Specifically, we found that prior experiences of symptom improvement with the same treatment were associated with higher symptom improvement. Further, treatment-related experiences of symptom worsening were associated with lower side-effect expectations, while side effect experiences predicted higher side-effect expectations. Interestingly, side effect expectations correlated positively with both symptom worsening and symptom improvement expectations in addition to the negative trait factors. While it might be surprising that higher side effect expectations are associated with higher expectations of symptom improvement, this association can be interpreted in the frame of a "no-pain, no-gain" mindset, indicating that participants expect effective treatments to go hand-in-hand with side effects [46].

Furthermore, our results are in line with previous research showing that past experiences with a treatment are some of the strongest determinators of treatment expectations [6,19,20]. Interestingly, we found distinct effects of different experiences on different expectations, supporting the notion that treatment expectations are not a unitary construct ranging from negative expectations to positive expectations. Our results indicate that positive experiences predict positive expectations and negative experiences, negative expectations. However, as the effect of improvement experience on worsening and side effect expectations was only non-significant based on a conservative estimate it remains possible

that all three experiences impact negative expectations, with side effect and worsening experiences having a stronger impact on this variable than improvement experience.

An additional interesting finding is the lack of impact of past worsening and side effect experiences on worsening and improvement expectations. The lack of association for side effect experience supports the idea that side effect expectations are distinct constructs from symptom-related expectations [47]. However, with regard to worsening experiences a reasonable hypothesis would have been, that improvement and worsening experiences have diametrically opposed effects on improvement and worsening expectations, which is not the case in our data. The distinct effects of improvement and worsening experiences observed in our study may be linked to inter-individual variation in feedback sensitivity. Basic research has demonstrated that some individuals learn better with positive feedback while others respond better to negative feedback [48,49]. Our findings suggest that participants in the analyzed studies may have been more sensitive to their improvement experience than their worsening experience, resulting in a greater influence on current treatment expectations. To further clarify the impact of learning experiences and feedback sensitivity, future research could incorporate assessments of learning strategies to determine which type of experience (improvement or worsening) has a more profound effect on treatment expectations.

Our results may also be explained in the context of reward learning, with research from various domains showing that reward (in our case symptom improvement) has longer lasting impacts on memory than punishment (symptom worsening) [50–53], which could explain how positive experiences have a stronger impact on current treatment expectations than negative experiences [54]. However, a number of studies have shown the opposite pattern (increased learning due to aversive stimuli) [55–57]. This difference might occur due to short-term learning being related to aversive stimuli, while long-term acquisition of expectations might be more strongly influenced by rewarding stimuli. Nonetheless, further studies are warranted to systematically investigate the interplay between the type of reward, the learning process, and the resultant expectations.

Another explanation for differences in experiential effects could be the role of context. Different lines of research have emphasized the importance of context factors for the effects of psychoactive drugs [58], placebo effects [59], learning [60], and even behavioral outcomes such as

substance use [61]. The general conclusion is that learned behavior, expectations, or predictions about the world [62] do not necessarily generalize across contexts. Unfortunately, we did not collect more detailed data regarding the context of our participants previous experiences with their treatment but it is possible that positive experiences (symptom improvement) have occurred in more similar contexts than negative experiences (symptom worsening), resulting in the distinct effects described above. As treatment expectations generally differed across the included projects, study contexts were apparently dissimilar enough to elicit distinct expectations, which might make the effects of previous experience less homogeneous.

Our results also provide further evidence that broad personality traits are, if at all, moderate to weak predictors of treatment expectations, and provide reason to doubt the existence of a clear placebo responder personality type. This is in line with recent findings from a comprehensive meta-analysis [22] failing to detect an effect of personality traits on placebo response. However, we also report a small but significant positive correlation between side effect expectations and our negative affect (i.e., stress, somatization, agitation, dysthymia). This relationship indicates that individuals who are prone to experiencing states of negative affect (i.e., stress, anxiety, or agitation) report higher side effect expectations, which might in turn predict nocebo responses. Nonetheless, the correlation is relatively small and thus our results point towards the need for an extended search for other determinants of treatment expectations and resulting placebo and nocebo responses. Promising directions might be individual neurobiological [63,64], genetic [65], or state instead of trait factors, more fine grained assessments of traits [26], as well as broader context variables such as experimenter/clinician behavior [66] or the influence of science communication and media reporting [27].

4.1 Limitations

First, the reported significant associations of treatment experiences and somatization tendencies with treatment expectations should be considered as preliminary findings, which however will form the basis for further confirmatory studies (22,23).

Second, our analysis was conducted across a variety of heterogeneous participant groups and experimental conditions. Therefore, we could not detect potential more distinct effects regarding expectations about specific interventions. However, we aimed to partly control for this issue by

standardizing our main outcomes, thus providing a measure that is generalizable across contexts. Additionally, due to this heterogeneity our results can be considered more robust to individual variation and may provide higher replicability.

Third, our psychological trait predictors have high levels of overlap, with multiple measures of different personality facets. This issue decreases our ability to detect interesting but small effects, since only large effects survive such a large number of predictors. We partially addressed this by conducting a factor analysis to reduce the number of predictors and merge plausibly overlapping variables.

Fourth, our measure of treatment expectation (G-EEE) only asks for general symptom expectations. This framing does not allow for an analysis for more specific expectations regarding the received interventions. While this leads to a loss of information about more specific expectations, the general wording of the measure did allow for an application across heterogeneous contexts, which can be considered a strength of our study.

Additionally, the G-EEE was collected in experimental studies only, meaning these expectations are not reflective of treatment expectations in clinical settings. All participants knew they were participating in a study and were given a certain amount (differing by study) of information about the upcoming intervention. Thus, our results are not transferable to clinical settings without replication. However, our results provide a useful starting point for clinical studies or investigations of clinical processes to examine the influences on expectations in these settings.

Finally, symptom worsening and side effect expectations exhibited floor effects insofar as the majority of participants reported 0 worsening or side effect expectations. This leaves little variance to be explained by our analyses, reducing the confidence in our results.

4.2 Conclusion

This study is the first large analysis merging data from different studies to investigate the association of psychological traits and prior treatment experiences on treatment expectations. Overall, previous experience with a treatment is a better predictor of expectations than psychological traits. There is some preliminary evidence that experiences of symptom improvement are associated with expectations regarding symptom improvement and worsening, while experiences of symptom worsening and side effects are only related to side effect expectations. Additionally,

the tendency to perceive somatic symptoms more strongly may be a predictor for side effect expectation and thus mediate the occurrence of nocebo responses. Future studies should aim to assess non-trait factors such as state variables or biological measures to investigate the determinants of treatment expectations.

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7. DECLARATION OF INTEREST

None.

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Figures

Figure 1. Exemplary SEM model including all parameters.

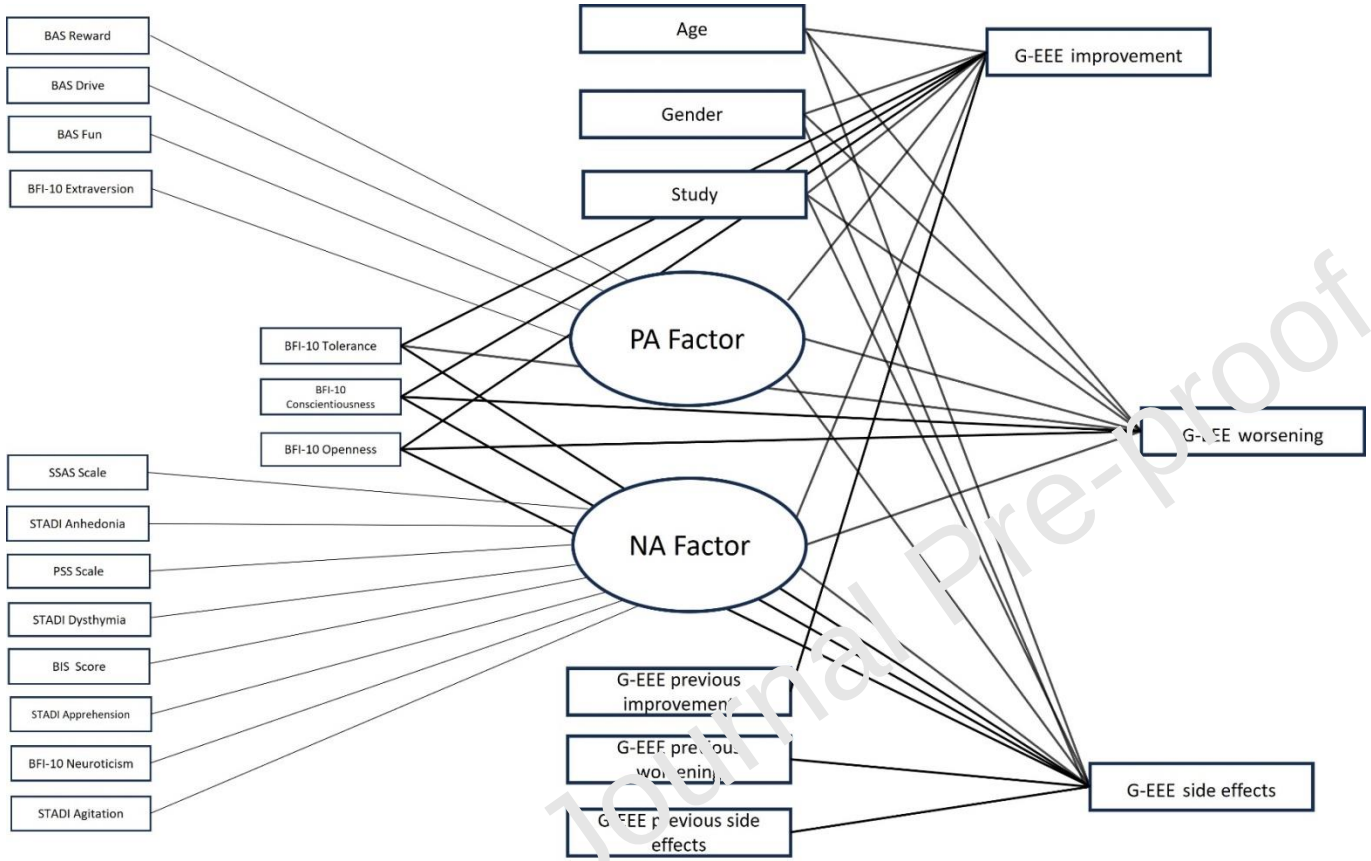
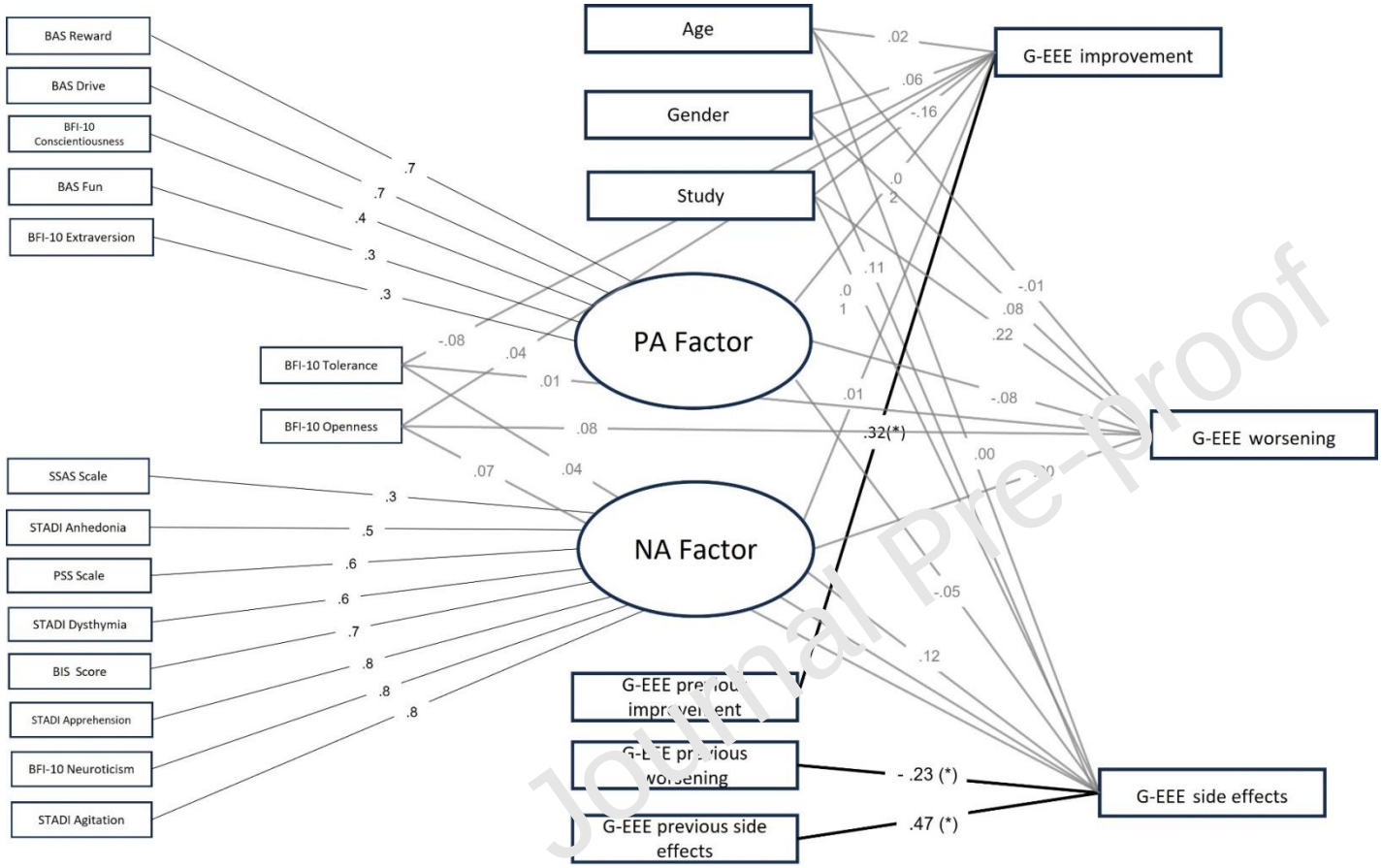


Figure 2. Resulting SEM model with baseline expectations as outcomes and containing previous experiences as parameters.



Highlights

- ‘No pain, no gain’: Positive and negative expectations are positively correlated.
- Higher negative affect is associated with increased side effect expectations.
- Previous treatment experiences are strong determinants of treatment expectations.