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Impact of childhood trauma on the course of panic disorder

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Abstract

Objective: To investigate the impact of childhood trauma on the clinical course of panic disorder.

Method: Longitudinal data of 539 participants with a current panic disorder were collected from the Netherlands Study of Depression and Anxiety (NESDA). Childhood trauma was assessed with a structured interview and clinical course after two years with a DSM-IV-based diagnostic interview and the Life Chart Interview.

Results: At baseline, 56.3% reported childhood trauma, but this was not predictive of persistence of panic disorder. Emotional neglect and psychological abuse were associated with higher occurrence of anxiety disorders other than panic disorder (social phobia) and with higher chronicity of general anxiety symptoms (anxiety attacks or episodes and avoidance). Baseline clinical features (duration and severity of anxiety and depressive symptoms) and personality traits (neuroticism and extraversion) accounted for roughly 30 to 60% of the total effect of childhood trauma on chronicity of anxiety symptoms and on occurrence of other anxiety disorders.

Conclusion: After two years, childhood trauma is associated with chronicity of anxiety symptoms and occurrence of social phobia, rather than persistence of panic disorder. These relationships are partially accounted for by duration and severity of anxiety and depressive symptoms, and neuroticism and extraversion.

Keywords: childhood trauma; panic disorder; course; anxiety disorder; longitudinal

Significant outcomes

- Childhood trauma is associated with an increased occurrence of other anxiety disorders (social phobia) rather than with the persistence of panic disorder at 2-year follow-up.
- Childhood trauma is associated with increased chronicity of anxiety symptoms at 2-year follow-up.
- Baseline clinical characteristics (duration and severity of anxiety and depressive symptoms) and personality traits (specifically neuroticism and extraversion) are important mediators between childhood trauma and the 2-year course of anxiety symptoms and anxiety disorders other than panic disorder.

Limitations

- We exclusively relied on retrospective self-reports of childhood trauma.
- We did not differentiate between panic disorder with and without agoraphobia or between early and late onset panic disorder.
- The follow-up period was limited to two years.

Introduction

Recent studies consistently conclude that childhood trauma is associated with an increased risk and comorbidity of anxiety disorders in adulthood, stating its important role in the aetiology of these disorders. Moreover, it was demonstrated that a self-reported history of childhood trauma in adults presenting with anxiety disorders was associated with higher levels of chronicity, thus implying its highly relevant impact on course (1-4). As many studies state that there are prognostic differences across anxiety disorders, despite high comorbidity rates, diagnostic distinction is important (5-7). In the current paper we focus on panic disorder (PD), which is characterized by recurrent and unexpected time-limited periods of intense fear or discomfort with at least four out of thirteen additional symptoms (8, 9). With a prevalence of 3.8% (NEMESIS; (10)), PD is a common disorder with a high burden. There is a substantial body of converging evidence suggesting a central role of childhood abuse in the pathogenesis of PD (11-21). Some studies focused on the course of PD (7, 12, 21, 22), but the role of childhood trauma within this domain has never been examined from a longitudinal perspective.

Previous literature has also shown that different types of childhood trauma are non-specific risk factors for adult psychiatric disorders (1, 23), making it equally interesting to examine the differential effects of subtypes of childhood trauma on the clinical course of PD. Emotional neglect, psychological and physical abuse have been linked to comorbid depression and anxiety in later life, and emotional neglect and psychological abuse to the chronicity of both depressive and anxiety symptoms (1, 2). Seganfredo et al. (23), however, observed that only emotional abuse remained significantly related to PD in the multivariate analyses. Based on these findings, we expect the more "hands-off" subtypes of childhood trauma (excluding physical and sexual abuse) to be associated with an adverse course of PD.

It is also important to describe factors that may influence the relationship between childhood trauma and the natural course of the disorder. Relationships between childhood trauma and the outcomes of interest could be "mediated" by a third factor (24). Basic clinical characteristics such as high severity, early onset and longer duration of symptoms are among the most consistent and strongest predictors of poor clinical course (25, 26). In addition, recent studies have demonstrated that certain personality traits, such as higher levels of neuroticism and hopelessness, external locus of control, and lower levels of extraversion ("anxious-fearful" cluster), appear to have a strong mediating effect on the relationship between childhood maltreatment and 4-year remission of depressive and/or anxiety disorders (27, 28). The presence of a personality disorder also appears to increase the risk of a chronic, unremitting, and more symptomatic course of illness (29).

Finally, it needs to be noted that previous studies on associations of childhood traumatic experiences and the later development of PD were limited in that they had cross-sectional designs and too small samples for reliable statistical comparisons (13, 16), and lacked sufficient consideration of potential mediators.

Aims of the study

By drawing on the extensive sample of the Netherlands Study of Depression and Anxiety (NESDA) and the use of a longitudinal design, we examine the influence of childhood trauma on the clinical course of panic disorder as well as the differential effects of childhood trauma types and the role of clinical and personality factors in this relationship.

Material and methods

Study sample

We extracted data from the NESDA, an ongoing, longitudinal cohort study in which 2,981 adults (aged 18-65 years), recruited from the community, general practice, and secondary mental healthcare, are monitored to investigate the course and consequences of depressive and anxiety disorders. Participants not fluent in Dutch and those with a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder were excluded. The research protocol was approved by the ethics committees of the participating universities and written informed consent was obtained from all participants. For further details on NESDA, see Penninx et al. (30).

All participants were screened for depression and anxiety during the baseline interview using the DSM-IV-based (31) Composite International Diagnostic Interview (CIDI; WHO version 2.1), a highly reliable and valid instrument for assessing depressive (minor and major depressive disorder, dysthymia) and anxiety (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) disorders. After two years, a face-to-face follow-up assessment was conducted with a response of 87.1% (n=2,596). We identified 668 participants who were diagnosed at baseline with a current (6-month recency) panic disorder for whom details of childhood trauma were known. At the 2-year follow-up, the data of 539 participants (80.7%) were available.

Measurements

Childhood trauma

At baseline, childhood trauma was assessed retrospectively by a structured interview used in the Netherlands Mental Health Survey and Incidence Study (NEMESIS).

The participants were asked whether they had experienced any kind of emotional neglect and/or psychological, physical or sexual abuse before the age of 16. The definition of emotional neglect included lack of parental attention or support and ignorance of one's problems and experiences. Psychological abuse was defined as verbal abuse, undeserved punishment, subordination to siblings and being emotionally blackmailed. Physical abuse was defined as being kicked or hit with hands or an object, being beaten up or being physically abused in any other way. Sexual abuse was defined as being sexually approached against one's will in terms of being touched or made to touch someone in a sexual way. Participants answered 'yes' or 'no' to each of the four forms of childhood trauma and were asked to give an indication of the frequency on a 5-point scale (i.e. once, sometimes, regularly, often, very often). As was done in earlier studies (1, 32), a cumulative childhood trauma index, defined as the sum scores ranging from 0 to 8 was created, with a higher score indicating more types and a higher frequency of adverse childhood events, which index we assumed to be indicative of the emergence of psychopathology.

Course of panic disorder

We assessed the course of PD from various perspectives: from a narrow focus on panic through a broader consideration of course. Our first - strict - outcome measure was psychiatric status after two years in terms of the presence of a diagnosis of PD as based on the CIDI DSM-IV (6-month recency). In additional analyses we also looked at the occurrence of anxiety disorders other than PD, including generalized anxiety disorder (GAD), social phobia or agoraphobia (CIDI DSM-IV, 6-month recency), again based on the 2-year CIDI.

The second - broader - outcome measure was the clinical course trajectory of anxiety symptoms (anxiety attacks or episodes and avoidance symptoms) as derived from the outcomes of the Life Chart Interview (LCI) (33) that all participants with self-reported anxiety symptoms took as part of the 2-year CIDI. For each month participants rated the severity of their symptoms (no/minimal severity, mild, moderate, severe, or very severe). A minimal score of "mild" was required for symptoms to be considered present. Based on the presence of anxiety symptoms over time, we inferred three clinical course trajectories: a) early sustained remission achieved within six months without recurrence of any symptoms during follow-up, b) late remission with or without recurrence: remission after six months without recurrence, or remission with recurrence of anxiety symptoms later on, and c) chronic course, with at least mild symptoms throughout the 2-year follow-up period. LCI-based remission of anxiety disorder was defined as the absence of symptoms for three consecutive months.

Determinants of clinical course

Besides the *socio-demographical data* age, gender and years of education, we considered the following *clinical characteristics*: the severity of depressive and anxiety symptoms as measured with the 30-item Inventory of Depressive Symptomatology (IDS) (34), the 15-item Fear Questionnaire (35), and the Beck Anxiety Inventory (BAI) (36), respectively. Information on the duration of anxiety (or avoidance) symptoms prior to baseline was derived from the LCI (33) conducted at baseline, where participants indicated the percentage of time (s)he had spent on anxiety (or avoidance) symptoms in the four years prior to baseline. Age of onset of PD was derived from CIDI. Duration of anxiety symptoms and avoidance, BAI scores and age of onset of PD were transformed (square root) for statistical purposes (normality condition).

The *personality characteristics* neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness were assessed using the Neuroticism-Extraversion-Openness Five Factor Inventory (NEO-FFI) (37), a 60-item self-report questionnaire measuring these "big 5" personality domains. Each domain consists of 12 items. Scoring for each item ranged from 1 (totally disagree) to 5 (totally agree).

Statistical analysis

We used descriptive statistics to determine the prevalence of childhood trauma and baseline characteristics. Baseline characteristics were compared across the childhood trauma indices using analyses of variance for continuous variables and chi-squared tests for categorical variables.

Associations (χ^2) between specific childhood trauma types and the 2-year course measures (i.e. diagnosis after 2 years and clinical course trajectory over 2 years) were examined. We used binary or multinomial logistic regression analyses to assess the odds ratios for the presence of PD ('no panic disorder' as reference group), other anxiety disorders ('no other anxiety disorder' as reference group), and clinical course trajectories ('early remission' as reference group) after 2 years according to childhood trauma type and index. P-values were derived by likelihood ratio tests.

We subsequently tested baseline clinical disease and personality characteristics as possible mediators of the associations between the childhood trauma index and 2-year course of PD that could at least partially explain why childhood trauma is associated with a worse course. To do so, we used the multiple mediation model proposed by Preacher and Hayes. (25) Mediation was investigated by directly testing the significance of the indirect effect of the independent variable (IV) on the dependent variable (DV) through the mediator (M) quantified as the product of the effects of the IV

on M (a) and the effect of M on DV (b), partialling out the effects of the IV. Analyses were also performed with a multiple mediator model using a bootstrapping approach in which a point estimate of the indirect effect was derived from the mean of the 1,000 estimates of $a \times b$. The 95% percentile-based confidence intervals (CIs) were computed using the cut-offs for the 2.5% highest and lowest scores of the empirical distribution. Mediating effects were considered significant when the corrected bias and accelerated CI did not include zero. (2)

A two-tailed $p < 0.05$ was considered statistically significant; the statistical software used was SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline sample and outcome characteristics

Of the 539 participants with a current panic disorder at baseline (6-month recency) for whom follow-up data were available, the mean age was 41.2 years (SD=11.9), 69.8% was female, and childhood trauma was reported by 54.5%. After two years, 31.5% still reported a PD and 40.8% another anxiety disorder (GAD, agoraphobia, social phobia). With respect to the 2-year course of anxiety symptoms, 35.8% had recovered from their anxiety disorder within six months after baseline testing, 21.0% after more than six months or had done so but had suffered at least one relapse during follow-up, and 43.2% showed a chronic course.

As to baseline disease characteristics, the childhood trauma index revealed several pronounced associations (Table 1): higher childhood trauma scores were associated with being female and having a lower level of education, earlier age of onset of PD, higher severity scores for both anxiety and depressive symptoms, higher scores for neuroticism, and lower scores for extraversion, agreeableness, and conscientiousness.

Impact of childhood trauma

No statistically significant associations were found between childhood trauma types or the childhood trauma index and the 2-year diagnostic status of PD (Table 2). Looking at the outcomes for other anxiety disorders, we did find a significant association between the childhood trauma index ($r_s=0.17$, $p<0.001$) and emotional neglect and psychological abuse in particular, making these types of trauma a risk factor for the presence of anxiety disorders other than PD. Interestingly, additional analyses showed that this association appears to be driven by its connection with social phobia (OR=1.16,

$p < 0.001$), and not by agoraphobia ($OR = 1.07$, $p = 0.18$) or GAD ($OR = 1.03$, $p = 0.67$). After two years, emotional neglect and psychological abuse were the most prevalent in participants with a chronic course of anxiety symptoms (anxiety attacks or episodes and avoidance). Also, a higher childhood trauma index was associated with a higher probability of a chronic course ($r_s = 0.15$, $p = 0.001$).

Table 3 shows the results of the binary and multinomial logistic regression analyses adjusted for age, gender and education. In line with the results reported above, none of the childhood trauma types nor the trauma index was associated with a higher probability of having a PD after two years, whereas a higher childhood trauma index, emotional neglect and psychological abuse were significantly associated with a higher probability of having another anxiety disorder (resp. $OR = 1.14$, $OR = 1.81$, $OR = 1.77$), and with the chronicity of anxiety symptoms (resp. $OR = 1.14$, $OR = 1.84$, $OR = 1.84$). No significant associations were found for physical and sexual abuse.

Mediating factors between childhood trauma and clinical course

Table 4 presents the results of the mediation analyses. The duration and severity of anxiety and depressive symptoms, and neuroticism and extraversion significantly mediated the relationship between the childhood trauma index and the chronicity of anxiety symptoms at the 2-year follow-up. These mediators accounted for a quarter (duration of anxiety symptoms: $P_M = 0.28$ (aXb/c)) to two thirds (severity of depressive symptoms: $P_M = 0.65$) of the total effect. All baseline clinical characteristics (age of onset of PD, duration and severity of anxiety symptoms and severity of depressive symptoms), and personality traits (neuroticism, extraversion, agreeableness and conscientiousness) significantly mediated the relationship between childhood trauma and the presence of anxiety disorders other than PD at follow-up. The largest mediating effect in this

association seems to be driven by the severity of depressive symptoms ($P_M=0.58$) and neuroticism ($P_M=0.49$).

Additional mediation analyses showed that the association between emotional neglect and persistence of anxiety symptoms at two years is mediated by the age of onset of PD, the severity of anxiety and depressive symptoms, and neuroticism and extraversion. The association between emotional neglect and other anxiety disorders is mediated by all clinical and personality characteristics, excluding the duration of anxiety symptoms. The relationship between psychological abuse and chronicity of anxiety symptoms is mediated by all clinical characteristics and neuroticism and extraversion, and the association between psychological abuse and the occurrence of other anxiety disorders by all clinical and personality characteristics, with the exception of conscientiousness.

After adjustment of all potentially mediating baseline characteristics, the effect of the childhood trauma index on the diagnostic status of anxiety disorders other than PD and the clinical course of anxiety symptoms after two years was no longer statistically significant (resp. $p>0.2$ and $p>0.7$), indicating the major mediating contribution of baseline clinical and personality characteristics to these relationships.

Discussion

Examining the influence of distinct types of childhood trauma on the course of panic disorder after two years in a large cohort (NESDA) with a confirmed diagnosis, and investigating mediating factors, we found no significant effect for childhood trauma on the persistence of PD. We did find an association between childhood trauma, more specifically emotional neglect and psychological abuse, and the presence of social phobia at follow-up. One possible explanation for this major finding is related to the concept of negative cognitions (failure, rejection, negligence), installed by the experience of traumatic events in childhood, which appears to be an important factor for the development and maintenance of social phobia (38). Negative cognitions can occur at any time while experiencing an aversive social situation, which emphasizes the long-term influence of childhood trauma in social phobia. According to the Harvard/Brown Anxiety Disorders Research Program, social phobia is the most common of all anxiety disorders (13.3%) and was found to be the most chronic and unremitting (12-years follow-up) (12).

As to PD, the sudden and overwhelming impact of fear and panic attacks and the enhanced self-monitoring of bodily perceptions may become an isolated problem in which its course is less dependent on childhood trauma events. Furthermore, from a neurobiological perspective, neuroimaging studies have shown differences in the regulation and reactivity of brain regions between the distinct anxiety disorders (39), so the impact of childhood trauma may be different as well. Moreover, specific dysfunctions (such as the hypersensitive suffocation alarm system) might be less influenced by childhood trauma in the course of PD, although further research on this topic is required. As to the dysfunction of the stress system, the most widely accepted theory is that early stressful life events provoke alterations of the stress response that can endure

during adulthood, predisposing individuals to develop psychopathology (40). However, this does not provide an explanation for the above-mentioned differential effect of childhood trauma on the course of anxiety disorders, because the impact of childhood trauma on the function of the hypothalamic-pituitary-adrenal axis is not very specific in the different subtypes of anxiety disorders (41).

The above-mentioned psychological suppositions might also explain the second prominent finding in our study, the associations of childhood trauma, and more specifically emotional neglect and psychological abuse and the chronicity of anxiety symptoms after two years, broadly confirming the findings of Hovens et al. (27). However, when we accounted for the baseline severity of anxiety symptoms, the associations with anxiety disorders other than PD and the chronicity of these anxiety symptoms were no longer significant. Associations for physical or sexual abuse were not significant, which is in line with Spinhoven et al. (3), who, in contrast to several other authors, found that childhood traumas characterized by danger/threat, such as physical and sexual abuse, did not differentially predict anxiety disorders.

Baseline clinical and personality characteristics were clearly the most important predictors of the ensuing prognosis of anxiety symptoms and of the emergence of other anxiety disorders. Consistent determinants were duration and severity of depressive and anxiety symptoms, neuroticism and extraversion at baseline. This is consistent with Hovens et al. (27, 42) who found that more unfavourable baseline clinical disease characteristics, such as (high)er severity of subsyndromal depressive symptoms and lifetime psychopathology, mediated the differences such that the direct relationship between childhood trauma and psychopathology became nonsignificant. Like us, they also found that personality traits such as higher levels of neuroticism and lower levels of extraversion appear to be strong mediators in the relationship between childhood

trauma and the 2-year course of anxiety symptoms. In addition, Batelaan et al. (43) stated that indices such as severity, duration of anxiety, and disability are better at identifying those at risk for severe chronic course trajectories than DSM categories.

The current study has several methodological strengths. We used a longitudinal design and a large representative cohort of adults with a confirmed diagnosis of PD to investigate the effects of different types of childhood trauma on the course of the disorder. We, moreover, used validated structured diagnostic interviews and clinical outcome measures (standardized self-report questionnaires), and a known mediation model to determine the predictive value of baseline clinical features and personality traits on the course anxiety symptoms and the presence of anxiety disorders other than PD. We feel that by doing so, our results and methods can be applied in clinical practice to help identify individuals at risk of chronicity.

A main limitation of our study is that we exclusively relied on retrospective self-reports of childhood trauma. Yet, although several studies using such retrospective accounts indeed showed a memory bias, this bias was never sufficiently large to invalidate the reports (44). Also, given the long time elapsed since the adverse childhood events and the onset of PD, we were not able to consider other possible mediating mechanisms in the period prior to the NESDA baseline wave. Furthermore, we did not differentiate between PD with and without agoraphobia. When interpreting our results it hence needs to be taken into account that PD without agoraphobia has a more favorable course as compared to PD with agoraphobia (7, 12, 26, 43). We also did not differentiate between early and late onset PD. Here, previous studies state that an earlier age of onset is independently associated with exposure to childhood trauma and appears to be related to greater severity and an increased likelihood of recurrence after a period of remission (20, 45).

In conclusion, although childhood trauma is a well-known factor in the aetiology of PD, it does not necessarily mean that the course of PD is equally vulnerable to its impact. Childhood trauma appears to contribute to the chronicity of anxiety or the presence of anxiety disorders other than PD, more specifically social phobia. Clinical features such as the duration and the severity of anxiety and depressive symptoms, as well as personality characteristics, neuroticism and extraversion in particular, appear to be more reliable predictors to consider and are, moreover easily assessed in clinical practice.

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Declaration of interest

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Table 1. Baseline demographics of participants with an initial diagnosis of panic disorder (N=539) and clinical characteristics according to				
	Childhood trauma score			
	0	1-4	5-8	P-value
No. of participants	245 (45.5%)	207 (38.4%)	87 (16.1%)	
Age in years, Mean (SD)	40.1 (12.3)	42.2 (11.8)	41.8 (10.7)	.131
Female gender (%)	65.3%	70.5%	80.5%	.029
Education in years, Mean (SD)	11.7 (3.3)	11.6 (3.5)	10.4 (2.9)	.004
Age of onset, Mean (SD)	27.8 (12.8)	24.6 (12.9)	22.4 (14.0)	.001
Duration of anxiety symptoms at baseline (% of time), Mean (SD) **	45.8 (34.1)	45.7 (34.9)	54.9 (34.6)	.081
NEO-FFI, Mean (SD)				
Neuroticism	39.6 (6.7)	42.6 (7.0)	43.2 (7.5)	<.001
Extraversion	36.1 (6.7)	33.5 (7.0)	33.5 (6.7)	<.001
Openness	37.5 (6.2)	38.4 (6.8)	38.7 (5.9)	.190
Agreeableness	44.0 (5.2)	42.8 (5.9)	41.4 (5.0)	.001
Conscientiousness	41.7 (6.3)	39.4 (7.0)	40.0 (7.5)	.001
Severity of symptoms:				
IDS-SR, Mean (SD)	26.6 (12.7)	32.1 (13.3)	34.9 (11.6)	<.001
BAI, Mean (SD)	19.4 (10.7)	21.4 (11.0)	23.4 (11.9)	.009
Fear Questionnaire, Mean (SD)	34.1 (19.7)	38.7 (20.8)	44.8 (23.2)	<.001
*P-values by one-way ANOVA or Chi Square tests.				
**% of months with anxiety symptoms in the past 4 years.				
Abbreviations: NEO-FFI=Neuroticism Extraversion Openness-Five Factor Inventory; BAI=Beck Anxiety Inventory; IDS-SR=Self Rated Inventory of Depressive Symptom				

[illegible]

Table 2. Independent contributions of childhood trauma to the 2-year diagnosis of panic disorder and clinical course in participants with a bas							
	Diagnosis after 2 years				Clinical course after 2 years**		
	No panic disorder	Panic disorder	P-value*		Early remission	Late remission	Chronic course
							P-value*
Childhood trauma							
Emotional neglect	166 (45.0%)	75 (44.1%)	.850		69 (35.8%)	53 (46.9%)	119 (51.1%)
Psychological abuse	99 (26.8%)	55 (32.4%)	.187		42 (21.8%)	31 (27.4%)	81 (34.8%)
Physical abuse	69 (18.7%)	26 (15.3%)	.335		31 (16.1%)	21 (18.6%)	43 (18.5%)
Sexual abuse	78 (21.1%)	37 (21.8%)	.869		36 (18.7%)	27 (23.9%)	52 (22.3%)
*P-value by chi-squared test or Spearman's rho (CTI).							
**This includes Generalized Anxiety Disorder, Social Phobia and Agoraphobia.							

eline diagnosis of panic disorder (N=539)		
Diagnosis after 2 years		
No other anxiety disorders**	Other anxiety disorders	P-value*
123 (38.6%)	118 (53.6%)	.001
75 (23.5%)	79 (35.9%)	.002
48 (15.0%)	47 (21.4%)	.059
62 (19.4%)	53 (24.1%)	.195

Table 3. Associations between childhood trauma variables and the presence of a panic disorder and clinical course of anxiety symptoms					
Baseline variable	Panic disorder after 2 years		Clinical course of anxiety symptoms after 2 years		
	OR (95% CI)	P-value	Late remission	Chronic course	P-value (Likelihood Ratio Tests)
Emotional neglect	.96 (.67-1.39)	.85	1.61 (1.00-2.59)	1.84 (1.24-2.72)	.01
Psychological abuse	1.28 (.86-1.92)	.23	1.36 (.78-2.34)	1.84 (1.18-2.89)	.02
Physical abuse	.75 (.45-1.23)	.25	1.15 (.62-2.14)	1.12 (.67-1.88)	.88
Sexual abuse	.98 (.62-1.55)	.94	1.31 (.73-2.33)	1.21 (.74-1.98)	.62
Childhood trauma score**	1.01 (.93-1.09)	.86	1.09 (.98-1.22)	1.14 (1.04-1.24)	.01
*P-values and odds ratios (with 95% confidence intervals) by binary or multinomial logistic regression analysis adjusted for age, gender					
**The childhood trauma score was considered a continuous variable.					
***This includes Generalized Anxiety Disorder, Social Phobia and Agoraphobia.					
Abbreviations: OR=odds ratio; CI=confidence interval					

ns at 2-year follow-up* (N=539)		
Other anxiety disorders after 2 years***		
OR (95% CI)	P-value	
1.81 (1.28-2.57)	.001	
1.77 (1.20-2.60)	.004	
1.48 (.94-2.33)	.087	
1.31 (.85-2.01)	.218	
1.14 (1.05-1.23)	.001	
r and education.		

Table 4. Explained variance of baseline disease characteristics in the relationship betw

Independent Variable (IV)	Mediating variable (M)	No. DV/reference
Childhood Trauma Index (CTI 0 - 8)	<i>Late remission (DV)</i>	
	Age of onset of panic disorder (SR)	113/193
	BAI (SR)	113/193
	IDS-SR	113/193
	FQ	113/193
	Duration of anxiety symptoms (SR)	113/193
	Neuroticism	113/193
	Extraversion	113/193
	Agreeableness	113/193
	Consciousness	113/193
	 <i>Chronic course (DV)</i>	
	Age of onset of panic disorder (SR)	233/193
	BAI (SR)	233/193
	IDS-SR	233/193
	FQ	233/193
	Duration of anxiety symptoms (SR)	233/193
	Neuroticism	233/193
	Extraversion	233/193
	Agreeableness	233/193
	Consciousness	233/193
	 <i>Other anxiety disorders (DV)****</i>	
	Age of onset of panic disorder (SR)	220/319
	BAI (SR)	220/319
	IDS-SR	220/319
	FQ	220/319
	Duration of anxiety symptoms (SR)	220/319
	Neuroticism	220/319
	Extraversion	220/319
	Agreeableness	220/319
	Consciousness	220/319

IV denotes independent variable; M denotes mediating variable; DV denotes depende

*<.05

**<.01

***<.001

****This includes Generalized Anxiety Disorder, Social Phobia and Agoraphobia.

Abbreviations: BAI=Beck Anxiety Inventory; IDS-SR=Self Rated Inventory of Depressive Symptomatology

een the childhood trauma index (IV) and the 2-year course outcomes (DV) in participan

Effect of trauma on M (a)	Effect of M on DV (b)	Direct effect of trauma on DV (c')
-0.104***	-0.002	0.011
0.095***	0.028	0.011
1.592***	-0.012	0.032
1.895***	-0.005	0.022
0.014**	0.099	0.005
0.711***	0.017	0.001
-0.522***	0.027	0.026
-0.478***	0.011	0.018
-0.308*	-0.008	0.010
-0.104***	-0.109	0.084*
0.095***	0.352***	0.080*
1.592***	0.044***	0.045
1.895***	0.034***	0.056
0.014**	1.986***	0.081*
0.711***	0.055***	0.071
-0.522***	-0.070***	0.076
-0.478***	-0.016	0.099*
-0.308*	-0.022	0.100**
-0.104***	-0.125	0.119**
0.095***	0.373***	0.113**
1.592***	0.051***	0.073
1.895***	0.035***	0.091*
0.014**	1.678***	0.115**
0.711***	0.097***	0.083*
-0.522***	-0.082***	0.107**
-0.478***	-0.065***	0.112**
-0.308*	-0.035**	0.131***

nt variable; a denotes effect of V on M; b denotes effect of M on DV; c' denotes direct c

r; FQ=Fear Questionnaire; SR=square root

its with a baseline diagnosis of panic disorder (N=539)

Mediating effect (aXb; 95% CI)	Total effect (c)
0.000 (-0.017-0.018)	0.011
0.003 (-0.012-0.020)	0.013
-0.019 (-0.049-0.006)	0.013
-0.009 (-0.031-0.008)	0.013
0.001 (-0.009-0.014)	0.007
0.012 (-0.006-0.036)	0.013
-0.014 (-0.033-0.001)	0.013
-0.005 (-0.025-0.010)	0.013
0.002 (-0.006-0.019)	0.013
0.011 (-0.001-0.031)	0.095*
0.034 (0.017-0.066)	0.108**
0.070 (0.042-0.105)	0.108**
0.064 (0.038-0.100)	0.108**
0.027 (0.009-0.054)	0.101**
0.039 (0.021-0.069)	0.107**
0.037 (0.016-0.061)	0.107**
0.008 (-0.007-0.028)	0.107**
0.007 (-0.000-0.020)	0.107**
0.013 (0.001-0.034)	0.131***
0.036 (0.015-0.064)	0.141***
0.081 (0.052-0.119)	0.141***
0.066 (0.038-0.103)	0.141***
0.023 (0.006-0.045)	0.131***
0.069 (0.041-0.108)	0.140***
0.043 (0.020-0.071)	0.140***
0.031 (0.014-0.057)	0.140***
0.011 (0.002-0.029)	0.140***

effect; a X b denotes indirect effect; c denotes total effect.