

# Does prior traumatization affect the treatment outcome of CBT for panic disorder? The potential role of the *MAOA* gene and depression symptoms

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**Abstract** Although cognitive behavioral therapy (CBT) is highly effective in the treatment of anxiety disorders, many patients still do not benefit. This study investigates whether a history of traumatic event experience is negatively associated with outcomes of CBT for panic disorder. The moderating role of the monoamine oxidase A (*MAOA*) gene and depression symptoms as well as the association between trauma history and fear reactivity as a potential mechanism are further analyzed. We conducted a post-hoc analysis of 172 male and 60 female patients with panic disorder treated

with CBT in a multi-center study. Treatment outcome was assessed at post-treatment using self-report and clinician rating scales. Fear reactivity before treatment was assessed via heart rate and self-reported anxiety during a behavioral avoidance test. Among females, we did not find any differences in treatment response between traumatized and non-traumatized individuals or any two-way interaction trauma history × *MAOA* genotype. There was a significant three-way interaction trauma history × *MAOA* genotype × depression symptoms on all treatment outcomes indicating that in traumatized female patients carrying the low-activity allele, treatment effect sizes decreased with increasing depression symptoms at baseline. No such

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effects were observed for males. In conclusion, we found no evidence for a differential treatment response in traumatized and non-traumatized individuals. There is preliminary evidence for poorer treatment outcomes in a subgroup of female traumatized individuals carrying the low-active variant of the *MAOA* gene. These patients also report more symptoms of depression symptomatology and exhibit a dampened fear response before treatment which warrants further investigation.

**Keywords** Panic disorder · CBT · Trauma · *MAOA* · Fear reactivity · Depression

## Introduction

Anxiety disorders are highly prevalent in the general population [1, 2] and associated with substantial individual burden and societal costs [3, 4]. Although anxiety disorders can be effectively treated with psychological interventions [5, 6], a considerable proportion of patients does not benefit from existing treatments or report a return of fear after an initially successful treatment [7, 8]. Arguably, the identification of patient characteristics and associated mechanisms underlying poor treatment outcome is essential to inform the modification of existing interventions for anxiety disorders into a more individualized treatment approach with assigning patients to an optimized therapy protocol depending on specific pre-treatment characteristics.

Previous exposure to traumatic events is not only related to the risk for the development of trauma-related disorders such as post-traumatic stress disorder (PTSD) but also for anxiety and depressive disorders with a higher risk for females compared to males [9–14]. Much less is known about the importance of a trauma history for the treatment response of these disorders. Although traumatic events have been associated with neurobiological and psychological changes that might moderate the response to later treatment of mental disorders [15, 16], empirical data are still limited. There is some evidence that a history of traumatic events, particularly in early life, negatively affects response to pharmacological and standardized psychological treatments for depressive disorders suggesting special need for that subgroup of patients [17–19]. In contrast, only very few studies have addressed the association between previous trauma exposure and treatment response for anxiety disorders. Mixed results were observed for the treatment of social anxiety disorders [20–22]. Whereas one study found detrimental effects of previous exposure to trauma on treatment efficacy [20], two studies did not [21, 22]. Further, two studies found no evidence for a differential response to pharmacological or psychological interventions for panic

disorder in traumatized as compared to non-traumatized individuals [23, 24]. In summary, trauma exposure might affect treatment effects in anxiety disorders with, however, existing data being highly inconclusive due to a very small number of published studies with generally small sample sizes. Against this background, the present study aims to investigate the association between trauma history and treatment outcome for anxiety disorders for a large group of patients with panic disorder and agoraphobia being treated with highly standardized exposure-based cognitive behavioral therapy (CBT) in a multi-center trial.

One reason for null findings when looking at the effects of traumatization on treatment of anxiety disorders might be the neglect of additional moderating factors in previous studies, such as genetic disposition. For a broad range of adverse neuropsychological and mental health consequences, evidence suggests that genetic influences moderate the effects of trauma exposure [25–29]. A gene that has been associated with pathological anxiety in general and with panic disorder in particular is the monoamine oxidase A (*MAOA*) gene [30]. *MAOA* is important for the degradation of monoamines, especially norepinephrine and serotonin [31]. A common genetic variation in the *MAOA* gene is a 30-bp variable number of tandem repeat (VNTR) polymorphism in the promoter region with longer alleles (3.5, 4 and 5) being associated with higher transcription rates compared to shorter alleles (2 and 3) [32]. Longer alleles have been shown to be associated with panic disorder, particularly in females [30, 33–35], although findings are not entirely consistent [36]. In accordance with case–control studies, a previous analysis from the MAC study framework, which used the same sample as the present study, demonstrated that females with longer alleles show a poorer treatment response to CBT for panic disorder as well as an altered fear reaction to a fearful situation [37]. Importantly, there is also first evidence that the *MAOA* gene is involved in the risk for mental disorders following traumatic events [38, 39]. Given these findings, we hypothesized that variation in the *MAOA* gene might moderate the association between traumatic experiences and treatment outcome. Since effects of traumatization on treatment outcome were already shown for depressive disorders [17], we also considered a potential role of depression symptoms before treatment. Given the limited sample size and little previous work, the simultaneous consideration of trauma history, *MAOA* gene and depression symptoms (three-way interaction) was laid out as an exploratory analysis.

To further explore possible mechanisms associated with trauma history, we also investigated whether traumatized individuals show altered fear reactivity assessed by self-report and autonomic measures in a fear-provoking standardized behavioral avoidance test.

## Methods

### Data source

Data were derived from a randomized clinical multi-center trial of 369 patients with panic disorder with agoraphobia according to the DSM-IV-TR diagnostic criteria randomized to one of the two standardized variants of CBT or a wait-list-control group and conducted in eight outpatient study centers. Treatment consisted of 12 sessions of manualized CBT treatment carried out over six weeks, followed by two booster sessions. The original study compared two exposure-based CBT variants: in situ exposures were either accompanied by the therapist ( $n = 163$ ) or planned and evaluated in detail in the therapy room with extensive instructions on how to engage in the in situ exposure exercises without the therapist being present ( $n = 138$ ). For the current analysis, patients of both active conditions were grouped together ( $N = 301$ ) since there were only few significant differences in CBT outcomes of limited effect size [40]. More details on recruitment procedure, inclusion and exclusion criteria and treatment specifics have been described previously [40, 41].

### Assessments

The DSM-IV diagnoses of panic disorder/agoraphobia and the experience of lifetime traumatic events according to the DSM-IV A1 criterion of PTSD were assessed by trained psychotherapists using the Composite International Diagnostic Interview (CIDI), a fully standardized computer-assisted diagnostic interview [42]. The diagnoses were subsequently verified by a senior clinician. Outcome measures that are reported in the present study include the Hamilton Anxiety Scale (HAM-A) [43], the Clinical Global Impression Scale—Severity Subscale (CGI) [44], patients self-report measures of the Panic and Agoraphobia Scale (PAS) [45], and the Mobility Inventory (MI) [46] indicating agoraphobic avoidance. Depression symptoms were assessed with the Beck Depression Inventory (BDI-II, German version) [47].

### Genotyping

Genetic data were available for 172 female and 60 male patients. All patients were genotyped for the *MAOA* VNTR according to published protocols [32, 37] with minor modifications and grouped into a low-activity (20 females and 19 males) and a high-activity (152 females and 41 males) *MAOA* variant as described previously [37]. The high-activity group consisted of 3.5, 4 and 5 allele males, and

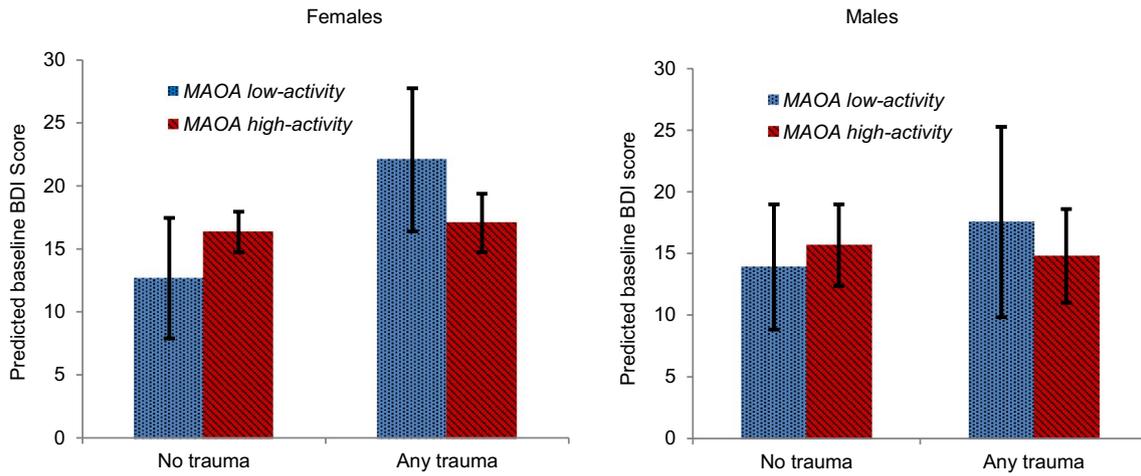
3/3.5, 3/4, 3/5, 3.5/4, 4/4, 4/5 and 5/5 allele females. All other individuals were grouped into the low-activity group (see Supplemental Table 1).

### Fear reactivity

Of the patients with available genetic data, 149 female and 57 male patients also participated in a standardized behavioral avoidance test (BAT) before and after treatment consisting of an exposure to a small, dark and locked test chamber. In the present analysis, only the baseline BAT data are considered since these are not confounded with treatment effects. During exposure, patients were placed in the chamber and instructed to stay as long as deemed possible. Patients were instructed to rate the intensity of their experienced fear during exposure on a scale from 1 to 10. The electrocardiogram was measured continuously during the whole procedure from which the mean heart rate during the exposure phase was derived. The BAT procedure is described in greater detail elsewhere [37, 48, 49].

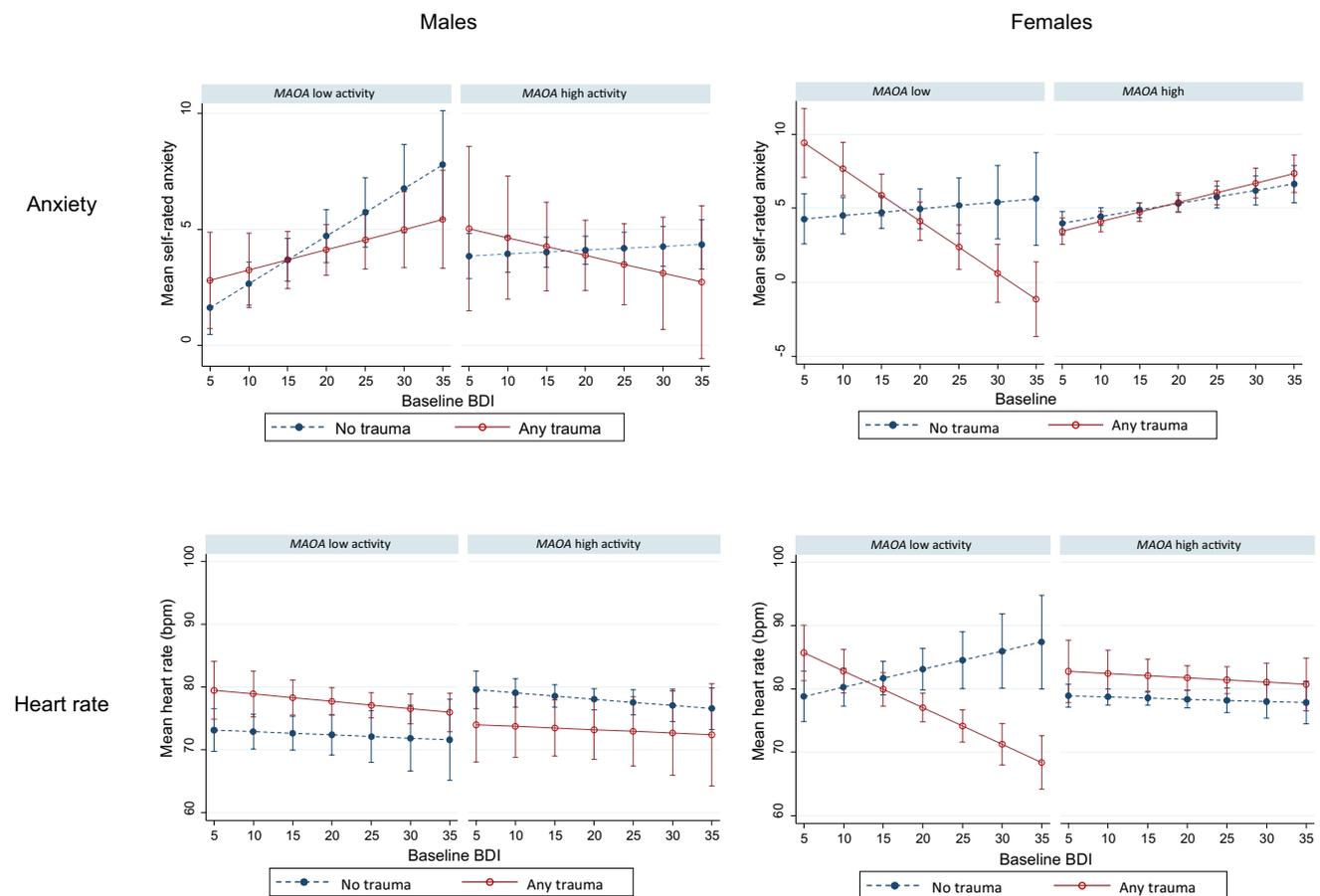
### Statistical analyses

Lifetime exposure to traumatic events was coded as a dichotomous variable (yes/no). We did not analyze the number of traumatic events since the small variance in the sample (range 0–4 events; 3.9% of the sample reported more than 2 events) would not allow meaningful analyses. Effect sizes (ES) in therapy outcomes were calculated as mean differences of standardized outcome scores between pre- and post-treatment, each divided by the pooled pre-treatment standard deviation. The last observation carried forward (LOCF) method was applied in cases of missing data to increase the available sample. Thus, outcome estimates can be considered as conservative. The dropout rate was 17.1% for the total sample and 15.1% for the subsample with available genetic and BAT data. Tests for selective dropout revealed no association ( $p > 0.05$ ) between dropout and sex, trauma history, *MAOA* genotype, baseline depression and severity of anxiety symptoms (as measured by CGI, PAS and MI) except for a higher baseline HAM-A score in dropouts [OR = 1.3 (95% CI 1.01–1.7)  $p = 0.041$  for z-standardized HAM-A score]. Associations between trauma exposure and baseline severity, therapy outcome and fear reactivity, respectively, were investigated using linear regressions. For the analysis of interactions between previous trauma exposure  $\times$  *MAOA* genotype (high vs. low-activity)  $\times$  depression symptoms (BDI score) at baseline, separate models were fitted that added the main effect term of the traumatic event variable and the interaction term with the respective moderator (two-way and three-way interactions). We also conducted all analyses including *MAOA* genotype separately



**Fig. 1** Interaction trauma experience × MAOA gene predicting baseline depression symptoms by gender. BDI Beck Depression Inventory, MAOA monoamine oxidase A. Error bars indicate 95% confidence

intervals. Two-way interaction among females is statistically significant ( $p < 0.05$ )



**Fig. 2** Interaction trauma experience × MAOA gene × baseline depression symptoms predicting fear reactivity in a behavioral avoidance test before treatment by gender. MAOA monoamine oxidase A,

BDI Beck Depression Inventory. Error bars indicate 95% confidence intervals. All three-way interactions among females are statistically significant ( $p < 0.05$ )

for males and females since previous studies suggest sex differences in the effect of *MAOA* genotype on treatment outcomes [30, 37]. Results for the total sample are reported in the online supplement (Supplemental Tables 2 and 3). All regression models with treatment outcome as dependent variable were adjusted for the baseline value of the respective outcome and the treatment condition of the original study design (accompanied vs. not accompanied by the therapist) in a first model and additionally for the potential confounding effect of a PTSD diagnosis ( $n = 8$  cases with PTSD) in a second model. Statistical inference was based on the robust Huber–White–sandwich estimator of standard errors [50] because this revealed considerably different results compared to the conventional model-based estimation of standard errors indicating that the robust method should be preferred. Statistical significance was evaluated at the two-sided 5% level. Since we considered multiple outcomes to test one hypothesis (i.e., association with treatment response), we run a multiple equation regression as sensitivity analysis. Multiple equation regressions estimate coefficients and standard errors taking into account correlated errors in the included models. The results were similar to the single models which are, therefore, reported. In graphical illustrations of results, the procedure MARGINS was used to calculate predicted probabilities. All analyses were conducted with Stata 12.1 [51].

## Results

### Trauma history and baseline severity

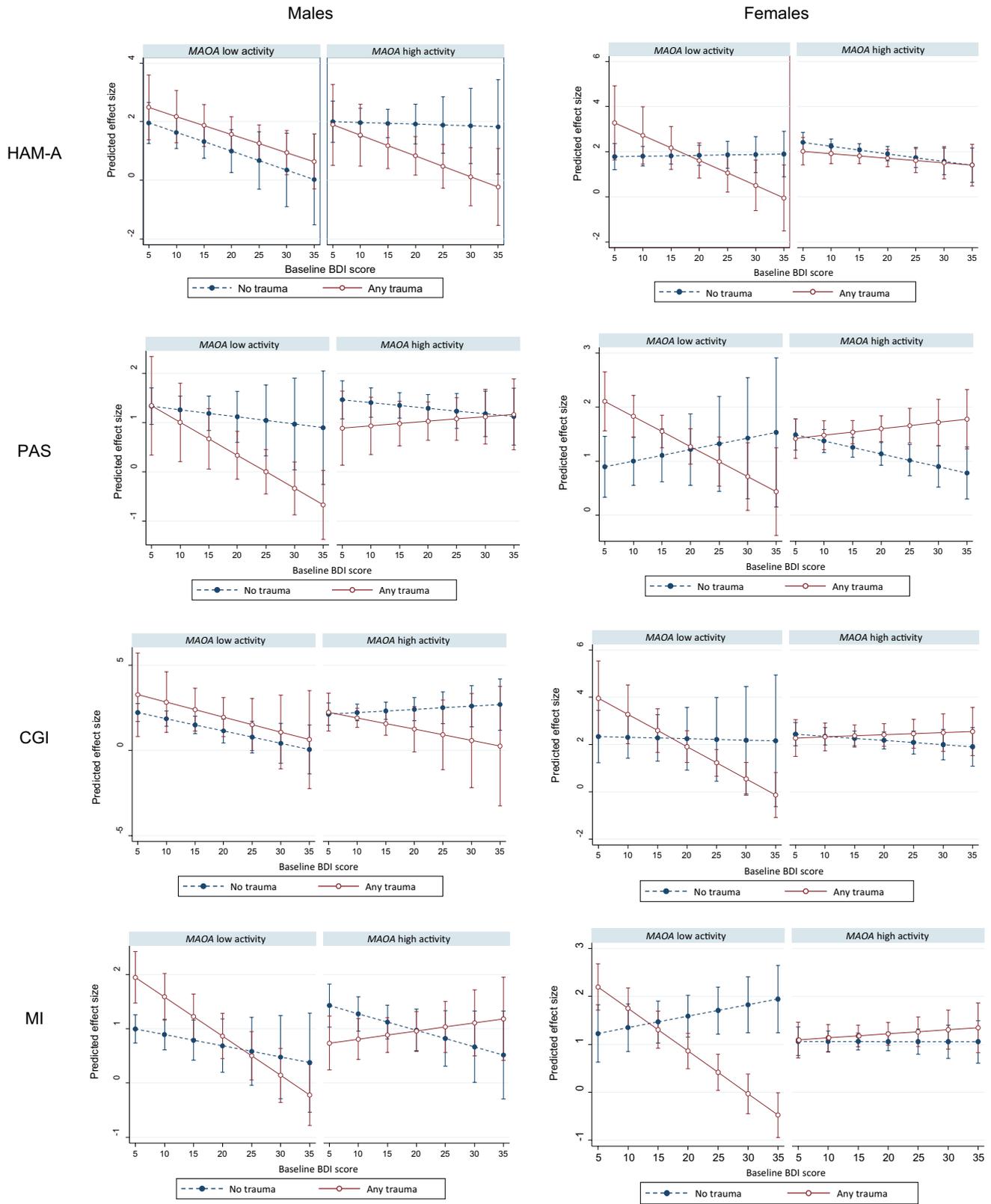
Among the patients with available genetic data, 30.0% of all male and 37.8% of all female patients reported at least one lifetime traumatic event. There were no differences in the probability of experiencing a traumatic event between low-active and high-active allele carriers. Among female patients, traumatized and non-traumatized individuals did neither differ in baseline severity of anxiety symptoms as assessed by HAM-A, PAS, CGI and MI nor in depression symptoms. The interaction between trauma history  $\times$  *MAOA* genotype on baseline severity measures was not significant except that in individuals carrying the low-activity allele, the HAM-A score was higher in traumatized than non-traumatized individuals, resulting in a significant interaction [ $b = 7.7$  (95% CI 1.0–14.3)  $p = 0.024$ ]. Among female patients carrying the low-active allele baseline depression symptoms were also higher in traumatized than in non-traumatized patients [interaction:  $b = 9.6$  (95% CI 1.7–17.6)  $p = 0.018$ ] (Fig. 1).

Among male patients, we found no main effects of trauma history or interactions with *MAOA* genotype on baseline severity and baseline depression symptoms although the patterns of results go into the same direction as for females.

**Table 1** Genotype, baseline variables and treatment effects by gender and trauma history

	No trauma		Any trauma	
	Males $n = 42$	Females $n = 107$	Males $n = 18$	Females $n = 65$
Genotype, $n$ (%)				
<i>MAOA</i> low activity	11 (26.2)	12 (11.2)	8 (44.4)	8 (12.3)
<i>MAOA</i> high activity	31 (73.8)	95 (88.8)	10 (55.6)	57 (87.7)
Psychological assessment at BL, mean (SD)				
HAM-A	24.3 (4.9)	23.7 (4.9)	26.1 (7.0)	25.1 (5.8)
PAS	26.9 (10.7)	26.5 (9.5)	28.6 (8.1)	27.9 (10.4)
CGI	5.3 (0.8)	5.2 (0.7)	5.3 (0.6)	5.2 (0.8)
MI	2.6 (0.7)	3.0 (0.9)	3.0 (0.9)	3.1 (0.8)
BDI	15.2 (9.0)	15.9 (8.2)	16.0 (8.7)	17.7 (9.2)
Treatment effects sizes, mean (SD)				
HAM-A	1.8 (1.3)	2.0 (1.6)	1.4 (1.3)	1.7 (1.3)
PAS	1.3 (0.8)	1.2 (1.0)	0.8 (1.0)	1.5 (1.1)
CGI	2.1 (1.4)	2.2 (1.6)	1.8 (1.8)	2.3 (1.8)
MI	1.0 (0.8)	1.2 (0.9)	0.9 (0.6)	1.3 (0.9)

*MAOA* monoamine oxidase A, *BL* baseline, *HAM-A* Hamilton Anxiety Scale, *PAS* Panic and Agoraphobia Scale, *CGI* Clinical Global Impression Scale, *MI* Mobility Inventory, *BDI* Beck Depression Inventory



**Fig. 3** Interaction trauma experience  $\times$  *MAOA* gene  $\times$  baseline depression symptoms predicting treatment outcomes by gender. *HAM-A* Hamilton Anxiety Scale, *PAS* Panic and Agoraphobia Scale, *CGI* Clinical Global Impression Scale, *MI* mobility inventory, *BDI* Beck Depression Inventory, *MAOA* monoamine oxidase A. Error bars indicate 95% confidence intervals. Models are adjusted for baseline values of the respective outcome and treatment condition of the original study design (accompanied vs not accompanied by the therapist). All three-way interactions among females are statistically significant ( $p < 0.05$ ). Three-way interactions among males are only statistically significant for MI scores

### Trauma history and fear reactivity

Among females, we did not find any differences between traumatized and non-traumatized individuals in self-reported anxiety or mean heart rate during exposure to a fearful situation before treatment. There were also no two-way interactions with the *MAOA* genotype. However, we found a three-way interaction trauma history  $\times$  *MAOA* genotype  $\times$  depression on both self-reported anxiety [ $b = 0.4$  (95% CI 0.2–0.7)  $p < 0.001$ ] and mean heart rate [ $b = 0.8$  (95% CI 0.3–1.4)  $p = 0.003$ ] during the exposure period indicating that in traumatized female patients carrying the low-activity allele, self-reported anxiety and mean heart rate decreased with increasing baseline depression symptoms at baseline (Fig. 2). Adjusting for the past 12-month PTSD diagnosis did not change these results. Among males, we did neither find differences between traumatized and non-traumatized individuals in self-reported anxiety or mean heart rate nor any two-way or three-way interactions with *MAOA*-genotype or baseline depression symptoms.

### Trauma history and treatment outcome

Table 1 shows the treatment effects for traumatized and non-traumatized patients. Among females, we did not find any differences in treatment response between traumatized and non-traumatized individuals. We did also not find a two-way interaction trauma history  $\times$  *MAOA* genotype on any of the examined outcome measures. However, there was a significant three-way interaction trauma history  $\times$  *MAOA* genotype  $\times$  depression symptoms on treatment outcome assessed by *HAM-A* [ $b = 0.1$  (95% CI 0.01–0.2)  $p = 0.027$ ], *PAS* [ $b = 0.1$  (95% CI 0.04–0.2)  $p = 0.004$ ], *CGI* [ $b = 0.2$  (95% CI 0.01–0.3)  $p = 0.037$ ] and *MI* [ $b = 0.1$  (95% CI 0.1–0.2)  $p < 0.001$ ] indicating that in traumatized female patients carrying the low-activity allele, effect sizes decreased with increasing baseline depression symptoms at baseline (Fig. 3).

Among males, we found a decreased treatment response in traumatized as compared to non-traumatized patients. However, this effect was limited to the *PAS* score [ $b = -0.6$  (95% CI  $-1.1$  to  $-0.1$ )  $p = 0.012$ ]. Further, no significant

two-way or three-way interactions with the *MAOA* genotype and baseline depression symptoms were found among males. Adjusting for the past 12-month PTSD diagnosis did not change the results patterns for females or males.

### Discussion

In a post hoc analysis, we investigated the association between trauma history and treatment outcome in patients with panic disorder also considering the moderating role of the *MAOA* gene. In a sample of patients treated with manualized CBT, we found no effect of trauma history on treatment response in both female and male patients. This finding is in line with previous studies [52, 53], suggesting that CBT for panic disorder appears to be equally effective in traumatized and non-traumatized individuals. Like the majority of individuals exposed to traumatic events do not develop mental disorders [9, 10], psychological and neurobiological changes that could have an effect on response to CBT [15, 16] are also likely to occur only in a subgroup of those with traumatic experiences. This implies that CBT for panic disorder is generally effective in patients with a history of traumatic events and that research should focus on the identification of such subgroups.

In our study, we aimed at identifying such subgroups by taking into account the potential moderating role of the *MAOA* gene and depressive symptoms before treatment. There was no interaction between trauma history and *MAOA* gene on treatment response. However, a subgroup of traumatized females carrying the low-activity allele and reporting more depressive symptoms responded less to CBT treatment. This subgroup also showed emotional numbing during fear provocation prior to treatment. It has to be noted that these findings should be treated as preliminary since the number of individuals included in this subgroup was very small. Notwithstanding, if further supported in future investigations, these findings could have important theoretical and practical implications.

The relevance of the *MAOA* gene for the treatment outcome of CBT for panic disorder has already been demonstrated with the high-activity allele (also conveying risk for developing a panic disorder) being associated with poorer treatment outcomes [37]. Our preliminary findings suggest that the relative advantage of the low-activity allele in panic disorder patients might not apply for the subgroup of traumatized individuals. At this point, we can only speculate about possible mechanisms. Genetic variation in the *MAOA* gene might influence treatment outcomes for panic disorder via the availability of norepinephrine and serotonin [37] which are involved in extinction learning [54] and the regulation of fear conditioning and retrieval [55, 56]. Through a decreased availability of norepinephrine and serotonin in

high-activity allele carriers, these individuals might constitute a high-risk group for panic disorder and benefit less from CBT as previously observed [30, 37]. However, norepinephrine and serotonin seem to be related to fear mechanisms in a bimodal rather than in a linear manner with very low and very high levels being related to increased fear conditioning [55] and impaired extinction learning [57]. The experience of traumatic events is associated with a long-lasting increase in overall monoamine levels including both norepinephrine and serotonin [58]. In interaction with a genetically driven altered set-point towards higher monoamine levels (i.e., upon presence of the low-activity isoform), such additional trauma-related changes of neurotransmitter levels might raise serotonin and norepinephrine to a pathological range, while less negative effects are conveyed in *MAOA* high-activity allele carriers. This might give a conceivable explanation for the diminishing effect of traumatic events on the advantage of the *MAOA* low-activity allele in the context of CBT.

High levels of serotonin and norepinephrine are further related to aversive emotional states such as hyperarousal and anxiety [55, 59]. It is likely that some individuals exhibiting these states might (either intentionally or automatically) counteract these effects by a downregulation of intense emotional responses via emotional and behavioral avoidance or dissociation—both of which are frequently observed in traumatized individuals [60, 61]. Dissociation and experiential avoidance might prevent the re-evaluation of fear-related situations during CBT which has been shown to be a potential mechanism underlying fear reduction [62]. In line, we observed the poorest treatment response in the avoidance behavior of these patients that seemed to be very stable. These assumptions are also supported by our finding that the subgroup with poor treatment outcomes was characterized by blunted fear reactivity when exposed to a fearful situation during the behavioral avoidance test. In accordance with this observation, reduced reactivity during the fear-provoking task has previously been associated with high levels of negative affect including depressive symptoms in patients with anxiety disorders [63, 64]. The fact that this subgroup of patients also reported more depressive symptoms at baseline is also highly conceivable since the frequent avoidance of emotional states is associated with the risk for depression symptoms [65, 66]. In summary, we hypothesize a theoretical model suggesting negative consequences of high levels of monoamines on cognitive processes and anxiety in traumatized low-activity *MAOA* allele carriers and an attempt to counteract these high levels with behavioral and emotional avoidance tendencies that diminish the effects of CBT. Although this model remains hypothetical so far, it fits well with both our findings and previous observations. Moreover, it provides a useful framework for future investigations on the

association between traumatic events and treatment outcomes including its genetic and non-genetic moderators. Importantly, it also provides several potential targets to adapt and improve existing interventions.

This study has some important limitations. First, as stated above, the careful consideration of a three-way interaction led to very small analysis groups. Thus, the respective findings have to be interpreted with caution and should be seen as exploratory. Second, this study is based on post hoc analyses of a randomized clinical trial. Thus, patients were not randomized based on the independent variables. Third, comorbid disorders other than PTSD were not considered in the present analyses but might have affected treatment outcomes. Fourth, patients were treated within academic centers according to a manual-based CBT and any generalization to less controlled natural therapy settings has to be done with caution. Finally, the existing literature suggests that the associations found in this study are more likely to be attributable to early traumatization than to traumatization in general which should be explored in greater detail in future investigations.

Taking these limitations into account, we provide evidence that CBT for panic disorder is equally effective in traumatized and non-traumatized individuals. There is first evidence that a subgroup of traumatized individuals carrying the low-active variant of the *MAOA* gene might not as much benefit from exposure-based CBT for panic disorder. These patients also report more symptoms of depression and show emotional numbing during fear provocation prior to treatment. These findings warrant further investigation specifically designed to investigate the interaction between trauma exposure, *MAOA* gene and depressive mood as well as potential mechanisms. Such investigations might reveal further insights into treatment-resistant subtypes of anxiety disorders and allow considering more strongly individual characteristics of heterogeneous patients currently grouped in distinct diagnostic categories exclusively based on subjective symptom reports. This might result in the adaptation of interventions to increase the number of patients that can be effectively treated.

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### Compliance with ethical standards

**Ethical standards** All participants provided informed consent. The study protocol was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (EK164082006).

**Conflict of interest** HUW has served as a general consultant (non-product related) for Lundbeck.

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