The role of \(FKBP5\) genotype in moderating long-term effectiveness of exposure-based psychotherapy for posttraumatic stress disorder

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Exposure-based therapies are considered the state-of-the-art treatment for Posttraumatic Stress Disorder (PTSD). Yet, a substantial number of PTSD patients do not recover after therapy. In the light of the well-known gene \(\times\) environment interactions on the risk for PTSD, research on individual genetic factors that influence treatment success is warranted. The gene encoding FK506-binding protein 51 (\(FKBP5\)), a co-chaperone of the glucocorticoid receptor (GR), has been associated with stress reactivity and PTSD risk. As \(FKBP5\) single-nucleotide polymorphism rs1360780 has a putative functional role in the regulation of \(FKBP5\) expression and GR sensitivity, we hypothesized that this polymorphism influences PTSD treatment success. We investigated the effects of \(FKBP5\) rs1360780 genotype on Narrative Exposure Therapy (NET) outcome, an exposure-based short-term therapy, in a sample of 43 survivors of the rebel war in Northern Uganda. PTSD symptom severity was assessed before and 4 and 10 months after treatment completion. At the 4-month follow-up, there were no genotype-dependent differences in therapy outcome. However, the \(FKBP5\) genotype significantly moderated the long-term effectiveness of exposure-based psychotherapy. At the 10-month follow-up, carriers of the rs1360780 risk (T) allele were at increased risk of symptom relapse, whereas non-carriers showed continuous symptom reduction. This effect was reflected in a weaker treatment effect size (Cohen’s \(D = 1.23\)) in risk allele carriers compared with non-carriers (Cohen’s \(D = 3.72\)). Genetic factors involved in stress response regulation seem to not only influence PTSD risk but also responsiveness to psychotherapy and could hence represent valuable targets for accompanying medication.

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INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is the most common mental health condition in the aftermath of traumatic stress. PTSD prevalence rates depend on cumulative trauma exposure\(^1\) and converge around 8% in the United States\(^2,3\), whereas the disorder occurrence is much higher in post-conflict settings.\(^4\)

Without treatment, PTSD may take a chronic course,\(^1\) associated with severe impairments in daily functioning, higher risk of physical illness\(^5,6\) and suicidality.\(^7\) However, even when treated with exposure-based psychotherapy, considered to be the most effective treatment for PTSD,\(^8,9\) a substantial proportion of survivors does not recover.\(^10\) Therefore, the identification of individual factors that influence PTSD treatment success is of utmost scientific and clinical importance.

The formation of strong fear memories of traumatic experiences\(^11\) and a failure to extinguish the associated reactions to trauma reminders\(^12\) are thought to be the key processes of PTSD development. Hence, exposure-based treatments aim at the modification of fear memories through extinction learning.\(^13\) The heritability of PTSD susceptibility after trauma is \(\sim 30–40\%\),\(^14,15\) and studies investigating gene \(\times\) environment interactions have identified several memory-related genetic factors that moderate the influence of cumulative trauma exposure on PTSD risk.\(^16\) Hence, the response to exposure-based PTSD treatments might be also moderated by particular genetic variants that are implicated in memory processes. To date, two studies identified genetic variations of the serotonin transporter gene\(^17\) as well as the brain-derived neurotrophic factor\(^18\) as genetic modulators of PTSD treatment outcome.

Hypothalamus–pituitary–adrenal axis regulation has been implicated in the etiology of stress-related disorders such as PTSD.\(^19\) The release of glucocorticoids facilitates the mobilization of resources for a fight or a flight response. Concurrently, binding of cortisol to the glucocorticoid receptor (GR) is critical to terminate the stress reaction via negative feedback.\(^20\) Hence, the functioning of the GR is necessary for an adequate stress response regulation. Several chaperones and co-chaperones, including FK506-binding protein 51 (\(FKBP5\)), modulate GR sensitivity.\(^21,22\) Binding of FKBP5 to the GR reduces its cortisol-binding capacity and prevents nuclear translocation,\(^21,22\) which leads to impaired negative feedback regulation of the hypothalamus–pituitary–adrenal axis and a prolonged stress response. Interestingly, \(FKBP5\) gene expression can be triggered by cortisol via intrinsic glucocorticoid response elements.\(^23\) Binding of cortisol to GRs leads to a rapid increase in \(FKBP5\) expression, which in turn reduces GR sensitivity—an ultrashort negative feedback loop of GR sensitivity.\(^24\) Therefore, traumatic stress and subsequent increased cortisol release could lead to enhanced \(FKBP5\) gene expression and reduced GR sensitivity.\(^25\) As glucocorticoid signaling can influence the risk of PTSD\(^26,27\) and is known to

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have an important role in fear memory formation and extinction. Recently, genetic variability of FKBP5 may influence PTSD vulnerability as well as responsiveness to trauma-focused treatments.

The FKBP5 gene, located on the short arm of chromosome 6, harbors several common polymorphisms in high linkage disequilibrium, found to be associated with different psychological disorders. Single-nucleotide polymorphism (SNP) rs1360780 is located closest to a functional glucocorticoid response element and has a putative functional role in the regulation of FKBP5 expression and GR sensitivity. In healthy individuals, the (T) allele was associated with higher FKBP5 expression and relatively reduced GR sensitivity as well as impaired recovery of cortisol levels in response to stress. Furthermore, the T allele predicted enhanced risk for depression, albeit with inconsistent findings. Elevated probability of anxiety disorder development and higher suicide risk. Most important in this context, FKBP5 genotype was also found to be associated with peritraumatic dissociation, a strong risk factor for PTSD. The latter study investigated four FKBP5 polymorphisms, including rs1360780, and found the highest PTSD probability in individuals with the risk genotype who had experienced physical and sexual child abuse. 47 Similarly, it was found that FKBP5 genotype × environment interaction effect only for one of the four SNPs investigated (rs9470080) in an African American sample. An extension study of the original study of Binder and colleagues replicated the interaction effect of rs1360780 and childhood trauma on current PTSD. Interestingly, rs1360780 risk allele carrier status was associated with a differential chromatin conformation, which promotes higher FKBP5 gene expression in response to early stress. Furthermore, risk allele carriers who experienced childhood trauma showed elevated DNA demethylation near and at functional glucocorticoid response elements of the FKBP5 gene, further enhancing FKBP5 gene expression in response to GR activation. Yet, in contrast to healthy subjects, FKBP5 risk genotype carriers with PTSD show lower FKBP5 gene expression and enhanced GR sensitivity compared with non-carriers, a finding that is in accordance with cumulative evidence of GR hypersensitivity in PTSD. Summing up, rs1360780, a putative functional SNP of the FKBP5 gene, has been shown to effect—in a PTSD disease status-dependent manner—FKBP5 gene expression and GR sensitivity. This is the first study to investigate whether FKBP5 rs1360780 genotype modulates treatment outcome of Narrative Exposure Therapy (NET), an exposure-based short-term trauma-therapeutic treatment approach especially developed for the context of mass conflict and organized violence. The efficacy of NET for the treatment of PTSD symptoms has been previously shown in multiple settings, including the post-war context of Northern Uganda. We hypothesized that carriers of rs1360780 risk (T) allele would benefit less from treatment with NET.

MATERIALS AND METHODS

Subjects

Participants were survivors of the rebel war led by the Lord’s Resistance Army in Northern Uganda, who had experienced numerous atrocities, including abductions and forced recruitment into the rebel forces, mutilations, forced participation in combats, killings and sexual violence. The recruitment for the present study took place in the former Internal Displaced People camps Anaka, Pabbo and Koch Goma. Inclusion criteria were (1) diagnosis of PTSD according to DSM-IV; (2) age between 18 and 65; (3) absence of any signs of alcohol or substance dependence; (4) absence of psychotic symptoms; (5) no psychotropic medication and (6) no prior trauma-focused psychotherapy. Fifty-three subjects were enrolled in the study and received treatment with NET by trained local counselors under the supervision of clinical experts in the field of trauma therapy. Chip-based genotyping was impossible for four individuals because of low DNA concentrations, and one further participant was excluded after genotyping quality control. In addition, three participants were excluded from the present study because of discontinuation of therapy (N = 1, rs1360780 genotype = C/T), unavailability for both follow-up interviews (N = 1, genotype = C/C) and an extraordinary strong of flashbacks, which required that a clinical expert replace the treated patient (N = 1, genotype = C/C). In the latter case, the therapy was completed successfully; however, comparability to the other treatments conducted by trained local counselors was no longer given. Individuals who we could only trace for one follow-up assessment (only 4 months, N = 1, genotype = C/C; only 10 months, N = 1, genotype = T/T) were still included in the analyses. Finally, chip-based genotyping of FKBP5 rs1360780 failed for two participants. Hence, results are reported on a final sample of N = 43 (29 females, mean age = 31.91, s.d. = 9.49, rs1360780 genotype C/C = 13, T/T = 15, T/T = 15).

Procedure

Clinical interviews were conducted before treatment (t1) and 4 and 10 months (t2 and t3, respectively) after treatment completion. Current PTSD diagnosis and symptom severity were assessed in a structured interview based on the Posttraumatic Diagnostic Scale (PDS). A 62-item event list, adapted for the context of the Lord’s Resistance Army war, was used to assess the number of experienced traumatic event types (traumatic load). We assessed suicidal risk utilizing the respective section of the Mini International Neuropsychiatric Interview (M.I.N.I.). Local interviewers who attended 6 weeks of training on the concepts of clinical interviews, quantitative data collection and PTSD conducted the interviews. The instruments were translated into the local language (Luo) following blind back-translations, group discussions and corrections by independent translators. Retest reliability and validity (consistency with expert ratings) of the psychological assessment by trained local interviewers were previously investigated and revealed good psychometric quality. Participants provided saliva samples in the first diagnostic interview using Oragene Self Collection Kits (DNA Genothek, Ottawa, Ontario, Canada). SNP-based genotyping was performed according to the Genome-Wide Human SNP Hsp/Sty 6.0 User Guide (Affymetrix Inc, Santa Clara, CA, USA). SNP rs1360780 is represented on the array (SNP ID: SNP_A-5889266). Genetic quality control was performed in PLINK v1.07.

Treatment

The study participants received an average of 12 sessions of NET. Sessions took place twice a week and generally lasted between 90 and 120 min. In brief, the aim of NET is to reconstruct the survivor’s life story with a particular focus on traumatic stressors. The first session comprises psychoeducation and serves to obtain a biographical overview of the client’s life. The subsequent sessions involve exposure therapy to the most severe traumatic experiences in chronological order and the last session comprises the re-reading of the narrated life story. Intensively trained local counselors performed the therapies under the supervision of expert psychologists. Treatment adhesion was monitored in case discussions, weekly supervision meetings as well as via reviews of detailed case documents. After a detailed explanation of the study protocol participants gave written informed consent. All procedures followed the Declaration of Helsinki and were approved by the Institutional Review Board of Gulu University, Uganda, the Ugandan National Council for Science and Technology and the ethics committee of the German Psychological Society (Deutsche Gesellschaft für Psychologie).

Statistics

Statistical analyses were performed in the statistical environment R 3.0.2. Demographic and clinical data of the genotype groups were compared using Fisher’s exact test for count data and one-factorial analyses of variance (ANOVA) for continuous data. If ANOVA residuals were non-normally distributed, a non-parametric Kruskal–Wallis H test was employed. PDS score was defined as the outcome variable, genotype as a between-subject fixed factor, time as a within-subject repeated fixed factor and participants as a random effect, with random intercepts for each participant. The correlations of the repeated measurements within participants were modeled with a general correlation structure, and
the maximum likelihood estimation method was employed to fit the model.

In the model selection procedure, we fitted nested models of increasing complexity and compared their goodness-of-fit. The initial analysis was performed including only time and FKBP5 rs1360780 genotype as predictors. Next, we analyzed whether a genotype model, comparing the three rs1360780 genotype groups (C/C, C/T and T/T), or a risk allele carrier model, combining C/T and T/T genotypes in one group, represented the data best. As traumatic load is known to strongly influence PTSD symptomatology, and FKBP5 gene × environment interactions have been observed previously, further analyses were performed with and without traumatic load as a covariate, and with and without allowing for potential time × FKBP5 genotype × traumatic load interaction effects. In addition, it was evaluated whether the inclusion of the covariates sex and age would improve model fit. As recommended by Burnham and Anderson, model selection was based on Akaike’s Information Criterion, which has a profound information-theoretic foundation and aims at minimizing the expected Kullback–Leibler divergence between the model and the true underlying data-generating process.

We expected T allele carriers to benefit less from NET treatment, which would result in a significant time × FKBP5 rs1360780 interaction. More specifically, we hypothesized that the difference between the pretreatment PDS score (time point $t_1$) and the follow-up PDS scores (time points $t_2$ or $t_3$) would be higher in individuals with the protective genotype (C/C) than in carriers of the T (risk) allele. We tested this specific hypothesis by evaluating the statistical significance of planned contrasts while adjusting for multiple comparisons (R package multcomp 1.3-1).58

RESULTS

FKBP5 rs1360780 genotype groups showed no differences in age, gender distribution, traumatic load, number of NET sessions, PTSD symptom severity, PTSD symptom scores and suicidality before treatment (Table 1).

Confirming our main hypothesis, we found a significant time × FKBP5 rs1360780 genotype interaction effect. This effect was present in every estimated linear mixed effect model. Our successive model selection procedure strongly suggested that a risk allele carrier model, including traumatic load and sex as covariates, represented the data best (Table 2). We therefore report statistical inference from this model.

The selected model revealed a significant treatment effect (main effect time, $F_{2,80} = 96.84$, $P < 0.001$), no significant main FKBP5 rs1360780 genotype effect, but a significant time × FKBP5 rs1360780 genotype interaction effect ($F_{2,80} = 5.40$, $P = 0.006$, Figure 1). Furthermore, the two included covariates, traumatic load ($F_{1,39} = 18.42$, $P < 0.001$) and sex ($F_{1,39} = 6.08$, $P = 0.018$) significantly predicted PTSD symptom severity.

To further examine the nature of the time × FKBP5 rs1360780 genotype interaction effect, we next calculated three planned orthogonal contrasts while adjusting $P$-values for multiple testing. There was no genotype-dependent difference in treatment success rates 4 months after treatment (comparison $t_1$–$t_2$). Yet,

| Table 1. Demographic and clinical information by FKBP5 rs1360780 genotype group |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | C/C (N = 13)    | C/T (N = 15)    | T/T (N = 15)    | Statistic*      | P-value         |
| N female (%)                   | 9 (69)          | 9 (60)          | 11 (73)         | Fisher's exact test | 0.78            |
| Mean age (s.d.)                | 35.38 (10.40)   | 30.60 (13.06)   | 30.20 (10.52)   | $H_2 = 3.58$     | 0.006           |
| Mean traumatic load (s.d.)     | 35.92 (5.54)    | 38.07 (7.06)    | 35.93 (7.25)    | $F_{2,40} = 0.50$ | 0.61            |
| Mean number of sessions (s.d.) | 11.46 (2.18)    | 11.67 (2.50)    | 12 (1.46)       | $H_2 = 2.03$     | 0.36            |
| Mean PDS score ($t_1$) (s.d.)  | 17.69 (4.44)    | 16.47 (4.76)    | 16.8 (5.27)     | $H_2 = 0.70$     | 0.70            |
| Mean PDS intrusions score ($t_1$) (s.d.) | 4.85 (2.51) | 3.87 (2.45) | 5.20 (2.01) | $F_{2,40} = 1.32$ | 0.28 |
| Mean PDS avoidance score ($t_1$) (s.d.) | 6.38 (2.10) | 6.67 (1.88) | 5.47 (2.07) | $H_3 = 3.68$ | 0.16 |
| Mean PDS hyperarousal score ($t_1$) (s.d.) | 6.46 (2.15) | 5.93 (1.91) | 6.13 (3.48) | $H_3 = 0.77$ | 0.68 |
| Mean M.I.N.I. suicidality score ($t_1$) (s.d.) | 12.69 (8.31) | 12.13 (10.21) | 11.67 (12.49) | $H_3 = 0.40$ | 0.82 |

Abbreviations: ANOVA, analysis of variance; M.I.N.I., Mini International Neuropsychiatric Interview; PDS, Posttraumatic Diagnostic Scale. *ANOVA F-test for continuous data if test residuals were normally distributed, Kruskal–Wallis H-test for continuous data if residuals were not normally distributed and Fisher’s exact test for categorical data.

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Figure 1. Carriers of the FKBP5 rs1360780 T allele display less symptom improvements following trauma-focused therapy. Depicted are the mean values and s.e.’s of measurement. PDS, Posttraumatic Diagnostic Scale; $t_1$, before treatment; $t_2$, 4-month follow-up; $t_3$, 10-month follow-up.

Table 2. Estimated models and model selection procedure

| Estimated model (fixed effects) | AIC |
|--------------------------------|-----|
| Model 1: Time × FKBP5 rs1360780 Genotype* | 789.52 |
| Model 2: Time × FKBP5 rs1360780 T allele carrierb | 783.82 |
| Model 3: Time × FKBP5 rs1360780 T allele carrier + traumatic load | 771.18 |
| Model 4: Time × FKBP5 rs1360780 T allele carrier × traumatic load | 773.54 |
| Model 5: Time × FKBP5 rs1360780 T allele carrier + traumatic load + sexc | 767.38 |
| Model 6: Time × FKBP5 rs1360780 T allele carrier + traumatic load + sex + age | 769.23 |

Abbreviations: AIC, Akaike’s Information Criterion; FKBS, FK506-binding protein 51. *The genotype model contrasts the three genotype groups (C/C, C/T and T/T).bThe T allele carrier model compares carriers of the T risk allele (C/T and T/T genotypes) with non-carriers (C/C genotype).cModel 5 (marked in bold letters) was chosen based on the model selection criteria as it yielded the smallest AIC.
10 months after the end of the treatment (comparison $t_1$–$t_3$), non-carriers of the risk allele had significantly higher symptom improvements than risk allele carriers ($Z = 3.37$, $P < 0.001$, Figure 1). Furthermore, there was a significant difference in the symptom development between the two follow-up assessments (difference $t_2$–$t_3$), whereas risk allele carriers had a greater risk for symptom relapse, non-carriers continued to show symptom improvements ($Z = 2.71$, $P = 0.009$, Figure 1).

To obtain a better understanding of the substantial main effect of traumatic load, we plotted the fitted values of the PDS score against traumatic load separately for the three time points and genotype groups (Figure 2). We observed a dose-dependent relationship between traumatic load and PDS score at all time points, yet T allele carriers showed a higher intercept 10 months post treatment.

We next analyzed the clinical significance of the genotype effect on therapy outcome by investigating the mean change scores between the 10-month follow-up and the pretreatment assessment, as well as the treatment effect sizes for each genotype group. Both genotype groups presented with large treatment effects according to the conventions of Cohen; however, for individuals with the protective (C/C) genotype the treatment effect size was approximately three times higher than for carriers of the risk allele (Table 3). Furthermore, 10 months after treatment, no individual in the C/C genotype group fulfilled the diagnosis of PTSD, whereas 43% of T allele carriers still met the diagnostic criteria according to DSM-IV (Table 3).

Finally, we exploratively investigated whether genotype differences in treatment success would be also reflected in the three PTSD symptom clusters and suicidality risk. T Allele carriers scored higher on all variables 10 months after treatment (Table 3, Supplementary Figures S1 and 2). These effects resulted in a significant rs1360780 × time interaction for avoidance ($F_{2,80} = 5.74$, $P = 0.005$) and hyperarousal symptoms ($F_{2,80} = 4.65$, $P = 0.012$), but not for intrusion symptoms ($F_{2,80} = 2.10$, $P = 0.130$). The interaction was marginally significant for the outcome suicidality ($F_{2,80} = 3.06$, $P = 0.053$).

**DISCUSSION**

Confirming our hypothesis, we found a significant effect of *FKBP5* rs1360780 genotype on therapeutic outcome of NET. This effect was present at 10 months, but not 4 months after treatment completion, indicating that the *FKBP5* genotype predominantly influences long-term therapeutic outcome. Psychotherapy—in contrast to pharmacological treatment—initializes a process of recovery that continues over time. Confirming this, evidence from Northern Uganda shows that NET treatment effects increase over time (that is, treatment effects assessed 1 year after therapy completion were more pronounced than 6 months post treatment).

Hence, genetic variants that are linked to psychotherapeutic outcome should show stronger effects on the long-term course of symptoms rather than on immediate psychotherapeutic outcomes. This is in line with the findings of Bryant et al., reporting a moderating influence of genetic variation at the serotonin transporter locus on trauma therapy outcome at the follow-up assessment, but not immediately post treatment.

The empirical data favored a risk allele carrier model: carriers of one or two copies of the T allele showed enhanced risk for symptom relapse 10 months after treatment, whereas individuals with the protective C/C genotype showed continuous symptom improvement. The genotype effect had significant clinical implications: individuals with the protective genotype had three times higher treatment effect sizes than risk allele carriers. Whereas 43% of risk allele carriers fulfilled the diagnostic criteria of PTSD, the entire C/C genotype group showed clinical remission 10 months post treatment. In addition, the strong effect of the *FKBP5* genotype on treatment success was descriptively reflected in all PTSD symptom clusters as well as in suicidality, with significant effects on the avoidance and hyperarousal symptom cluster. Hence, trauma-related symptoms of distress and arousal seem to be more resistant to modification through trauma-focused therapy in carriers of the rs1360780 T allele.

How might *FKBP5* rs1360780 genotype influence psychotherapy success? Extensive evidence indicates that the stress hormone cortisol facilitates memory formation, impairs retrieval and enhances memory extinction processes. Both the formation of
enhanced cortisol responses to stress in healthy individuals reduce symptoms in PTSD.67

non-carriers,32,44 corresponding well to repeated genotype with PTSD show enhanced GR sensitivity compared with unaffected individuals. In contrast, carriers of the prolonged cortisol response seems to be only valid for PTSD-disorders.60

coids enhances the effects of exposure therapy for anxiety studies.66 In line with these findings, cortisol administration has been shown to improve exposure therapy success60 for successful exposure-based trauma therapy, 65,66 which was not moderated by traumatic load. Instead, the number of traumatic events experienced increased PTSD symptom severity at all time points. This result replicates earlier findings of a dose-dependent effect of traumatic load on PTSD symptom severity1,68 extending them by illustrating that higher trauma load also leads to higher PTSD symptoms after treatment. Several explanations may account for the lack of an interaction effect. First of all, genetic risk × trauma exposure interaction effects might be more central to the onset of PTSD than to its treatment. However, our results do not exclude the possibility of an interaction with this assessment of childhood trauma, which was found in previous investigations.30,32,69 Our trauma questionnaire only includes four items of experienced or witnessed physical childhood abuse and we did not find any interaction effect with this assessment of childhood trauma. A more detailed assessment of childhood trauma and the investigation of a larger sample with greater variations in childhood trauma might be required to detect potential interactions. The relatively small sample size clearly represents a limitation of this study, as it prevents the assessment of potential underlying population stratification. Replication

| Table 3. Treatment-associated changes in clinical variables by genotype groups |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                   | $t_1$ (pretreatment) | $t_2$ (4 months) | $t_3$ (10 months) | Change score | Effect size Cohen’s D* |
| N PTSD diagnosis (%)              |                  |                  |                  |              |                  |
| C/C                               | 13 (100)         | 4 (31)           | 0 (0)*           |              |                  |
| T allele carrier                   | 30 (100)         | 7* (29)          | 13 (43)          |              |                  |
| Mean PDS score (s.d.)             |                  |                  |                  |              |                  |
| C/C                               | 17.69 (4.44)     | 8.15 (5.00)      | 3.92 (2.78)      | −13.58 (6.37) | 3.72             |
| T allele carrier                   | 16.63 (4.94)     | 7.90 (6.03)      | 9.37 (6.73)      | −7.27 (5.60)  | 1.23             |
| Mean M.I.N.I. suicidality score (s.d.) |                  |                  |                  |              |                  |
| C/C                               | 12.69 (8.31)     | 5.31 (6.47)      | 2.08 (4.94)      | −11.08 (8.67) | 1.55             |
| T allele carrier                   | 11.90 (11.21)    | 8.45 (10.60)     | 7.37 (8.31)      | −4.53 (6.85)  | 0.45             |
| Mean PDS intrusions score (s.d.)  |                  |                  |                  |              |                  |
| C/C                               | 4.85 (2.51)      | 2.54 (1.51)      | 1.50 (1.68)      | −3.08 (3.32)  | 1.57             |
| T allele carrier                   | 4.53 (2.30)      | 1.83 (2.25)      | 2.53 (2.36)      | −2.00 (3.25)  | 0.86             |
| Mean PDS avoidance score (s.d.)   |                  |                  |                  |              |                  |
| C/C                               | 6.38 (2.10)      | 2.46 (1.94)      | 0.83 (1.27)      | −5.50 (2.54)  | 3.20             |
| T allele carrier                   | 6.07 (2.03)      | 2.52 (2.23)      | 3.17 (2.36)      | −2.90 (2.29)  | 1.32             |
| Mean PDS hyperarousal score (s.d.)|                  |                  |                  |              |                  |
| C/C                               | 6.46 (2.15)      | 3.15 (2.41)      | 1.58 (1.00)      | −5.00 (2.45)  | 2.92             |
| T allele carrier                   | 6.03 (2.76)      | 3.55 (2.68)      | 3.67 (2.68)      | −2.37 (2.51)  | 0.87             |

Abbreviations: M.I.N.I., Mini International Neuropsychiatric Interview; PDS, Posttraumatic Diagnostic Scale; PTSD, Posttraumatic Stress Disorder. aChange score describes the difference between pretreatment and 10-month follow-up assessment. bCohen’s D describes the within-group treatment effect size between pretreatment and 10-month follow-up assessment. cOne individual was not found for 10-month follow-up. dOne individual was not found for 4-month follow-up.

traumatic memories and their modification through psychotherapy rely on learning and memory processes: whereas fear conditioning is thought to be responsible for the onset of PTSD, extinction learning is the basis of exposure therapy.16 Indeed, stress and associated elevated cortisol levels increase extinction memory consolidation,59 and the administration of glucocorticoids enhances the effects of exposure therapy for anxiety disorders.60,62 Accordingly, FKBP5 genotype might influence the initial fear memory strength as well as the process of extinction learning.

The FKBP5 rs1360780 T allele is characterized by a different three-dimensional structure of the FKBP5 gene, which allows direct interaction between the glucocorticoid response element at intron 2 and the promoter region.30 This leads to higher FKBP5 induction by glucocorticoids, reduced GR sensitivity and consequently to a prolonged cortisol response following stress exposure.30 This corresponds well with findings of reduced GR sensitivity52,64 and enhanced cortisol responses to stress in healthy individuals carrying the high induction risk allele.33,34 Furthermore, higher FKBP5 mRNA expression in peripheral blood hours after the traumatic experience predicted PTSD symptom development in survivors 4 months later.43 However, the described relationship between FKBP5 risk genotype, higher FKBP5 expression, relative GR resistance and prolonged cortisol response seems to be only valid for PTSD-unaffected individuals. In contrast, carriers of the FKBP5 risk genotype with PTSD show enhanced GR sensitivity compared with non-carriers,32,44 corresponding well to repeated findings of GR supersensitivity in PTSD.25 In addition, lower FKBP5 gene expression has been reported in individuals with PTSD,41,63,65 and was associated with FKBP5 risk genotype.43 Furthermore, two recent studies reported an increase in FKBP5 gene expression as a marker for successful exposure-based trauma therapy,65,66 which was accompanied by an increase in plasma cortisol in one of the studies.65 In line with these findings, cortisol administration has been shown to improve exposure therapy success65–67 and to reduce symptoms in PTSD.65 The present study is the first to show that the FKBP5 genotype modulates psychotherapeutic outcome. Reasons for the reduced long-term therapeutic benefits in risk allele carriers may include stronger stress reactions at the time of trauma and hence stronger memories of the encountered traumas, which are more resistant to modification. On the other hand, initial evidence indicates that once PTSD is developed, FKBP5 risk genotype may be associated with higher GR sensitivity and hence a rapid reduction in cortisol levels following stress.32,44 Assuming that exposure to traumatic experiences during psychotherapy triggers the stress response, a shortened cortisol response may impair the process of extinction learning or extinction memory consolidation,48 which could explain the resurgence of symptoms in T allele carriers. We did not find a three-way interaction effect of time, FKBP5 genotype and traumatic load. In other words, genotype influenced the symptom improvement following NET; however, this effect was not moderated by traumatic load. Instead, the number of traumatic events experienced increased PTSD symptom severity at all time points. This result replicates earlier findings of a dose-dependent effect of traumatic load on PTSD symptom severity1,68 and extends them by illustrating that higher trauma load also leads to higher PTSD symptoms after treatment. Several explanations may account for the lack of an interaction effect. First of all, genetic risk × trauma exposure interaction effects might be more central to the onset of PTSD than to its treatment. However, our results do not exclude the possibility of an interaction with childhood trauma, which was found in previous investigations.30,32,69 Our trauma questionnaire only includes four items of experienced or witnessed physical childhood abuse and we did not find any interaction effect with this assessment of childhood trauma. A more detailed assessment of childhood trauma and the investigation of a larger sample with greater variations in childhood trauma might be required to detect potential interactions. The relatively small sample size clearly represents a limitation of this study, as it prevents the assessment of potential underlying population stratification. Replication
studies with much larger samples are warranted to confirm the
moderating role of FKBP5 on trauma therapy outcome.
Nevertheless, this investigation provides initial evidence of a
strong effect of the FKBP5 genotype that influences long-term
treatment outcome at all investigated levels of traumatic load.
What do these results imply for PTSD treatment development?
According to a meta-analysis performed by Bradley et al.\textsuperscript{10}
approximately one-third of clients treated with exposure-based
therapies still meet diagnostic criteria for PTSD. Comparable rates
(32\%) were found 12 months after treatment with NET in survivors.
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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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REFERENCES
1 Kolassa IT, Ertl V, Kolassa S, Onyut LP, Elbert T. The probability of spontaneous
remission from PTSD depends on the number of traumatic event types experi-
tenced. Psychol Trauma 2010; 3: 169–174.
2 Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress
disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1995; 52: 1084–1090.
3 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime
prevalence and age-of-onset distributions of DSM-IV disorders in the National
Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 593–602.
4 Neuner F, Schauer M, Karunakara U, Klaschik C, Robert C, Elbert T. Psychological
trauma and evidence for enhanced vulnerability for posttraumatic stress disorder
through previous trauma among West Nile refugees. BMC Psychiatry 2004; 4: 34.
5 Kubiszyn BD, Bordelos P, Jun HI, Roberts AL, Cerdà M, Bluemstone N et al. The
weight of traumatic stress: a prospective study of posttraumatic stress disorder
symptoms and weight status in women. JAMA Psychiatry 2013; 71: 44–51.
6 Glæsmer H, Brahler E, Gundel H, Riedel-Heller SG. The association of traumatic experiences
and posttraumatic stress disorder with physical morbidity in old age: A
german population-based study. Psychosom Med 2011; 73: 401–406.
7 Jakupcak M, Cook J, Imel Z, Fontana A, Ruzenheck R, McFall M. Posttraumatic stress
disorder as a risk factor for suicidal ideation in Iraq and Afghanistan War
veterans. J Trauma Stress 2009; 22: 303–306.
8 Bisson JI, Ehlers A, Matthews R, Pilling S, Richards D, Turner S. Psychological
treatments for chronic post-traumatic stress disorder. Systematic review and
meta-analysis. Br J Psychiatry 2007; 190: 97–104.
9 Ehlers A, Bisson JI, Clark DM, Creamer M, Pilling S, Richards D et al. Do all psychologi-
cal treatments really work the same in posttraumatic stress disorder? Clin
Psychol Rev 2010; 30: 269–276.
10 Bradley R, Greene J, Russ E, Dutra L, Westen D. A multidimensional meta-analysis
of psychotherapy for PTSD. Am J Psychiatry 2005; 162: 214–227.
11 Elbert T, Schauer M. Burnt into memory. Nature 2002; 419: 883.
12 Jovanovic T, Ressler KJ. How the neurocircuity and genetics of fear inhibition may
inform our understanding of PTSD. Am J Psychiatry 2010; 167: 648–662.

13 Rothbaum BO, Davis M. Applying learning principles to the treatment of post-
traumatic reactions. Ann N Y Acad Sci 2003; 1008: 112–121.
14 True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ et al. A twin study of
genetic and environmental contributions to liability for posttraumatic stress
symptoms. Arch Gen Psychiatry 1993; 50: 257–264.
15 Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental
influences on trauma exposure and posttraumatic stress disorder symptoms: a
twin study. Am J Psychiatry 2002; 159: 1675–1681.
16 Wilker S, Kolassa IT. The formation of a neural fear network in posttraumatic stress
disorder: Insights from molecular genetics. Clin Psychol Sci 2013; 1: 452–469.
17 Bryant RA, Felmingham KL, Falconer EM, Pe Benito L, Dobson-Stone C, Pierce KD
et al. Preliminary evidence of the short allele of the serotonin transporter gene
predicting poor response to cognitive behavior therapy in posttraumatic stress
disorder. Biol Psychiatry 2010; 67: 1217–1219.
18 Felmingham KL, Dobson-Stone C, Schofield PR, Quirk GJ, Bryant RA. The brain-
derived neurotrophic factor Val66Met polymorphism predicts response to expo-
sure therapy in posttraumatic stress disorder. Biol Psychiatry 2013; 75: 1059–1063.
19 Pervandou P, Chrousos GP. Neuroendocrinology of post-traumatic stress dis-
order. Prog Brain Res 2010; 182: 149–160.
20 Sapolsky RM, Romero LM, Muncz AK. How do glucocorticoids influence stress
responses? Integrating permissive, suppressive, stimulatory, and preparative
applications. Endocr Rev 2000; 21: 55–89.
21 Wochnik GM, Ruegg J, Abel GA, Schmidt U, Holsboer F, Rein T. FK506-binding
proteins 51 and 52 differentially regulate dynein interaction and nuclear trans-
location of the glucocorticoid receptor in mammalian cells. J Biol Chem 2005; 280: 4609–4616.
22 Denny WB, Valentine DL, Reynolds PD, Smith DF, Scammell JG. Squirrel monkey
immunophenil FKBP51 is a potent inhibitor of glucocorticoid receptor binding.
Endocrinology 2000; 141: 4107–4113.
23 Hubler TR, Scammell JG. Intrinsic hormone response elements mediate regulation
of FKBP5 by progestins and glucocorticoids. Cell Stress Chaperones 2004; 9: 243–252.
24 Vermeen H, Hendriks-Stegeman BL, van der Burg B, van Buul-Oeffs SC, Jansen M.
Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic
acid expression: a potential marker for glucocorticoid sensitivity, potency, and
bioavailability. J Clin Endocrinol Metab 2003; 88: 277–284.
25 Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the
pathogenesis and therapy of affective and anxiety disorders. Psychoneu-
roendocrinology 2009; 34: 516–519s.
26 Yehuda R. Status of glucocorticoid alterations in post-traumatic stress disorder.
Arch Gen Psychiatry 1989; 46: 641–648.
27 van Zuiden M, Kavelaars A, Geuze E, Ollf M, Heijnen CJ. Predicting PTSD: pre-
existing vulnerabilities in glucocorticoid-signaling and implications for preventive
interventions. Brain Behav Immun 2013; 30: 12–21.
28 de Quervain DJ-F, Aerni A, Schelling G, Roozendaal B. Glucocorticoids and the
regulation of memory in health and disease. Front Neuroendocrinol 2009; 30:
358–370.
29 Pitman RK, Rassmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW et al.
Biological studies of post-traumatic stress disorder. Nat Rev Neurosci 2012; 13:
754–767.
30 Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM et al.
Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma
interactions. Nat Neurosci 2013; 16: 33–41.
31 Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Putz B et al. Poly-
morphisms in FKBP5 are associated with increased recurrence of depressive
episodes and rapid response to antidepressant treatment. Nat Genet 2006; 38:
1319–1325.
32 Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB et al. Association
of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress
disorder symptoms in adults. JAMA 2008; 299: 1291–1305.
33 Ising M, Deppeing AM, Siebertz A, Lucrea S, Unschuld PG, Klober S et al. Poly-
morphisms in the FKBP5 gene region modulate recovery from psychosocial stress
in healthy controls. Eur J Neurosci 2008; 28: 389–398.
34 Buchmann AF, Holz N, Boecker R, Blomeyer D, Ritschel M, Witt SH et al. Mod-
erating role of FKBP5 genotype in the impact of childhood adversity on cortisol
stress response during adulthood. Eur Neuropsychopharmacol 2013; 23: 837–845.
35 Mahon PB, Zandi PP, Potash JB, Nestadt G, Wand GS. Genetic association of FKBP5
and CRHR1 with cortisol response to acute psychosocial stress in healthy adults.
Psychopharmacology (Berl) 2013; 227: 231–241.
36 Zimmermann P, Bruckl T, Novoa A, Pfister H, Binder EB, Uhr M et al. Interaction
of FKBP5 gene variants and adverse life events in predicting depression onset:
results from a 10-year prospective study. Am J Psychiatry 2011; 168:
1107–1116.
37 Lekman M, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ et al. The FKBP5 gene
in depression and treatment response—an association study in the Sequenced
The role of FKBP5 genotype in exposure-based psychotherapy
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