Research Paper

Childhood trauma but not FKBPS gene variants associated with peritraumatic dissociation in female rape survivors

E. Thomas a,b,* , S.M.J. Hemmings a,d,c , G. Spies a,c , J. Nothling b,c , S. Seedat a,b,c

a South African Research Chairs Initiative (SARCHI), PTSD program, department of psychiatry, Stellenbosch university, South Africa
b Department of psychiatry, faculty of medicine and health sciences, Stellenbosch university, P.O. Box 19063, Tygerberg, 7505 Stellenbosch, South Africa
c MRC Unit on Anxiety and Stress Disorders, department of psychiatry, Stellenbosch university, South Africa
d Division of molecular biology and human genetics, Stellenbosch university, South Africa

A R T I C L E   I N F O

Article history:
Received 3 October 2017
Received in revised form 16 January 2018
Accepted 4 February 2018

Keywords:
Childhood trauma
FKBP5 gene
Interpersonal violence dissociation
Post-traumatic stress disorder

A B S T R A C T

Introduction. – Peritraumatic dissociation has been shown to be a strong predictor for development of PTSD.

Objectives. – This study explored the relationship of four putative FK506 binding protein 5 (FKBP5) genetic variants and childhood trauma in predicting peritraumatic dissociation.

Method. – Extracted DNA from 81 female rape survivors in Cape Town, South Africa were analysed for common FKBP5 polymorphisms. Dissociative experiences, childhood trauma, depression and resilience were also measured.

Results. – Childhood trauma was associated with a significant increase in peritraumatic dissociation, whilst resilience conferred a significant protective effect. No significant associations were observed between the single loci or haplotypes under investigation and peritraumatic dissociation.

Conclusion. – This study provides evidence that, among female rape survivors, exposure to childhood trauma may increase risk of peritraumatic dissociation independent of genetic variation of the FKBP5 gene.

© 2018 Published by Elsevier Masson SAS.

1. Introduction

Post-traumatic stress disorder (PTSD) is a prevalent, disabling and often chronic mental disorder that may develop following exposure to a significant traumatic event (TE). PTSD may present with re-experiencing of the trauma, active avoidance of stimuli or situations that are trauma reminders, negative alterations in cognition and mood and alterations in arousal and reactivity (American Psychiatric Association, 2013; Kessler et al., 2005). Factors known to increase risk include: female gender, history of previous traumas, childhood trauma, pre-existing mental health disorders and peritraumatic dissociation (Yehuda et al., 2015). Peritraumatic dissociation (PTD) describes an acute individual response to a TE including disruption in usually integrated functions of consciousness, memory, identity, or environmental perception (American Psychiatric Association, 2013). PTD has been shown to be a strong predictor of PTSD-development (Ozer, Best, Lipsey, & Weiss, 2003), including following rape (Nöthling, Lammers, Martin, & Seedat, 2015).

Accumulating evidence indicates that variants in genes that encode for neural mechanisms involved in PTSD may confer risk for PTSD (Almli, Fani, Smith, & Ressler, 2014; Marinova & Maercker, 2015). The hypothalamic-pituitary-adrenal (HPA)-axis plays a key role in neuroendocrine stress response and HPA-dysregulation is thought to underlie PTSD pathogenesis (van Zuiden, Kavelaars, Geuze, Olff, & Heijnen, 2013). The HPA axis is vulnerable to persistent changes in function following childhood trauma, as evidenced by dysregulated glucocorticoid cortisol release. Genetic variants of the glucocorticoid receptor (GR), for example, single nucleotide polymorphisms (SNPs) in the FK506 binding protein 5 (FKBP5) gene, appear to contribute to inter-individual variability in HPA-axis function (Castro-Vale, van Rossum, Machado, Mota-Cardoso, & Carvalho, 2016a). FKBP5 SNPs have been shown to interact with childhood abuse to predict adult PTSD symptoms (Binder et al., 2008; Watkins et al., 2016a). Interestingly, preliminary data exists demonstrating an association between FKBP5 and PTD (Koenen et al., 2005).

This study investigates potential associations between selected FKBP5-alleles and childhood trauma exposure in predicting the
occurrence of peritraumatic dissociation in a sample of female rape survivors.

2. Materials and methods

2.1. Participants

This cross-sectional sub-study is nested within a larger longitudinal study examining PTSD in a South African cohort of female rape survivors. Participants were recruited from two clinics serving rape victims in Cape Town, South Africa from January 2008 to June 2012. Participants were at least 14 years old, and were excluded if they met criteria for PTSD, or another psychiatric or medical disorder at the time of the initial, screening visit. This study was approved by the Health Research Ethics Committee at Stellenbosch University in Cape Town, South Africa (N08/02/040). Informed consent was obtained from all adult participants and from a parent or legal guardian in the case of adolescent participants.

2.2. Procedure

DNA samples were obtained from all participants by means of a blood draw. DNA was extracted from blood samples using the standard phenol/chloroform method. Following DNA extraction, samples were nanodroped to determine their concentration, and subsequently diluted to 20 ng/μL. The selected SNPs (rs4713916, rs9296158, rs1360780 and rs3800373) were genotyped at LGC (Middlesex, United Kingdom), using KASP genotyping technology.

2.3. Measures

Participants completed a demographic questionnaire, the eight item Dissociative Experiences Scale-Taxon (DES-T) assessing current dissociative symptoms and dissociation at the time of the trauma (Waller et al., 1996) designed to distinguish between pathological from non-pathological dissociation. A higher total score indicates a stronger tendency to dissociate (Giesbrecht et al., 2007; Waller et al., 1996). The Early Trauma Inventory Self-Report-short form (ETISR-SF) is a 27-item questionnaire assessing previous physical, emotional and sexual abuse, as well as general traumas occurring before the age of 18 years, with a highest possible score of 27 (Bremner, Bolus, & Mayer, 2007). The number of exposure events are added to yield a total scale score as well as domain scores (general trauma, physical abuse, emotional abuse, sexual abuse). The Connor-Davidson Resilience Scale (CD-RISC) a 25-item scale assessing resilience with reference to the past month, higher scores indicate greater resilience (Connor & Davidson, 2003), and the Center for Epidemiologic Studies Depression Scale (CESD), a 20-item instrument assessing depressive symptomatology on a four point Likert Scale, a score of 16 or higher is considered indicative of depression (Radloff, 1977).

2.4. Statistical analyses

Simple descriptive statistics were computed to summarize sociodemographic and clinical variables. Statistical modelling was done with functions from R (http://www.r-project.org), and R packages SNPassoc and haplo.stats (inferred haplotypes) (González et al., 2007). Pairs of haplotypes were inferred for each participant using the expected-maximisation algorithm, implemented in haplo.stats (version 1.7.7) (Schaid, Rowland, Tines, Jacobson, & Poland, 2002), developed in R language (http://www.r-project.org). Genetic associations were tested by including the terms (genotype or haplotype) in the models as fixed effects. Analyses were adjusted for known confounders, namely age, ethnicity, depression score, resilience and experience of previous sexual trauma by including them in the statistical models as fixed effects.

Haplotype associations were tested using the function haplo.glm implemented in haplo.stats, which applies a haplotype-trait association test based on a general linear model framework. We regressed the trait of interest (PTD) on haplotypes with a frequency of >5% and examined the significance of the regression coefficients. The effect of the haplotypes was assumed to be additive. Haplotype were then inferred in the blocks constructed using the solid spine of linkage disequilibrium (LD) method, implemented in Haploview software (version 4.2) and were investigated as additive models only.

3. Results

3.1. Sociodemographic characteristics of participants

The sample included 81 female rape survivors with a mean age of 25.28 (range: 14–44) years. Ethnicities were as follows: coloured/mixed ancestry (n = 64; 79%), black (n = 14; 17%); white/Caucasian (n = 2; 2%) and Asian (n = 1; 1%). A total of 28 (34.8%) women reported a previous sexual trauma (rape and other sexual assaults). Participants were predominantly single (n = 61; 75%). The majority of women had attained high school education (n = 63; 77.7%) with only 10 (12.3%) women a tertiary education.

3.2. Clinical measures

The mean score on the DES-T was 33 (range: 0–100), suggesting high rates of pathological dissociation. With regards to childhood trauma, the mean score on the ETISR-SF was 9 (range: 0–24, SD = 5.9) with mean (SD) domain scores for physical abuse of; 3 (range: 0 – 5, SD = 1.6), for emotional abuse; 2.2 (range: 0–5, SD = 1.9) and sexual abuse; 2 (range: 0–6; SD = 2.0), respectively. The majority of the sample (n = 76, 93.8%) scored above 16 on the CES-D, suggesting high levels of depressive symptomatology. Resilience scores as measured on CD-RISC were high (mean = 68, range: 23–96; SD = 33.0).

Regression analysis revealed that both childhood trauma (p = 0.007) and current depressive symptomatology (p = 0.005) were significantly associated with PTD during the trauma, whilst a higher resilience-score showed a lesser likelihood (p = 0.045) of PTD occurring (Table 1).

3.3. Genetics

Four SNPs in FKBP5 (rs4713916, rs1360780, rs3800373, rs9296158) were genotyped for each subject. All markers were in Hardy-Weinberg equilibrium [rs4713916 GC; n = 59 (73.8%)]; GA, n = 18 (22.5%); AA, n = 3 (3.8%) (p = 0.37); rs1360780 CC, n = 29 (36.2%); CT, n = 38 (47.5%); TT, n = 13 (16.2%) (p = 1.0); rs3800373 AA, n = 26 (34.2%); AC, n = 33 (43.4%); CC, n = 17 (22.4%) (p = 0.35); rs9296158 AA, n = 22 (27.8%); GA, n = 40 (50.6%); GG, n = 17 (21.5%) (p = 1.0).

No significant associations were observed between the single loci and peritraumatic dissociation, controlling for possible confounders of age, ethnicity, previous sexual assault, depression and resilience scores (rs4713916, p = 0.62; rs1360780, p = 0.28; rs3800373, p = 0.91; rs9296158, p = 0.32) (Table 1).

D’values revealed that rs9296158, rs1360780 and rs4713916 exhibit a high degree of linkage disequilibrium (LD), forming a haplotype block (Fig. 1). No significant associations between rs9296158, rs1360780 and rs4713916 haplotypes and PTD were observed (Table 2).
Table 1
Summary statistics and unadjusted association P-values.

<table>
<thead>
<tr>
<th>Characteristics median (range)</th>
<th>Childhood trauma</th>
<th>Peritraumatic dissociation</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritraumatic dissociation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>9 (0–24)</td>
<td>0.002*</td>
<td>0.002*</td>
</tr>
<tr>
<td>Age</td>
<td>24 (14–44)</td>
<td>0.416</td>
<td>0.968</td>
</tr>
<tr>
<td>Resilience</td>
<td>70 (23–96)</td>
<td>0.262</td>
<td>0.016*</td>
</tr>
<tr>
<td>Depression</td>
<td>28 (12–52)</td>
<td>0.026*</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics count (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-black</td>
<td>14 (17.3)</td>
<td>0.028*</td>
<td>0.733</td>
</tr>
<tr>
<td>Caucasian/white</td>
<td>2 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coloured</td>
<td>65 (80.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>53 (65.4)</td>
<td>0.000*</td>
<td>0.206</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (34.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (6.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (93.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01.

4. Discussion

In this sample of adult female rape survivors, no associations were found between selected genetic variants of the FKBP5 gene and the occurrence of PTD during the sexual traumatic event, as measured retrospectively. A history of childhood trauma was associated with an increased risk of PTD; whilst higher resilience scores were shown to confer a protective effect.

There is strong evidence of genetic influences to explicate how PTSD may develop (Almli et al., 2014). Specifically genes regulating the HPA axis and the stress response have been identified as potential candidates (Castro-Vale, van Rossum, Machado, Mota-Cardoso, & Carvalho, 2016b). Genetic variants of FKBP5 have been associated with a dysregulated HPA-axis, altered stress reactivity and risk of developing PTSD (Binder et al., 2008; Fuji et al., 2014). FKBP5 bind to glucocorticoid receptor decreasing cortisol-binding capacity and preventing nuclear translocation. This impairs negative feedback regulation of the HPA axis resulting in a prolonged stress response (Ising et al., 2008). FKBP5 may thus be an important therapeutic target for the prevention and treatment of PTSD (Zannas, Wiechmann, Gassen, & Binder, 2016). There may be genetic contributors to PTD risk and more specifically, these genetic influences may be shared with PTSD. A study found that rs3800373 and rs1360780 were associated with the occurrence of PTD during and since time of traumatic injury in a cohort of medically injured children (Koenen et al., 2005). However, the same effect was not replicated in the present study; possible reasons may include the developmental stage at which PTD occurred (adult versus child), trauma-type (sexual trauma versus medical injury), ethnicity (different population groups), and the timing of trauma (de Lima et al., 2010). A study by Yaylaci, Cicchetti, Rogosch, Bulut, & Hetzel (2017) demonstrated that the timing and chronicity of childhood trauma exposure predicted dissociative tendencies as moderated by FKBP5 genetic variants (Yaylaci et al., 2017), while another recent study found that exposure to childhood physical trauma may increase the risk for sub-clinical depressive and anxiety symptoms dependent on FKBP5 genetic variability (de Castro-Catala et al., 2017).

Evidence suggests FKBP5 genetic variants may alter HPA-axis functioning through exposure to childhood trauma (Koenen & Uddin, 2010; Yaylaci et al., 2017; Zannas & Binder, 2014). SNPs in FKBP5 have been shown to modify the association between childhood abuse and PTSD (Binder et al., 2008; Watkins et al., 2016b). In keeping with existing literature, a history of childhood trauma was associated with an increased risk of peritraumatic dissociation whilst more resilient individuals were less likely to experience peritraumatic dissociation. The small sample size and ethnic diversity of the sample however limits generalisability of these findings to other populations.

5. Conclusions

In this study, childhood trauma was found to significantly increase peritraumatic dissociation, whilst resilience conferred a significant protective effect. These associations were not modified by the absence or presence of any of the selected SNPs or haplotypes. These findings need to be replicated in larger samples of rape-exposed survivors and in diverse population groups.

Funding support

This work is supported by the South African Research Chair in PTSD hosted by Stellenbosch University, funded by the DST and
administered by NRF and the South African Medical Research Council.

Author contributions

ET in collaboration with co-authors designed concept and content of the manuscript; reviewed and summarised statistical results; wrote the first full draft of the manuscript and prepared for submission. SI performed all statistical analyses included in the manuscript; assisted with the conception design and content of the manuscript and critical revision of the final draft manuscript. GS provided guidance for the conception, design and content of the manuscript and assisted with critical revisions of the final draft manuscript. JN assisted in data acquisition and management and critical revision of the final draft manuscript. SS provided senior guidance of the study as a whole and assisted with critical intellectual revision of the final draft manuscript. All authors have read and approved the final version of this manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors would like to thank Prof. L. van der Merwe for her helpful comments and contributions.

References


