Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Brief report

Interactions between childhood maltreatment and brain-derived neurotrophic factor and serotonin transporter polymorphisms on depression symptoms

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ARTICLE INFO

Article history:
Received 7 November 2014
Received in revised form
17 April 2015
Accepted 25 April 2015

Keywords:
BDNF gene
Serotonin transporter gene
Depression

ABSTRACT

This study represents the first replication of the *BDNF* Val66Met ∗ 5-HTTLPR ∗ childhood maltreatment effect on self-reported depression symptoms using a rigorous maltreatment interview. Participants included a community sample of 339 adolescents/young adults (age 12–33; 265 female). In the context of childhood neglect, among *BDNF* Met-carriers, s-allele carriers of 5-HTTLPR reported significantly higher depression than l/l homozygotes, whereas a differential relation of 5-HTTLPR genotype to depression was not seen among *BDNF* Val/Val homozygotes.

1. Introduction

Several studies have investigated the interaction of a history of childhood maltreatment with the rs6265 Val66Met SNP of the *BDNF* gene and the 5-HTTLPR polymorphism of the *SLC6A4* gene on depression symptoms. Two studies reported that the *BDNF* Met-allele, in 5-HTTLPR short (s)-allele carriers, was associated with higher depression in those with childhood maltreatment (Kaufman et al., 2006; Wichers et al., 2008). In contrast, two reports found the *BDNF* Val-allele in 5-HTTLPR s-carriers was associated with elevated depression symptoms in those with maltreatment (Grabe et al., 2012; Comasco et al., 2013). Further, Grabe et al. (2012) found that this interaction was specific to emotional maltreatment. Failures to replicate this interaction have also been published (Aguilera et al., 2009; Nederhof et al., 2010; Carver et al., 2011).

Inconsistencies in the above results may be due, in part, to problems with self-report checklists of childhood maltreatment. Checklists are highly susceptible to depressive biases (Brewin et al., 1993), particularly for experiences that do not have behavioral indicators, such as emotional abuse and/or neglect. Our goal was to replicate the BDNF Val66Met ∗ 5-HTTLPR ∗ childhood maltreatment relation to depression symptoms using a contextual interview that provides independent and standardized ratings of maltreatment. Consistent with neuroimaging data identifying *BDNF* Met as the risk allele (Carballedo et al., 2013), we hypothesized that among those with maltreatment, and particularly emotional maltreatment, Met carriers with the 5-HTTLPR s-allele would have significantly higher depression severity than long/long (l/l) homozygotes.

2. Methods

2.1. Participants

Participants were recruited from advertisements and referrals to the University of Toronto or Queen's University between March,2007 and March,2013. This study received ethics board approval and participants provided written consent/assent. The project from which the participants were drawn was a case-control study of adolescents/young adults matched on sex, age, and ethnicity (Harkness et al., 2015) that included a group meeting DSM-IV (APA, 1994) criteria for a current unipolar depressive disorder, and a non-psychiatrically ill group. Exclusion criteria were lifetime bipolar/psychotic/substance disorder. Initial contact was made to 1587

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http://dx.doi.org/10.1016/j.psychres.2015.04.040
0165-1781/

individuals. Of these, 547 could not be re-contacted or declined, 691 failed to meet criteria, and 10 were missing data, leaving 339 (187 depressed)[1].

2.2. Measures

Demographic and clinical characteristics were assessed with the child/adolescent Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1996) or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P; First et al., 2002). Depression symptoms were assessed with the self-report Beck Depression Inventory (BDI-II; Beck, 1996). The Childhood Experience of Care and Abuse (CECA; Bifulco et al., 1994) interview queried history of physical, sexual, and emotional maltreatment, and neglect. Variables were independently rated (1-*marked*, 2-*moderate*, 3-*some*, 4-*little*/*none*) using the CECA manual (κ=0.86–1.00). Variables were dichotomized as 'present' (at least 3-some) or 'absent' (4-little/none). Due to the small numbers of participants with physical or sexual maltreatment, these variables were combined. Participants completed the diagnostic interview, BDI-II, and genetic sampling during one session, and the CECA one week later.

2.3. Genotyping

Participants in Toronto had three 10cc EDTA tubes of blood drawn, and at Queen's University provided a saliva sample. DNA from blood samples was extracted manually using a high salt method (Lahiri and Nurnberger, 1991). DNA from saliva samples was extracted per manufacturer instructions. We performed 10% repeats for quality control and achieved 100% concordance with the original genotypes. Genetic testing of the 5-HTTLPR and *BDNF* failed for two participants. The 5-HTTLPR was assessed using RFLP methods with PCR primers (Heils et al., 1996): l/l (n=100); l/s (n=157); s/s (n=82) (Hardy–Weinberg: χ^2=1.72, p=0.19). We compared l/l homozygotes to those with at least one s-allele. The *BDNF* Val66Met was genotyped according to manufacturer's directions: Met/Met (n=19); Met/Val (n=104); Val/Val (n=216) (Hardy–Weinberg: χ^2=1.84, p=0.17). We compared Val/Val homozygotes to those with at least one Met allele.

2.4. Statistical analysis

Analyses were performed using SPSS v.22 software. Preliminary univariate odds ratios were conducted to determine the relation among our primary variables of interest, and between our primary variables and demographic characteristics. Our main analyses involved three 2 * 2 * 2 fully factorial ANOVAs with BDI-II scores as the dependent variable. Independent variables were dummy-coded *BDNF* (0-Val/Val vs. 1-Met), 5-HTTLPR (0–l/l vs. 1-s), and each of the three maltreatment variables, respectively (0-absence vs. 1-presence). Significant interactions were followed up using pairwise comparisons. In preliminary models we entered study site, gender, age, and ethnicity separately, as well as their interactions with *BDNF*, 5-HTTLPR, and maltreatment type (Keller, 2014). Preliminary model results, as well as descriptive statistics of the main and lower-order interaction effects are available by request.

3. Results

3.1. Demographic and clinical characteristics of the sample

Females were more likely than males to report emotional maltreatment (*OR*, 1.83; 95% CI=1.00–3.37) and neglect (*OR*, 3.24; 95% CI=1.42–7.40) (see Table 1). European–Canadians were more likely to report neglect than non-European–Canadians, (*OR*, 2.30; 95% CI=1.31–4.03). *BDNF* Met-carriers were more likely to be non-European–Canadian than Val/Val homozygotes, (*OR*, 1.98; 95% CI=1.19–3.03).

BDNF Val66Met and 5-HTTLPR were not related to each other or to the maltreatment types (all *ps* > 0.16), except for 5-HTTLPR to neglect (ll: 29% vs. ls/ss: 19%; *OR*, 1.76; 95% CI=1.03–3.02). As expected, there was co-occurrence among maltreatment types: 57% (n=60) with emotional maltreatment reported neglect; 55% (n=66) with emotional maltreatment/neglect reported physical/sexual maltreatment. Therefore, physical/sexual maltreatment was entered as a covariate in models for emotional maltreatment and neglect, and vice-versa.

[1] Depressed and non-depressed participants did not differ on any demographic variable (all *ps* > 0.15).

3.2. Genotype by childhood maltreatment on BDI-II scores

Age, ethnicity, and study site were not significant covariates, either alone or in interaction with genotype or maltreatment. Therefore, models are presented without covariates. Neither the main effects or interactions of BDNF and 5-HTTLPR were significant in any model (all *ps* > 0.20). Those with physical/sexual maltreatment had significantly higher BDI-II scores than those without, F(1, 330)=7.05 [95% CI=1.60–10.68], p=0.008, η^2=0.02. However, no other main or interaction effects were significant.

In the model with emotional maltreatment, there was a significant main effect of maltreatment, F(1, 330)=16.80 [95% CI=4.48–12.76], p < 0.001, η^2=0.05, and a significant *BDNF* * emotional maltreatment interaction, F(1, 330)=3.98, p=0.047, η^2=0.012. Among those with emotional maltreatment, Val/Val carriers had significantly higher BDI-II scores than Met carriers, F(1, 334)=4.45 [95% CI=0.33–11.60], p=0.04, η^2=0.01 (see Table 1), whereas genotypes did not differ in BDI-II scores among those with no maltreatment (p=0.54, η^2=0.001). Interactions with 5-HTTLPR were not significant (*ps* > 0.29, η^2 < 0.003).

In the model with neglect, there was a main effect of neglect, F(1, 330)=19.00 [95% CI=4.99–13.21], p < 0.001, η^2=0.05, qualified by an interaction with *BDNF*, F(1, 330)=7.11, p=0.008, η^2=0.02. Further, the *BDNF* * 5-HTTLPR * neglect interaction was significant, F(1, 330)=10.31, p=0.001, η^2=0.03 (see Table 1). Among those with no neglect, the 2-way interaction of *BDNF* * 5-HTTLPR was not significant (p > 0.05, η^2=0.02), whereas this interaction was significant among those with neglect, F(1, 70)=9.52, p=0.003, η^2=0.12. Among Met-carriers with neglect, s-carriers scored significantly lower on the BDI-II than l/l homozygotes, F(1, 70)=8.33, p=0.005 [95% CI=4.22–23.12], η^2=0.11, whereas this difference was not significant among Val homozygotes (p=0.20, η^2=0.02). Further, among l/l homozygotes, Met-carriers with neglect scored significantly lower on the BDI-II than Val/Val homozygotes, F(1, 70)=15.74, p < 0.001 [95% CI=8.52–25.74], η^2=0.18, whereas this difference was not significant among s-carriers (p=0.80, η^2=0.001).

4. Discussion

Two main results emerged from this study. First, among those with emotional maltreatment or neglect, *BDNF* Val/Val homozygotes scored higher on the BDI-II than Met-carriers. These results are inconsistent with meta-analysis identifying Met as the risk allele in depression in the face of *recent* stress (Hosang et al., 2014); however, they are consistent with some studies on the moderating effect of *childhood* stress on the BDNF-depression link (Comasco et al., 2013). Therefore, further research is needed to clarify the differential contribution of the Met and Val alleles to depression in the face of specific environments (e.g., recent vs. early stress).

Second, among those with neglect specifically, the above relation was further modified by the 5-HTTLPR. Among Met-carriers, those with the risk s-allele of the 5-HTTLPR scored significantly higher on the BDI-II than l/l homozygotes, whereas a differential relation of 5-HTTLPR genotype to depression was not seen among Val/Val homozygotes. The pattern of means is consistent with a differential susceptibility model of psychopathology (Belsky, 1997). Specifically, Met-carriers with the non-risk l/l genotype of 5-HTTLPR scored lowest of all groups on the BDI-II and, thus, may show a resiliency to neglect relative to s-carriers if they are also Met-carriers of *BDNF*. These findings support a functional link between BDNF and serotonin. Further, they suggest that it may be the Met-allele in particular that 'trains' the differential susceptibility engendered by 5-HTTLPR in the face of

Please cite this article as: Harkness, K.L., et al., Interactions between childhood maltreatment and brain-derived neurotrophic factor and serotonin transporter polymorphisms on depression.... Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.04.040