Brief report

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


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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/youth 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
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., 1995) or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; 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-severe, 4-little/none) using the CECA manual (\(\chi = 0.86\pm 1.00\)). Variables were dichotomized as ‘present’ (at least 3-severe) or ‘absent’ (4-little/none). Due to the small number 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 were conducted to determine the relation among our primary variables of interest. The 5-HTTLPR was assessed using RFLP methods with PCR primers (Heils et al., 1996): l/l (\(\chi = 1.19\)); Met/Val (\(\chi = 4.48\pm 12.76\)), \(p < 0.01\), and a significant BDNF * emotional maltreatment interaction, \(F(1, 330) = 3.98\), \(p = 0.047\), \(\eta^2 = 0.012\). Among those with emotional maltreatment, Val/Val carriers had significantly higher BDI-II scores than Met carriers, \(F(1, 334) = 4.45\) [95% Cl. 0.03–11.60], \(p = 0.04\), \(\eta^2 = 0.01\) (see Table 1), whereas genotypes did not differ in BDI-II scores among those with no maltreatment (\(p = 0.54\), \(\eta^2 = 0.001\)). Interactions with 5-HTTLPR were not significant (\(p > 0.29\), \(\eta^2 < 0.003\)).

In the model with neglect, there was a main effect of neglect, \(F(1, 330) = 19.00\) [95% Cl. 4.99–13.21], \(p < 0.01\), \(\eta^2 = 0.05\), qualified by an interaction with BDNF, \(F(1, 330) = 7.11\), \(p = 0.008\), \(\eta^2 = 0.02\). Further, the BDNF × 5-HTTLPR × neglect interaction was significant, \(F(1, 330) = 10.31\), \(p = 0.001\), \(\eta^2 = 0.03\) (see Table 1). Among those with no neglect, the 2-way interaction of BDNF × 5-HTTLPR was not significant (\(p > 0.05\), \(\eta^2 = 0.02\), whereas this interaction was significant among those with neglect, \(p = 0.005\), \(\eta^2 = 0.012\). Among Met-carriers with neglect, s-carriers scored significantly lower on the BDI-II than l/l homozygotes, \(F(1, 70) = 38.33\), \(p = 0.005\) [95% Cl. 4.22–23.12], \(\eta^2 = 0.01\), whereas this difference was not significant among Val homozygotes (\(p > 0.20\), \(\eta^2 = 0.02\)). 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% Cl. 8.52–25.74], \(\eta^2 = 0.08\), whereas this difference was not significant among s-carriers (\(p = 0.80\), \(\eta^2 = 0.001\)).

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 recent 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

\(^1\) Depressed and non-depressed participants did not differ on any demographic variable \((\text{all } p > 0.15)\).
early neglect (Kaufman et al., 2006; Wichers et al., 2008; Bhang et al., 2011).

Results of the current study should be interpreted with caution given the small cell sizes, which limit the power of the study. This small sample size prevented us from stratifying analyses by ethnicity or sex and from analyzing all three genotypes of 5-HTTLPR. Further, our volunteer sample may not be representative of the population of Canadian youth. Replication is also warranted using clinician-rated depression measures. To date, no gene-by-environment studies have examined non-co-occurring subtypes of maltreatment given the high level of maltreatment co-occurrence in the population. Thus, this is an important area for further research. Finally, while the study used retrospective reports of childhood maltreatment, ratings were standardized to manualized examples to minimize bias. As Caspi et al. (2010) note, small-scale studies of gene by environment effects are possible when they are hypothesis-driven and use strong measurement of the environment.

In summary, polymorphisms in serotonergic and neurotrophic genes known to affect stress reactivity significantly interacted with early emotional neglect in relation to depression. Future epigenetic and neuroimaging studies are required to clarify the developmental timing of these effects and to identify the specific disruptions in serotonergic and neurotrophic signaling.

**Contributors**

Conception of study – KLH, JS, RMB, AR, JK.

Data collection, entry and analysis – KLH, JS, RMB, JGS, CL, RM, JK.

Interpretation of results and manuscript drafting – KLH, JS, JK.

Review of manuscript – all authors.

**Conflict of interest**

No financial or other conflicts of interest.
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