The Effects of a *BDNF* Val66Met Polymorphism on Posttraumatic Stress Disorder: A Meta-Analysis

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Keywords

Meta-analysis · Brain-derived neurotrophic factor · Posttraumatic stress disorder

Abstract

Objective: Given evidence that posttraumatic stress disorder (PTSD) is moderately heritable, a number of studies utilizing candidate gene approaches have attempted to examine the potential contributions of theoretically relevant genetic variation. Some of these studies have found support for a brain-derived neurotrophic factor (*BDNF*) variant, Val66Met, in the risk of developing PTSD, while others have failed to find this link. **Methods:** This study sought to reconcile these conflicting findings using a meta-analysis framework. Analyses were also used to determine whether there is significant heterogeneity in the link between this variant and PTSD. We conducted a systematic review of the literature on *BDNF* and PTSD from the PsycINFO and PubMed databases. A total of 11 studies were included in the analysis. **Results:** Findings indicate a marginally significant effect of

the *BDNF* Val66Met variant on PTSD ($p < 0.1$). However, of the 11 studies included, only 2 suggested an effect with a non-zero confidence interval, one of which showed a z score of 3.31. We did not find any evidence for heterogeneity. **Conclusions:** Findings from this meta-analytic investigation of the published literature provide little support for the Val66Met variant of *BDNF* as a predictor of PTSD. Future well-powered agnostic genome-wide association studies with more refined phenotyping are needed to clarify genetic influences on PTSD.

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Introduction

Exposure to traumatic events is common, with 50–70% of individuals experiencing at least one such event in their lifetime [1]. Of those who report experiencing a

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traumatic event, 5–31% meet the criteria for posttraumatic stress disorder (PTSD; [2–4]). Those who develop PTSD are at risk of adverse outcomes including major depression [5], substance misuse [6], physical health problems [7, 8], unemployment, and marital instability [9]. These substantial deleterious effects of PTSD reinforce the clinical and public health significance of research aimed at identifying factors that increase the risk of PTSD following trauma.

Existing literature suggests that biological processes may underlie the risk of developing PTSD [10], and there is mounting evidence that stress response processes are largely determined by genetic influences [11, 12]. Additionally, evidence from twin [13, 14] and molecular [15] studies suggests that PTSD itself is moderately heritable. However, minimal progress has been made in elucidating its genetic architecture. Although a candidate gene methodology allows researchers to choose polymorphisms using an *a priori* approach, work in this area has yielded conflicting evidence in terms of the impact of individual single-nucleotide polymorphisms (SNPs) on PTSD [16, 17]. Perhaps the most widely studied candidate gene marker in psychiatric genetics, particularly in studies incorporating trauma, is the promoter region of the serotonin transporter gene, *5-HTTLPR*, with work examining the relation between *5-HTTLPR* and PTSD yielding a “mixed picture” [18, 19]. However, meta-analyses examining the promoter region of this gene have recently provided further evidence on the effect of *5-HTTLPR* SNPs and variable number tandem repeats (VNTRs) on PTSD, indicating that individuals with at least one of the “s” alleles are more vulnerable to adverse environments (for examples, see [10, 11, 20]).

Some recent research has implicated neurotrophins, a group of proteins that support synaptic plasticity and long-term potentiation (LTP; Chao, 2003) in elevating the risk of PTSD. Specifically, BDNF within the neurotrophin family plays a role in modulating synaptic changes, including hippocampal LTP, integral to associative memory formation [12, 13]. The hippocampus also interacts with the amygdala, implicated in the response to affective material, including visual and auditory cues [14]. Therefore, following a traumatic event, some individuals may perceive sensory information in their environment as a cue for danger even when it is not paired with the traumatic event. The result is that these individuals have difficulty discriminating between real danger and non-dangerous cues associated with the traumatic event [15] and typically display increased hyperreactivity when reminded of the trauma [21].

Candidate studies of PTSD have identified >50 genes that exert significant effects (for reviews, see [22, 23]), with some finding a significant effect of the Val66Met *BDNF* polymorphism on PTSD [24]. This polymorphism is functional, as the Met allele is associated with reduced *BDNF* gene expression [25], impeding the extinction of conditioned fear [26]. Therefore, the Met allele of this SNP may be associated with increased risk for PTSD. Given the mixed research examining *BDNF* Val66Met and PTSD, and the evidence suggesting that the Met allele is important in fear responses, meta-analyses reconciling this literature are needed.

Two meta-analyses examining the relation between the *BDNF* Val66Met polymorphism and PTSD have been conducted [27, 28]. Wang [27] ($n = 6$ studies) found no overall effect of the Met allele on PTSD symptoms or correlates; however, when the controls (i.e., the subjects not exposed to trauma; $n = 3$ studies) were excluded, there was a significant increasing effect of the Met allele on PTSD/correlates. A more recent meta-analysis also found no overall effect of the Met allele on PTSD ($n = 9$ studies), but a marginal effect when comparing those with trauma exposure with and without PTSD ($n = 5$ studies) [28].

These findings highlight the importance of examining trauma-exposed controls in genetically informed investigations of PTSD. However, a major limitation in the extant literature is that potential ethnicity and sex differences were not examined. Examination of sex effects is critical, considering the finding that PTSD may be more genetically driven in females [29]. To illustrate, preliminary evidence has shown that estrogen induces the synthesis of BDNF in several brain regions [30], which could contribute to an elevated risk for PTSD in females versus males. Given differences in minor allele frequency across ethnic groups, there is also a need to test ethnicity as a moderator. This study adds to the existing literature by: (1) investigating the Val66Met polymorphism of *BDNF* on PTSD, including a larger number of studies comparing trauma-exposed controls to subjects with PTSD ($n = 11$ studies), and (2) testing whether sex and ethnicity potentially moderate the effect of genotype on PTSD.

Method

Search and Selection of Studies for Inclusion

We identified existing studies examining the main effects of *BDNF* Val66Met polymorphism on risk for PTSD. Potential studies were identified via the PubMed and PsycINFO databases following a two-step search strategy of association studies for (1) neurotrophin genes broadly, and (2) targeted genes more specifically,

Fig. 1. PRISMA-style flow chart showing selection of studies for meta-analysis of the Val66Met *BDNF* SNP and PTSD (adapted from [48]).

up to March 2017. This search process was repeated closer in time to the publication of this article (in October 2017), to ensure that no new articles had been missed between March and October of 2017. Search terms for step (1) were: posttraumatic stress disorder OR PTSD OR traumatic stress AND gene OR genetic AND neurotrophins. Step (2), i.e., the search for specific genes, replaced the search term “neurotrophins” with a specific gene of interest. Additionally, any other articles identified through in 2 recent PTSD genetics reviews were included ([22, 23]: *BDNF* OR brain-derived neurotrophic factor OR brain-derived neurotrophic factor. The reference sections of these review articles were examined to identify articles missed by applying the above search strategy. Figure 1 details the search steps and results that yielded 21 unique articles.

Screening of Search Results

The first author screened the search results to select studies for possible inclusion. The following inclusion criteria were applied to articles: (1) original research; (2) use of human subjects; (3) association study including the *BDNF* gene; (4) PTSD as an outcome; and (5) trauma-exposed control group. Only effect sizes resulting from main effects of *BDNF* Val66Met and PTSD were included. In cases where the criteria were unclear, articles were more thoroughly examined, coauthors were consulted, and a consensus was reached. Supplemental material was also reviewed for the identification and extraction of relevant data. Of the 21 unique articles initially identified, 11 met these inclusion criteria (Table 1).

Data Extraction and Coding

Two review authors (K.J.K. and R.L.T.) coded each included article based on a predetermined coding manual that included relevant variables. The information they extracted from each article included, but was not limited to, each study’s outcome variable (i.e., PTSD diagnosis vs. symptoms), the coding of alleles (e.g., additive, dominant, or recessive), and what/if any variables were controlled for (e.g., sex, age, or race/ethnicity). Concerns (e.g., one coder indicated that the authors used additive coding and the other indicated that dominant coding was used) were resolved throughout the coding process, and changes were made to the coding manual as necessary. Next, data from the coding manual were transferred into an appropriate meta-analysis worksheet, which included space for the input of proper statistics and effect sizes for all studies. Following data extraction and entry, an independent reviewer (T.T.H.) checked for agreement between coders. The first author reconciled any discrepancies identified.

Effect Size Calculation

An odds ratio (OR) was calculated for each study to examine whether the Met risk allele was associated with PTSD diagnoses and symptoms. In addition to the OR data, descriptive data, including means and standard deviations or frequency of occurrence, were used to calculate an effect size. When studies reported results from multiple regression analysis, the OR was calculated using the natural exponential of the unstandardized regression co-

Table 1. Descriptives of the 11 studies included in our meta-analysis

First author [ref.], year	Patients analyzed, <i>n</i>	Outcome	Coding
Bruenig [28], 2016	257	PTSD diagnosis	additive
Dai [49], 2017	175	PTSD diagnosis	dominant
Dretsch [37], 2016	689	PTSD diagnosis	additive
Dunn [35], 2014	205	PTSD symptoms	additive
Hemmings [50], 2013	150	PTSD symptoms	additive
La Greca [51], 2013	115	PTSD symptoms	additive
Li [52], 2016	524	PTSD diagnosis	dominant
Pivac [24], 2012	500	PTSD diagnosis	dominant
Valente [17], 2011	144	PTSD diagnosis	additive
van den Heuvel [36], 2016	115	PTSD diagnosis	dominant
Zhang [16], 2014	461	PTSD diagnosis	additive

Fig. 2. Forest plot depiction of effect sizes and confidence intervals.

efficient. In cases where no estimate of standard error was reported, the confidence interval (CI) was computed by using equations provided by Altman and Bland [31]. We contacted authors ($k = 1$) to request further information in cases of missing data necessary for effect size computation and all studies that met inclusionary criteria were included in the meta-analysis.

Statistical Analysis

Meta-analyses were conducted using the MAc R package on effect size data with combined sexes and ethnicities ($k = 11$). To account for various modes of inheritance, diagnosis type, duration, sex, and ethnic distribution in the studies analyzed, we employed a random-effects model variance [32]. Homogeneity of the effect size distribution was examined with Cochran's Q statistic, which investigates the null hypothesis that all studies are evaluating the same effect, by summing the squared deviations of each study's estimate from the overall meta-analytic estimate and weighting each study's contribution in the same manner as in the meta-analysis; p values are obtained by comparing the statistic with a χ^2 distribution with a $k-1$ df [33]. In order to test for moderation, the

meta-regression function (mareg) in MAc package in the statistical program R was employed.

Some studies explored associations between *BDNF* and PTSD reported findings from multiple outcomes, e.g., reporting effect sizes for PTSD severity and diagnosis. In these cases, we prioritized associations with enough data to calculate an OR. When studies reported findings providing enough data to calculate multiple effect sizes, we followed a protocol selected a priori used in a previous meta-analysis [34]. When studies reported raw/descriptive data in addition to parameter estimates for a specific outcome, raw/descriptive data were selected.

Results

Quality Assessment

Studies included in the final analysis ($k = 11$; Fig. 1) met quality standards. Studies either clearly described the recruitment processes and inclusion/exclusion criteria in the published articles ($k = 10$) or the researchers provided us with details in the form of individual correspondence ($k = 1$). All included studies identified a psychometrically sound instrument or clinical interview used to measure PTSD. Four of the studies reported employing correction for multiple testing [16, 35–37], but the rest did not.

Primary Analyses

A total of 3,335 participants from 11 samples were included in the meta-analysis examining the effect of variation within the *BDNF* Val66Met SNP on PTSD. Results indicate a marginally significant effect for the Met allele on the risk of PTSD (OR 1.20; CI 0.99–1.26; $p = 0.057$). Forest plots depicting effect sizes and their CIs for the included studies can be seen in Figure 2. It should also be noted that 1 of the studies [16] showed an effect size of

3.31; after omitting this article, the marginally significant effect became nonsignificant (OR 1.10; CI 0.97–1.24; ns). The homogeneity of variance analysis suggests no significant between study variability in this effect, either in the full sample of studies ($Qp = 0.11$) or when excluding the Zhang et al. [16] study ($Qp = 0.39$). We thus failed to demonstrate between study variation. Additionally, we found a nonsignificant moderating effect of gender within the full sample ($\beta = 0.0002$; ns) or when [16] was excluded ($\beta = -0.0002$; ns). We also found that ethnicity did not moderate the effect in the full sample or when [16] was excluded (β for percent African-American, -0.0002 [ns] and -0.0003 [ns], respectively; β for percent European American, 0.0002 [ns] and -0.0001 [ns], respectively; and β for percent Asian, 0.0007 [ns] and 0.0005 [ns], respectively). Publication bias analyses were not conducted because the overall p value did not meet conventional standards for significance (i.e., $p < 0.05$), so no unreported null studies would be needed for a nonsignificant effect.

Discussion

Given the conflicting candidate gene research examining *BDNF* Val66Met and PTSD, a meta-analysis was conducted to examine the link between this polymorphism and PTSD. The Met allele, hypothesized to be related to PTSD risk, is associated with reduced *BDNF* gene expression [25], which impedes the extinction of conditioned fear [26]. Consistent with the mixed findings in previous candidate gene studies of Val66Met and PTSD, our meta-analysis did not support a significant effect of *BDNF* Val66Met on PTSD. The overall p value in the meta-analysis was marginally significant, and the hint of an effect was driven by 1 study with a large z score [16], as 9 of the 11 studies included in the meta-analysis suggested no effect of *BDNF* on PTSD. Additionally, no significant hits of *BDNF* were found in any of the 8 genome-wide association studies (GWAS) [38–45]. Candidate gene studies and GWAS select SNPs for inclusion in variable ways (e.g., 1 SNP was chosen a priori based on functional literature vs. agnostic tests across the entire genome) and apply different p value thresholds (e.g., $p < 0.05$ and $p < 5 \times 10^{-8}$). This meta-analysis reconciles this discrepancy in candidate gene findings, supporting the findings of the GWAS in this area, specifically that there is not a significant direct effect of Val66Met *BDNF* on PTSD.

Our investigation extended the published literature by examining heterogeneity across findings, and whether we might detect sex or ethnicity as a potential moderator in

the relation between *BDNF* and PTSD. Ethnic differences in the minor allele frequency of this variant have been demonstrated in the literature, but tests of ethnic differences in the impact of this polymorphism on PTSD have been largely ignored.

Sex has been shown to influence the likelihood of a PTSD diagnosis, and preliminary work suggested that these genetic influences were stronger in women than men [29]. However, other works on *BDNF* by sex interactions to predict related phenotypes have mixed results [46, 47].

Our analyses suggest that there is no significant moderation by ethnicity or sex, meaning that the findings do not differ for men and women, or across ethnic groups. It should be noted that 4 of the 11 studies in this meta-analysis (including [16]) had $\geq 89\%$ male participants, which may have impacted our finding of no significant sex moderation effect.

This study is not without its limitations. Specifically, we included analyses of candidate gene studies which provide sparse coverage of genes, include small samples with a low power, and are heterogeneous in terms of quality control approaches (e.g., a lack of genomic control for ancestry). Additionally, there were limitations common to meta-analytic approaches. Specifically, methods of sampling varied across studies, different ancestral groups were represented, with varying treatment of that heterogeneity, and type of phenotypes measured also varied (e.g., diagnosis vs. clinical symptoms). Our findings were limited by such inconsistencies across the available studies.

However, we expanded on previous meta-analytic research by including only trauma-exposed controls, exclusively examining individuals with PTSD, and including the largest number of studies ($k = 11$). Our investigation did not support a significant association between the Val66Met marker of *BDNF* and PTSD. Additionally, our meta-analysis of published studies and previous meta-analyses investigating the effect of *BDNF* on PTSD suggest that it may be beneficial for future research to utilize more precise phenotypic measurements, include measures of epigenetic influences, or perhaps examine interactions between *BDNF* and other markers (rather than simply examining a single marker) in predicting PTSD risk.

Acknowledgments

Funding was provided to N.N. (R01MH105379 and R01MH108641) and C.S. and M.J.L. (MH020030-17).

Statement of Ethics

As this study did not involve subjects, no IRB approval was sought.

Disclosure Statement

The authors declare no conflicts of interest.

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