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

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Introduction

Exposure to traumatic events is common, with 50–70% of individuals experiencing at least one over their lifetime [1]. Of those who report experiencing a traumatic event, between 5–31% meet lifetime criteria for posttraumatic stress disorder [PTSD; [2–4]]. Those who develop PTSD are at risk for adverse outcomes including major depression [5], substance misuse [6], physical health problems ([7, 8], and 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 risk for PTSD following trauma.

Existing literature suggests that biological processes may underlie risk for PTSD [15] and there is mounting evidence that stress response processes are largely determined by genetic influences [16, 17]. Additionally, evidence from twin [18, 19] and molecular [20] 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 SNPs on PTSD [[10, 11]]. Perhaps the most widely studied candidate gene marker in psychiatric genetics, particularly

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Conflicts of Interest

The authors declare no conflicts of interest.

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' [12, 13]. However, meta-analyses examining the promoter region of this gene have recently provided further evidence on the effect of *5-HTTLPR* SNPs and VNTRs on PTSD, indicating that those with at least one of the 's' alleles are more vulnerable to adverse environments (e.g. [14–16]).

Some recent research has implicated neurotrophins, a group of proteins that support synaptic plasticity and long-term potentiation (LTP; Chao, 2003), in elevated risk for PTSD. Specifically, BDNF within the neurotrophin family plays a role in modulating synaptic changes, including hippocampal LTP, integral to associative memory formation [17, 18]. The hippocampus also interacts with the amygdala, implicated in the response to affective material, including visual and auditory cues [19]. 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 [20] and typically display increased hyper-reactivity when reminded of the trauma [21].

Candidate studies of PTSD have identified more than 50 genes that exert significant effects [for reviews, see [22, 23]], with some finding a significant effect of the Val66Met *BDNF* polymorphism on PTSD (e.g., [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]. The Wang et al. (2015, n=6 studies) paper found no overall effect of the Met allele on PTSD symptoms or correlates. However, when the authors excluded non-trauma exposed controls (i.e., n=3 studies) they found a significant increasing effect of the Met allele on PTSD/correlates. Another more recent meta-analysis [28] also found no overall effect of the Met allele on PTSD (n=9 studies), but found a marginal effect when comparing those with trauma exposure with and without PTSD (n=5 studies). 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, which is critical given that findings that PTSD may be more genetically driven in females [29]. To illustrate, preliminary evidence has shown that estrogen induces 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. Thus, the current study adds to existing literature by: (1) investigating the Val66Met polymorphism of *BDNF* on PTSD, including a larger number of studies comparing trauma-exposed controls to those with PTSD (n=11 studies) and (2) testing whether sex and ethnicity potentially moderate the effect of genotype on PTSD.

Method

Ethical Approval

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

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 through the PubMed and PsycINFO databases following a two-step search strategy of association studies for 1) Neurotrophins genes broadly and 2) targeted genes more specifically up until March of 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. In step one, search terms were: [posttraumatic stress disorder OR PTSD OR traumatic stress] AND [gene OR genetic] AND [Neurotrophins]. The step two search for specific genes replaced the Neurotrophins search term with a specific gene of interest. Additionally, any other articles identified through two 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 through the above search strategy. Figure 1 details the search steps and results, yielding 21 unique articles.

Screening of search results

The first author screened 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, co-authors were consulted, and a consensus was made. Supplemental material was also reviewed for identification and extraction of relevant data. Of the 21 unique articles initially identified, 11 met these inclusion criteria. See Table 1 for information on included articles.

Data extraction and coding

Two review authors (KK and RT) coded each included article based on a pre-determined coding manual that included relevant variables. Information that the two coders extracted from each article included, but was not limited to, each study's outcome variable (i.e., PTSD diagnosis versus symptoms), coding of alleles (e.g., additive, dominant, or recessive coding), and what/if any variables were controlled for (e.g., sex, age, race/ethnicity). Concerns (e.g., one coder indicated that the authors used additive coding and the other coder indicated 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 was transferred into an appropriate meta-analysis worksheet, which included space for inputting proper statistics and effect sizes for all studies. Following data extraction and entry, one

independent reviewer (TH) checked for agreement across coders. The first author reconciled identified discrepancies.

Effect Size Calculation

An Odds Ratio (OR) and Confidence Interval 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 coefficient. In cases where no estimate of standard error was reported, the confidence interval was computed using equations provided by [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 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 analyzed studies, we employed a random effect 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^2distribution with k-1 degrees of freedom [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, for example 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, see Figure 1) met quality standards. Studies either clearly described recruitment processes and inclusion/exclusion criteria in published manuscripts (k =10) or researchers provided details to the current study authors in separate correspondences (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 (i.e., [10, 35–37]), while 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 risk for PTSD (OR: 1.20, CI: .99–1.26, p=.057). The forest plots depicting effect sizes and their confidence intervals for the included studies can be seen in Figure 2. It should also be noted that one of the studies (Zhang et al., 2014) evidenced an effect size of 3.31. After omitting the Zhang et al. (2014) article, the marginally significant effect became non-significant (OR: 1.10, CI: .97–1.24, NS). The homogeneity of variance analyses suggests no significant between study variability in this effect either in the full sample of studies (*Qp*=0.11) or when excluding Zhang et al., (2014) (*Qp*=0.39). Thus, we fail to demonstrate between study variation. Additionally, we found a non-significant moderating effect of gender within the full sample (β: .0002, NS) or when the Zhang et al., (2014) article is excluded (β: −.0002, NS). We also found that ethnicity did not moderate the effect in the full sample, or excluding the Zhang et al., (2014) article (β's for percent African-American, with [−.0002, NS] and without this article [−.0003, NS] ; β's for percent European American, with [.0002, NS] and without this article [−.0001, NS] ; β's for percent Asian, with [.0007, NS] and without this article [.0005, NS]). Publication bias analyses were not conducted because the overall p-value did not meet conventional standards for significance (i.e., p<.05), so no unreported null studies would be a needed for a non-significant effect.

Discussion

Given the conflicting candidate gene research examining *BDNF* Val66Met and PTSD, a meta-analysis was conducted to examine the relation 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 prior candidate gene studies of Val66Met and PTSD, our meta-analysis does not provide support for 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 is being driven by one study with a large z-score [10], as nine of the 11 studies we included in this meta-analysis suggested no effect of *BDNF* on PTSD. Additionally, none of the eight GWAS of PTSD found *BDNF* to be a genome-wide significant hit [38–45]. Candidate gene studies and GWAS select SNPs for inclusion in discrepant ways (i.e., one SNP chosen a priori based on functional literature versus agnostic tests across the entire genome) and apply different p-value thresholds (i.e., p<.05 and $p < 5 \times 10^{-8}$). This meta-analysis reconciles the discrepant candidate gene findings, supporting the findings of GWAS in this area, specifically that there is not a significant direct effect of Val66Met *BDNF* on PTSD.

The present investigation further extended 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 have 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 likelihood of PTSD diagnosis and preliminary work suggested that these genetic

influences were stronger in women than men [29]. However, other work on BDNF by sex interactions to predict related phenotypes has been mixed [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 of the participants from studies included in this meta-analysis, four (including Zhang et al., 2014) of the 11 articles having 89% or more male participants, which may have impacted our not finding a significant sex moderation effect.

This study is not without its limitations. Specifically, our meta-analysis included analyses of candidate gene studies which provide sparse coverage of genes, include small samples with low power, and are heterogeneous in terms of quality control approaches (e.g., lack of genomic control for ancestry). Additionally, there were a number of limitations common to meta-analytic approaches. Specifically, studies used varied methods of sampling, different ancestral groups were represented with varying treatment of that heterogeneity, and studies differed on the type of phenotype they measured (i.e., diagnosis versus clinical symptoms). Thus, the current study findings are limited by these inconsistencies across currently available studies.

However, this study expands previous meta-analytic research by including only trauma-exposed controls, exclusively examining individuals with PTSD, and including the largest number of studies (k=11). The present meta-analytic investigation did not support a significant association between the Val66Met marker of *BDNF* and PTSD. Additionally, our meta-analysis of published studies and prior meta-analyses investigating the effect of *BDNF* on PTSD suggests 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.

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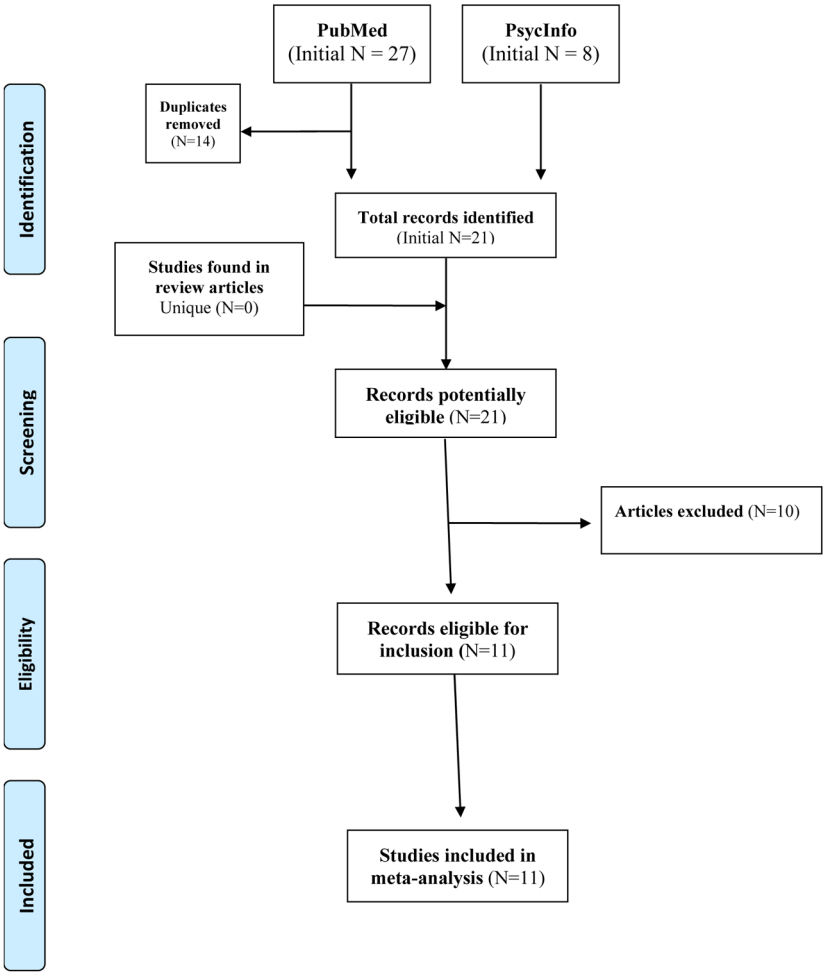

Figure 1.

PRISMA-style flow chart showing selection of studies for meta-analysis of Val66Met *BDNF* SNP and PTSD. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

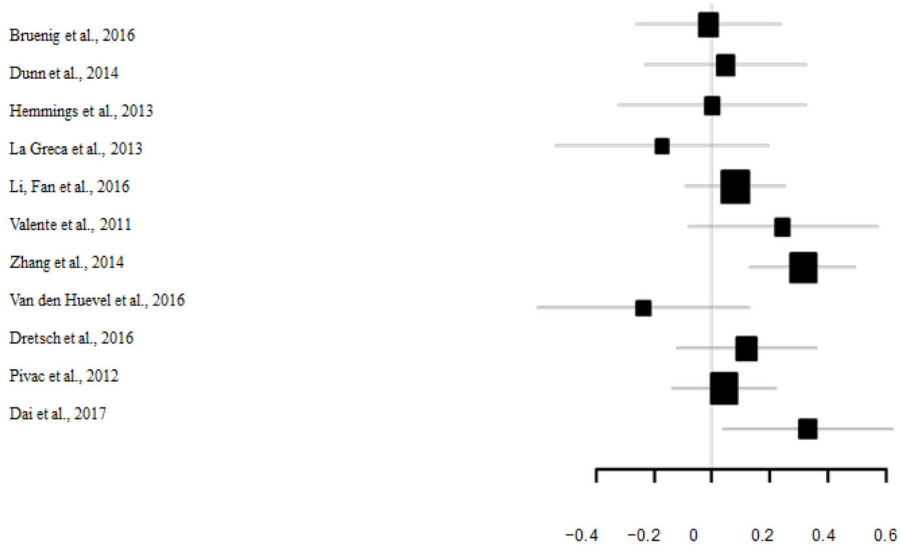

Figure 2.
Forest plot depiction of effect sizes and confidence intervals.

Table 1

Included Study Descriptives.

Study Number	First Author (Year)	Analyzed N	Outcome	Coding
1	Bruenig (2016)	257	PTSD Diagnosis	Additive
2	Dai (2017)	175	PTSD Diagnosis	Dominant
3	Dretsch (2015)	689	PTSD Diagnosis	Additive
4	Dunn (2014)	205	PTSD Symptoms	Additive
5	Hemmings (2013)	150	PTSD Symptoms	Additive
6	La Greca (2013)	115	PTSD Symptoms	Additive
7	Li (2016)	524	PTSD Diagnosis	Dominant
8	Pivac (2012)	500	PTSD Diagnosis	Dominant
9	Valente (2011)	144	PTSD Diagnosis	Additive
10	Van den Hueval (2016)	115	PTSD Diagnosis	Dominant
11	Zhang (2014)	461	PTSD Diagnosis	Additive