Author's response to reviews

Title: Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis

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Author's response to reviews: see over
Addressing reviewers’ comments for: Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis (MS: 9098804749773235)

- **Reviewer One: Lars Kessing**

  1) Inclusion of Vinberg et al (2009)

  The study conducted by Vinberg and colleagues (2009) does not examine the direct interaction between stressful life events and the BDNF Val66Met polymorphism in depression (we have contacted the author of the article to confirm). However some of the results of the Vinberg et al (2009) study are pertinent to the current article and have been included in the introduction (see page 7).

  ‘Individuals with at least one Met allele of the BDNF gene and at high risk of affective disorders (co-twin diagnosed with a mood disorder) have elevated evening cortisol levels which suggests altered stress response [59]’

- **Reviewer Two: Charles Nemeroff**

  1) Number of participants included in the meta-analyses and discussion of sufficient power to draw conclusions.

  We recognise that this is an important issue and thank the reviewer for highlighting this point. To reflect this we have amended sections in the abstract, results and discussion (see below). It should be noted the total number of participants included in each set of analyses are provided in the versions of Tables 2-4 in the penultimate rows.

  **Amended sentence in abstract (page 3):**

  ‘Twenty-two studies with a pooled total of 14,233 participants met the inclusion criteria,...’

  **Amended sections in Results section:**

  - Page 10 for the life stress-BDNF interaction meta-analyses
    “Combining the results from the identified studies with a total of 14,233 participants, showed that the interaction between the Met variant of the BDNF Val66Met polymorphism significantly moderates the relationship between life stress and depression (p=0.03).”

  - Page 11 for the childhood adversity-BDNF interaction meta-analyses
    “In meta-analysing the results from included studies with a combined sample of 10,521 individuals, a trend towards a significant interaction between childhood adversity and BDNF in depression was detected (p=0.051), but was not improved on when only those studies with Caucasian samples were analysed (p=0.12).”

  - Page 11 for the stressful life events-BDNF interaction meta-analyses
    “The stressful events-BDNF interaction in depression was investigated in eleven studies; five uncovered a significant effect using a combined sample of 7594 individuals (see Table 4).”
Amended sections in Discussion

- Page 12
  “Twenty-two studies with a combined sample of 14,233 participants were identified through the literature search and met the eligibility criteria, eight of which reported a significant interaction between life stress and the Met variant of BDNF Val<sup>66</sup>Met.”

- Page 15
  “Twenty-two studies with a pooled sample of 14,233 individuals were included in this review, of which eight provided evidence in support of an interaction between life stress and the BDNF Val<sup>66</sup>Met polymorphism in depression.”

To address the issue of power to detect significant effects the following sections have been added to the manuscript.

Discussion (page 15)

   Thirdly, several included studies had restricted sample sizes thus limiting their statistical power [eg. 66, 79]. Power analyses revealed that using the pooled samples provided greater than 80% power to detect significant effects of all three interactions tested in this study (e.g. life stress x BDNF, childhood adversity x BDNF, stressful life events x BDNF in depression).

2) BDNF, antidepressant and neurogenesis discussion.

The reviewer highlights an excellent point, however commenting on the debate this area is outside the remit of this paper and is not possible due to space limitations (Reviewer 3 requests a shortening of the Introduction). However we have included a sentence which acknowledges the controversy in this area. (see pages 6-7 in the Introduction)

“There is evidence that stress and trauma result in decreased BDNF levels in both rodents [47, 48] and humans [49, 50]. The findings from several meta-analyses show that lower serum BDNF levels are detected among depressed patients relative to controls but these levels are normalised with antidepressant treatment [51, 52]. There is some debate surrounding the link between BDNF antidepressants and (hippocampal) neurogenesis (see [53] for more a detailed discussion).”

3. BDNF and CNS availability

   Reviewer comment: There is reference to studies showing differences in serum concentrations of BDNF in depression. What is the source of serum BDNF and is there any reason to believe that this reflects in any way CNS availability of BDNF?

   The studies referred to in the manuscript generally examined BDNF levels in blood. A recent paper provides convincing evidence that the brain contributes to 70-80% of circulating BDNF levels

*BDNF x Stress in depression*
BDNF x Stress in depression

(Rasmussen et al., 2009). A full discussion is outside the remit of the current paper and there has not been included for this reason and because of space limitations.

4) Inclusion/Discussion of other polymorphisms in the BDNF gene
Several polymorphisms exist within the BDNF gene (e.g. rs7103411) the most common ones are tagged by the Val66Met SNP (highly correlated; see Uher et al 2009; Liu et al., 2008). The Val66Met polymorphism has the most published data available of all the BDNF polymorphisms and is thus the best candidate for meta-analysis. To account for this issue the following section has been included in the introduction (page 7).

“Although the BDNF gene consists of several polymorphisms many are in high linkage disequilibrium and thus highly correlated [55, 56].”

5) Include reference to other candidate genes researched within gene-environment interactions in depression

The interaction between the 5-HTTLPR and stress in depression is the most widely researched gene-environmental interaction in psychiatry but we acknowledge that it would be more balanced to highlight other genes that have been shown to moderate the impact of life stress in depression. Thus we have included the following section in the introduction (page 6).

“Other genes have been implicated in stress vulnerability including the CRHR1 [41, 42], FKBP5 [43] and BDNF [44] genes. The relationship between the Val66Met variant in the BDNF gene and stress in depression has been widely researched and thus a systematic review and meta-analysis is warranted to synthesize the literature.”

6) Childhood adversity x life stress x BDNF in depression

The possible three way interaction between childhood adversity, stressful life events and BDNF in depression has been largely ignored in the literature and thus not possible to examine in this meta-analysis. The importance of exploring this three way interaction is highlighted in the following section that appears in the discussion (page 13)

“The aetiology of psychiatric disorders such as major depression is complex and is likely to involve multiple interactions between genetic variants and environmental factors. Few studies have explored the three-way interaction between childhood adversity, stressful life events and stress vulnerability genetic variants [87]. A wealth of research shows that adversity in childhood sensitizes individuals to adult stressful life events increasing their risk for major depression [88]. Given the mounting evidence that genetic variants such as BDNF Val66Met polymorphism are important stress vulnerability factors sets the stage for future studies that should explore the childhood adversity x stressful life events x BDNF interaction in the context of depression.”

BDNF x Stress in depression
1) Literature review date & sources
The literature review for this study has been updated (up until 22\textsuperscript{nd} November 2013; documented in the abstract and method section) which yielded some additional studies and led to a re-analysis which is evident throughout the paper.

- Abstract (page 3)
  “A literature search was conducted using PsychINFO and Pubmed until 22\textsuperscript{nd} November 2013.”

- Method (page 7)
  “The literature searches were undertaken using PsycINFO and Pub Med up until 22\textsuperscript{nd} November 2013 for original research studies.”

2) Sources used for literature search
Given that the Medline and PubMed are similar in our new search we have used PubMed and PsychINFO which is reflected throughout the paper (abstract and method).

- Abstract (page 3)
  “A literature search was conducted using PsychINFO and Pubmed until 22\textsuperscript{nd} November 2013.”

- Method (page 7)
  “The literature searches were undertaken using PsycINFO and Pub Med up until 22\textsuperscript{nd} November 2013 for original research studies.”

3) Better structuring of abstract with more information concerning results
The abstract has been amended so that it is structured and provides sufficient detail on each aspect of the paper (see abstract page 3).

**Background:** Major Depression is a disabling psychiatric illness with complex origins. Life stress (childhood adversity and recent stressful events) is a robust risk factor for depression. The relationship between life stress and Val\textsuperscript{66} Met polymorphism in the Brain-derived neurotrophic factor [BDNF] gene has received much attention. The aim of the present article is to review and meta-analyse the results from published studies examining this interaction.

**Method:** A literature search was conducted using PsychINFO and Pubmed until 22\textsuperscript{nd} November 2013. Twenty-two studies with a pooled total of 14,233 participants met the inclusion criteria, the results of which were combined and a meta-analysis performed using the Liptak-Stouffer z-score method.

**Results:** The results suggest that the Met allele of BDNF Val\textsuperscript{66} Met significantly moderates the relationship between life stress and depression (p=0.03). When the studies were stratified by type of environmental stressor, the evidence was stronger for an interaction with stressful life events (p=0.01) and weaker for interaction of BDNF Val\textsuperscript{66} Met with childhood adversity (p=0.051).

**Conclusions:** The interaction between BDNF and life stress in depression is stronger for stressful life events rather than childhood adversity. Methodological limitations of existing studies include poor measurement of life stress.”

**BDNF x Stress in depression**
4) **Shortening of the introduction**
As requested the introduction has been shortened. The readership of the journal is diverse thus the audience may not be familiar with the broad number of topics covered in the article (depression, life stress, gene-environment interactions and BDNF). Therefore these areas are still outlined in sufficient detail to ensure comprehension of the areas. Please also note that additional sections have been added to the introduction to account for the comments of the other two reviewers.

5) **Combined p-values rather than effect sizes**
As with the majority of research areas, there is a large amount of heterogeneity in the studies examining the interaction between life stress and BDNF in depression. This leads to diverse populations, measures and thus statistical analyses. Using the combined p-value allows for the inclusion of all of the available studies rather than a strict selection of more homogenous sub-group, which may effect or bias meta-analytic results.

6) **Use of one-sided p-value**
The evidence points to the Met variant of the BDNF polymorphism being linked to stress vulnerability and it is this hypothesis that we are testing. The research question has been refined to explicitly reflect this (see Introduction, page 7).

“The purpose of the current paper is to systematically review and meta-analyse the literature concerned with this interaction addressing the specific question: ‘is there a significant interaction between the Met variant of BDNF Val^{66}Met and life stress in depression?’”