Author's response to reviews

Title: Association of childhood trauma with cognitive functioning in healthy adults: a pilot study

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Author's response to reviews: see over
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Association of childhood trauma with cognitive function in healthy adults
Submission of Revised Manuscript

Dear Ms. Neilan,

Thank you for sending us the Reviewers’ comments for the above manuscript and for considering a revised version of the manuscript. The Reviewers’ comments were extremely thoughtful and helped us to significantly improve the presentation and interpretation of the results.

Please find responses to the Reviewers’ comments below. We changed the manuscript as described in these responses. We would be very pleased if the manuscript was accepted for publication in the BioMed Central.

Yours sincerely,

William C. Reeves, MD, MSc
Reviewer #1:
We thank the reviewer for stating that our study is interesting. We appreciated the thoughtful comments of this reviewer and have addressed the concerns as follows:

1) The sample should be described much more in detail. I wonder if someone can figure what emotional abuse $= 1.54$ (SE $0.10$) really means. I would like to suggest a) to present the dichotomized prevalences for the subscales of the CTQ, b) to present the CTQ total score and c) to describe the anchors of the CTQ and give the reader some probes of the items.

   We thank the reviewer for this important comment. In order to provide a more detailed description regarding the meaning of the CTQ scores, we added the following information:

   1a) We added the prevalence rates of each type of CTQ exposures as well as any exposure across all subscales in Table 1 based on moderate-severe cut-off scores provided by Bernstein & Fink (1998). A proportion of 25.5% of subjects had reported at least one type of maltreatment above the moderate-severe cutoff.

   1b) We further included the CTQ total score in Table 1. We further discuss in the text that the mean subscale scores are in the non-mild range for all scales.

   1c) We now present examples of items for each subscale in the Methods section. We explain that these items are scored on a 5 point Likert scale from “not true” to “very often true”. We explain that scores for each subscale range between 5 and 25. The CTQ provides cut-off scores to classify cases according to none-mild versus moderate-severe exposure. We now provide these cut-off scores. We then explain that a score above the cutoff for an individual scale reflects that most items were scored with “often true”.

2) I wonder if there was no subthreshold depression or anxiety in the sample. Lack of assessment of depression and anxiety severity is a weakness of the study, which should be discussed at least.

   Indeed, we did assess depression and anxiety severity in the larger study and we did include these data for the subjects studied here in the revised manuscript. Depression severity was measured using the Zung Self-rating Depression Scale (SDS). We further measured state and trait anxiety using the Spielberger State-Trait-Anxiety Inventory (STAI). Mean scores for the sample were in the normal (no depression) and low anxiety (state and trait) ranges. None of the subjects in this sample had a depression or anxiety rating in the clinical range or at the threshold for clinical relevance. We have added this information to Table 1 and to the text of the manuscript.
3) I wonder if it is possible to dichotomize the sample in persons with substantial childhood adversities and subjects not having been exposed. As a discretionary revision, I would like to suggest to test group differences also.

We thank the reviewer for this suggestion. We now present in Table 1 the prevalence rate for each maltreatment type in the current sample. In the current sample, exposure frequencies for different types of CTQ subscales ranged between 2 and 8 subjects. Twelve subjects had experienced any type of maltreatment across different categories. Since our data show that there may be differential effects of different types of abuse, it would have been necessary to compare groups by abuse type. We feel that the small prevalence of abuse above the cutoff in each subscale would not permit to dichotomize subjects and perform group comparisons; therefore, we chose to use regression analyses taking advantage of the availability of dimensional scores.

4) I wonder if it is possible to line out a bit more the clinical relevance of the findings, e.g. by comparing them to results of clinical samples.

We thank the reviewer for this suggestion. Also, please see response to Reviewer 2. We did add a discussion of the clinical literature (i.e., PTSD) in the Introduction and Discussion sections. In the discussion, we further implemented clinical recommendations for individuals with childhood trauma based on our findings.
Reviewer #2:

1) The authors describe some of the animal literature which shows that early-life stress can have profound consequences on cognitive functioning. Some authors in the field of PTSD assume that these cognitive consequences are a result of hippocampal damage caused by traumatic stress and its associated chronically increased cortisol levels (see, for example, Bremner, 1999, 2002). This idea has sparked criticism from other scientists (e.g., Jelicic & Merckelbach, 2004). The theoretical framework might benefit inclusion this literature.

_We thank the reviewer for this critical point. Indeed, there is an extensive literature that demonstrates in humans that early-life trauma is linked with increased HPA axis reactivity (Heim et al 2000, 2001, 2004, 2008) that in turn is linked to depression risk. Heim and colleagues also have shown that reduced hippocampal volume in depressed patients is linked to early-life trauma, potentially due to repeated bursts of cortisol in response to stressors. We thus agree that cognitive changes after early-life trauma might plausibly be caused by hypercortisolemia and resulting hippocampal volume loss. Others have criticized this notion. Specifically, small hippocampi are not observed in maltreated children (DeBellis et al. 1999); it has been argued that repeated episodes of depression cause hippocampal volume loss (Sheline and colleagues). On the other hand, there is also evidence that small hippocampi might be pre-existing risk factors that enhance the risk to develop psychopathology (Gilbertson et al. 2003). Lupien, McEwen, Gunnar and Heim (2009) and colleagues in a recent review have suggested that the neurotoxicity and vulnerability hypotheses in fact may not be mutually exclusive. We now have added discussion of these considerations to the manuscript._

2) The authors might include reference to the resilience literature showing that most people do not develop overt psychopathology after a traumatic event (Ozer, Best, Lipsey, & Weiss, 2003; Bonano, 2004).

_We have included discussion of the concept of resilience._

3) I do not find the theoretical framework convincing. The authors should outline specific predictions based on prior findings and describe assumed mechanism in more detail.

_The introduction has been rewritten to focus around hippocampus, neuroendocrine and neurocognitive findings in depression and PTSD, and that some of the neurocognitive changes seen in these disorders may indeed be the consequence of early-life trauma, which is a risk factor for these disorders._

4) The authors state in the discussion that memory deficits were associated with trauma and that working memory deficits are predictive of academic achievement. It seems that the authors assume that memory mediates academic achievement. Mediation between achievement and memory could be determined statistically as outlined by (Baron & Kenny, 1986).

_The memory deficits (measured by CANTAB) and academic achievement (measured by WRAT-3) were performed at the same time point. Therefore, we feel that it is not sufficient to test the predictive association and so we have deleted this statement._
5) Please also report standardized regression coefficients.

We added the standardized regression coefficients in Tables 2-4.

6) Why would income be a possible confounder?

We thank the reviewer for questioning the statement. Initially we thought that income might be associated with access to education during childhood and hence influence academic achievement. We have now removed the statement from the discussion.

7. The authors state that a Bonferroni correction would be overly conservative given the sample size. I do not understand their line of reasoning. Keep in mind that chance findings/extreme values are also more likely in small samples.

We were trying to make the correction of the p-values for the multiple statistical tests. According to Bonferroni correction, a significance level should become 0.005 (=0.05/10) if alpha was set up at 0.05 and 10 independent statistical tests are performed. However, a Bonferroni adjustment has been shown to be conservative (Perneger 1998). In our study, we applied a 0.01 alpha level of statistical significance to adjust for multiple testing instead of the popular standard level of 0.05. We acknowledge that our approach increases our confidence that we are not falsely rejecting a true null hypothesis (a Type I error), but increases the risk of failing to reject a false null hypothesis (a Type II error), and therefore reduces the statistical power. In the current version, we have deleted this statement regarding the Bonferroni correction.

Reference:

8. Please determine Cronbach's alphas for the current sample.

In the previous version, we referenced a previous manuscript where we mention that “Based on a sample of 223 individuals enrolled in the initial study [19], the internal consistency coefficients (Cronbach’s alpha) for the five subscales range from 0.68 to 0.92.” We now have included the Cronbach’s alphas for the current sample. We made the following changes in the text: “Based on the current sample of the 47 healthy subjects, the internal consistency coefficients (Cronbach’s alpha) for the five subscales range from 0.41 to 0.89.”

9. Could the analysis be substantially compressed by predicting trauma-exposure from all cognitive measures? This would only show the unique portion of the effects.

Types and severity of trauma-exposure were measured by the CTQ scale which asked the subject to recall their experiences growing up as a child and a teenager, whereas all cognitive measures were measured at the later time during their participation at the clinic for cognitive function in their adulthood. For time sequential events, we feel that it might not be statistically sound to perform the analysis in using cognitive measures to predict trauma-exposures.
10. Were axis II disorders also screened and excluded?

    *We did not screen or exclude for personality disorders. This is an important limitation which we now acknowledge in the discussion.*

11. The authors state in the discussion that their sample was randomly selected from the general population. I find this unlikely given the skewed gender distribution. This approach would require, for example, selection from a phonebook. Self-refereed would not be randomly selected from the general population.

    *The subjects included in the current manuscript were part of a larger population-based survey and clinical study on chronic fatigue syndrome (CFS) that was conducted by the CDC in Wichita, KS. The CDC study used random digit dialing of >30,000 households, representing 90,000 people in Wichita, to identify cases with CFS-like illness. These cases were then invited to participate in a clinical study. From the same population, healthy controls were identified to match the CFS cases based on sex, race, age, etc.; hence the skewed distribution of sex. The healthy controls included here are the proportion of subjects who were free of medical/psychiatric illness and free of psychotropic medication. Thus, these controls were randomly identified and are representative of the Wichita population. We have clarified this in the manuscript text.*