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Title: Relationship of recent stress to amygdala volume in depressed and healthy adults

**Background:** The authors focus on the stress response system and its effects on amygdala volumetric differences in the context of depression. The study focused on right-handed participants experiencing a major depressive episode during major depressive disorder or bipolar depression, and healthy volunteers. A detailed psychiatric history included self-reported history of physical or sexual abuse. Stressful life events within the past six months were recorded using the St. Paul-Ramsey Scale. The authors found no association between physical and/or sexual abuse history and amygdala volume. Life stress within the last six months, however, was associated with smaller left amygdala volume. The association between stress and amygdala volume did not differ by diagnostic group. The authors conclude that amygdala volume changes may occur rapidly and reversibly, and independent of depression status.

***Comment:*** I commend the authors for exploring the link between stress and brain structure in individuals with depression. There is indeed an increasing body of research linking trauma and mental illness. Thus research highlighting the importance to predict who may be more at risk to develop mental illness later in life. Given these strength I would have however expected more clarity and precision in terms of both brain measures, overall clinical status and stress-related measures. Thus, I believe this paper could be further strengthened by addressing the following points.

Abstract: I would add at least a sentence linking stress/amygdala/depression. In methods please provide means and SDs for age and gender for each group of participants. Please mention the type of analyses performed to extract amygdala volumes. Also mention what kind of statistical analyses you performed on the data. Please discard F/p-values, they are usually not mentioned in the abstract.

Introduction:1.overall the authors should provide additional citations/information on the effects of acute, long-term and “past” stress on the brain. If not available, one should highlight this gap. 2.There is no explicit rationale for studying brain volumes, stress and depression/mood. 3. Did the authors have apriori hypotheses? 4. Since the authors included both bipolar and unipolar depression one could also explain why these two groups were selected and then merged together. 5. Why did the authors focus on the amygdala? 6.Page 3, lines 1-3: it is unclear if the authors mean that combat-related PTSD and cancer related intrusive thoughts lead to greater/smaller amygdala volumes.7. The authors do not provide an explicit rationale for linking stress/child abuse and mood overall. 8. Also I think that comparing the stress associated with physical/sexual abuse to daily stress events is not really “fair”. Could the authors provide a better rationale or at least address this important point somewhere. 9. is there evidence suggesting that abuse may change stress response, reactivity/resilience to stress etc.? If so please discuss it. If not please state/criticize this if suitable. For instance, there are models of stress response that the authors could explore such as social defeat (van Nierop et al., 2014), attachment (Sitko et al., 2014), dysphoric mood (Marwaha and Bebbington, 2015), affective dysregulation (van Nierop et al., 2014 and Marwaha and Bebbington, 2015), anxiety (Fisher et al., 2013) and negative self-schemas (Fisher et al., 2012). 10. Is the number of individuals who experienced child abuse and who develop unipolar depression equal or greater than for bipolar depression? Please address this.

Methods: 1.could the authors explain why they selected the St. Paul-Ramsey scale of stressful life events? In particular I wonder if testing the impact of stress on someone’s life is equal to measuring stress response? 2. Could the authors provide additional details on the psychometric properties of this instrument. For instance Cronbach alpha, validity, sensitivity etc. 3. Could the authors provide additional details in terms of the type of information collected the history of child/sexual abuse? Did the authors categorize it as presence/absence of abuse or did they consider splitting it into physical vs abuse? 5. Overall did the authors collect information in terms of timing/duration of both abuse and recent stressful events? This would appear to me to be a potential mediator of stress response and possibly brain structure. 6. MRI: could the authors provide additional information on reported reliability of manual tracing compared to other “automatized” techniques? Why did the authors select this technique?

Statistical analyses: 1. did the authors check for the distribution of clinical measures? 2. Did the authors think of comparing individuals with high/low stress scores, based on the median score for instance. 3. Did the authors use a hierarchical regression? 4. Did the authors consider including depression scores instead of rather entering a dichotomous variable such as e.g. depressed/non-depressed? If not why? 5. Why did the authors select individuals who had been off medication for 2 weeks. 2 weeks is obviously too short to make any difference in terms of brain measures but may have had an impact on the evaluation of the stressful event. 6. Also why didn’t the authors include a measure of anxiety/stress as a “trait” rather than a “state”? It could have informed the authors as to whether individuals have a particular way of handling stress for instance.

Results: 1. Table 1 does not provide information on illness duration, number of mood episodes, age of onset etc. could the authors information on this. Also I wonder if annual income is truly informative. 2. Could the authors explicitly state if there were differences in amygdala volumes between HC and the clinical population(s)? 3. Also did the authors calculate correlations between stress and amygdala volumes, and or severity of depression and stress etc. to explore the data further.

Discussion: 1. it would be helpful to have a paragraph outlining how stress affects human physiology and the timing of these effects. For instance, I assume the stressful life events may be of shorter duration than child abuse? 2. Also did unipolar and bipolar depression patients differ in terms of stress/amygdala volumes and clinical status? 3. I would recommend that the authors include a more critical overview of what stress really means for brain functions and what child/sexual abuse may lead to. Also please consider restricting your discussion by addressing how the current finding can be linked to current knowledge on amygdala volumes and mood, stress and mood, childhood and stress, resilience and neurodevelopment. Also what are the clinical implications of these findings?