**JAMA**

"Effects of Early Life Stress on Depression, Cognitive Performance, and Brain Morphology," by Warren Taylor. We would appreciate your assistance in reviewing it. The abstract, if available, is pasted in below.

*Background:* The authors aimed to identify which childhood early life stressors (ELS) were predictive of adult depression and examine their effect on cognitive function and brain structure. They used a cross-sectional study utilizing neuropsychological testing magnetic resonance imaging. Conclusions showed that the effect of total ELS exposure differed between depressed and nondepressed groups. Greater ELS exposure was associated with slower processing speed and smaller OFC volumes in depressed subjects, but faster speed and larger OFC volumes in nondepressed subjects. In contrast, exposure to predictive ELSs had similar effects in both groups. Subjects reporting predictive ELSs exhibited poorer processing speed and working memory performance, smaller volumes of the lateral OFC and caudate, and decreased cortical thickness in multiple areas including the insula bilaterally. The effects of predictive ELS exposure differed between diagnostic groups only in the left hippocampus, in which depressed subjects' ELS exposure was associated with smaller volumes.

Comments: I would like to commend the authors to expand current knowledge on the effects of stressful life events on the brain by including measures of cold cognition. This manuscript is novel and findings are of clinical relevance. I would therefore support its publication in JAMA pending a few changes that should be easily addressed by the authors.

1. The authors may consider adding to their conclusions that including stress-related physiological measures in a longitudinal study may be beneficial. Indeed, repeated exposure to stress triggers the activation of the hypothalamus-pituitary-adrenal (HPA) axis, resulting in production of glucocorticoids by the adrenal gland. Expression of glucocorticoids may have long lasting effects on the regions of the brain that regulate their release (see LUPIEN, S. J., MCEWEN, B. S., GUNNAR, M. R. & HEIM, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci, 10, 434-445).
2. A reference to the developmental trajectory of the brain areas found to be associated with ELS may be of interest. For instance, the hippocampus continues to develop till the age of two years, and so it is extremely vulnerable to the effects of chronic stress (e.g. severe abuse in the early years of life is associated with reduced brain volume). This reduction in volume decreases with increasing age of onset and increases with increased duration of the maltreatment. (Essex, M. J., Shirtcliff, E. A., Burk, L. R., Ruttle, P. L., Klein, M. H., Slattery, M. J., ... & Armstrong, J. M. (2011). Influence of early life stress on later hypothalamic–pituitary–adrenal axis functioning and its covariation with mental health symptoms: a study of the allostatic process from childhood into adolescence. Development and psychopathology, 23(04), 1039-1058).
3. The authors mention in their limitations that the ELS questionnaire does not measure severity and chronicity of the events. I would also address somewhere the fact that in the current studies life events occurred between the ages of 0-17 years and that
   1. trauma at different time points in an individual’s life might be associated with different outcomes, depending on the brain structure that was affected at the time of exposure to adversity e.g. the frontal cortex undergoes major development during adolescence. Stress during adolescence may result in various psychopathologies such as anxiety and depression.
   2. The brain structures that are developing or undergoing age-related changes at the moment of the stressful life event are more vulnerable to the effects of stress.
4. I noticed that all the events listed in Table 2 have a pronounced negative connotation. However a growing body of literature shows a link between stress associated with (perceived) positive life events, e.g. wedding, birth etc. and mental health. Did the authors consider adding a scale including both positive and negative life events? I think this topic could be addressed in the conclusions.

Frank, E., Tu, X. M., Anderson, B., Reynolds, C. F., Karp, J. F., Mayo, A., ... & Kupfer, D. J. (1996). Effects of positive and negative life events on time to depression onset: an analysis of additivity and timing. Psychological Medicine, 26(03), 613-626.

Methods

1. Overall would the authors consider adding eta squares when they report F statistics
2. Table 1: can the authors provide additional information on IQ or estimated verbal abilities (e.g. WAIS, WRAT etc.)
3. I noticed that Ns of table 2 and etable1 differ. Could the authors clarify whether significance of demographic and ELS variables found to be different between depressed/non-depressed was maintained when considering only those included in subsequent predictive/regression models?
4. In etable 3 please explain acronym OFC

Typos

Page 6, line 143: atrained

Page 10 line 244 Subjects should be “subjects”