Reviewer’s report

Title: Biological embedding of childhood adversity: from physiological mechanisms to clinical implications

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Reviewer: Joan Luby

Reviewer’s report:

This is a very interesting and well done review overall that sheds a lot of light and nicely synthesizes a broad literature making it quite understandable. I found it very informative and easy to read and I feel the message is quite important to the public health. Along that line, I do feel that based on the available literature (much of which is cited with a few exceptions mentioned below), the public health recommendations going beyond screening could be quite a bit stronger, more targeted and more elaborated.

Along this line, there are a number of early interventions that focus on parenting support, many known to have effects on biological and neural markers that are relevant here. I think the paper might review and include this work. Related to this, another aspect that is missing is the key role of parenting support in the risk trajectory described. There are two independent areas of work that bear on this—one the work of Miller and Chen (some of which is cited) which demonstrated that maternal support has a positive effect on the inflammatory state related to early adversity (Molecular Psychiatry). Another is the finding that maternal support mediated the effect of poverty on brain development from Luby and colleagues (JAMA Pediatrics). Further, a recent intervention study focused on parenting support reported changes in brain volumes (Brody et al., JAMA Pediatrics). Based on these findings it would seem that stronger and more specific public health recommendations could be made and are particularly important to be made in the current environment. The critique is really that in the context of a very strong empirical database, the recommendations are too nebulous and open ended and could (and in this reviewer’s mind should) in fact be more directed and specific.

While the paper is quite comprehensive and should be applauded for this, one area that seems a bit under-developed is the immune section where again some compelling work by Miller, Chen and colleagues describing the pro-inflammatory phenotype could be added. Another is the area of the gut brain axis where a good deal of animal data and some interesting human studies (see Mazmanian) would enrich the argument and fill in the scientific picture. With the enhancements to the paper—I believe this will be an important addition to the literature.

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