Reviewer’s report

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

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Reviewer: Cyrille Delpierre

Reviewer’s report:

This is a very interesting review that aims to survey evidence on physiological mechanisms thought to link early childhood adversity (or early life adversity, ELA) and subsequent health. Authors try to adopt a comprehensive approach of the biological mechanisms involved in the phenomenon of biological embedding and try to propose recommendation for clinicians. In that way, this paper is useful and important.

I would have minor comments that may improve the document:

In the background part, I would suggest to the authors to read the following papers published by Kelly-Irving et al. on the link between adverse childhood experiences and cancer/mortality (Kelly-Irving M et al. BMC Public Health. 2013; Kelly-Irving M et al. Eur J Epidemiol. 2013) and by Barboza et al. on the link between adverse childhood experiences and allostatic load (Barboza Solís C et al. Proc Natl Acad Sci U S A. 2015). These papers are important contribution using birth cohort studies showing the effect of ACE on later health and on global physiological wear and tear. These papers could also balance the affirmation made by authors on the fact that prior literature has tended to focus on changes in one disease. I agree with this tendancy but it may be relevant to underline also effort made by some research teams to propose a more comprehensive approach of ELA effects.

In the paragraph entitled "defining early life adversity", I think more details are needed to explain why the authors do not conceptualize early adversity as synonymous of "stress". For justifying this choice authors differentiate excessive stress and for example deprivation of needed environemental inputs in sensory domain. But literature on ELA and stress show that this is not only extreme stress that matters but also chronic stress. And chronic stress involves a lot of potential exposures such as lack of sensorial stimulation. Moreover the large majority of the physiological systems involved in the biological embedding of ELA are also involved as biological system of stress responses. I think that clarifications about how authors link ELA and stress are then needed.

Regarding methodological challenges, maybe more information is needed on how authors conceive their review in particular regarding human studies they consider. In my opinion, birth cohort studies and prospective lifecourse approach are particularly relevant to analyse the longstandinf effects of ELA on biology. Do authors privilege such data in their review?
Information regarding types of studies, type of databases (medline, others?) and key word used to do the review may be useful.

In the part entitled "axis 3: immune functioning", in the last paragraph, considering health implications I would add that immunity/inflammation has also implications on cancer risk and progression.

In the part entitled "interactive effects across axes", I think that authors should talk about allostatic load (AL) that is conceptualized as a global physiological wear and tear, a multiple physiological deregulations that is in line with the idea of interactive effects across systems. The concept of AL would deserve some lines here.

In the "clinical and research applications", authors should insist on the importance to propose interventions not only focused on specific disease but on health. This paper can help clinicians to understand better health and physiological functioning and not only the etiology of one specific disease. This paper can reveal the common soil by which ELA may influence many chronic diseases. Consequently, professionals who should be targeted by this work are not only physicians or the medical world but more generally all the professionals and institutions working with children (preschool institutions, schools).

Minor points

Some acronyms need to be defined: COMT; CNS; PFC in table and figure 1

In figure 1, I would suggest to stay focused on health impact and not on social outcomes that are strongly associated with the social and political context (in particular incarceration or employment)

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