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PERSPECTIVES

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Potential Societal and Cultural Implications of Transgenerational Epigenetic Methylation of Trauma and PTSD: Pathology or Resilience?

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Psychological trauma is unique in that it is an environmental event that could induce biological changes and post-traumatic stress disorder (PTSD), depression, or other mood disorders in some patients. On the other hand, there may be no psychopathology (in most cases), or even sometimes post-traumatic growth and resilience. According to the DSM-5, trauma is a prerequisite for PTSD and traumatic stress disorder, but not for depressive episodes or mood disorders, or other psychiatric conditions. This paper brings attention to the preliminary literature on transgenerational inheritance due to trauma exposure and its societal and cultural implications. There is accumulating evidence that exposure to trauma can be passed transgenerationally through epigenetic inheritance leading to changes in gene expression and possible disorders or resilience. The effects of resilience from transgenerational inheritance have not been studied, but should be, for a full understanding not only of the disease risk across generations, but also of its social and cultural implications. The epigenetic pathologic effects across generations also need further studies, as the current research is preliminary; larger replications are needed for definitive and more complete understanding. I present here a glimpse of where we are, a vision of where we should go in terms of future research direction for disease risk transmission, and recommend studies of resilience and post-traumatic growth across generations, as well as other studies related to the societal implications at the population level.

INTRODUCTION

Psychological trauma is unique in that it is an environmental event that could induce biological changes and post-traumatic stress disorder (PTSD) or depression or other mood disorders in some patients. On the other hand, there may be no psychopathology (in most cases) or even sometimes post-traumatic growth and resilience. According to the DSM-5, trauma is a prerequisite for PTSD and traumatic stress disorder, but not for depressive episodes or mood disorders, or other psychiatric conditions. That is to say, PTSD cannot occur, or be diagnosed in absence of trauma, but mood disorders can.

The occurrence of PTSD has long been established

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Abbreviations: PTSD, post-traumatic stress disorder; PTG, post-traumatic growth.

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to be due to exposure to trauma, and it has been assumed that only environmental factors could contribute to the development of PTSD. Interestingly enough, though, twin studies have found that the heritability of PTSD has been much larger than previously thought. Heritability of PTSD was found to be between 30% and 70% in twin studies [1-5]. However, with evolving understanding and studies, it is now clearer that structural genetics do not fully explain the biological component of PTSD [6-8].

Thus, epigenetics, affecting the functionality of the genes (and having the ability to respond to environmental stimuli) could be the missing link in explaining the differential susceptibility. Among all the functional changes to the gene, the best-studied mechanism is DNA methylation. Increased methylation of the promoter region typically represses the transcription of the gene.

Not only has this epigenetic change been associated with trauma in certain individuals, but these epigenetic changes might also be transmitted transgenerationally [9], meaning transmission from parents to children and across generations. Research from cells and animal studies has ignited this understanding, as well as more recent research in humans. However, much more research needs to be done to replicate these findings and to provide further understanding on these relationships.

Studies That Support the Transgenerational Effects of Trauma

We presented an extensive prior review on the transgenerational effects of trauma on epigenetic methylation [9]. We will thus only briefly highlight below the evolving literature and will then present new early data on resilience and future directions.

A study of genocide examined its impact on women who were pregnant at the time (1995) in Rwanda [10]. Over 20% of the population in Rwanda in 2011 had PTSD [11]. The researcher studied the epigenetic modifications in the children of those women who were pregnant at the time [10]. The study group included 25 widows and their children, and the control group included 25 Rwandan pregnant women who at the time of the genocide were living abroad. Mothers and their children who experienced the genocide in Rwanda had significantly higher levels of PTSD and depression than the control group. The promoter regions at exon 1F promoter of the glucocorticoid receptor *NR3C1*, at CpG3-CpG9 had higher methylation levels.

An examination of the transgenerational methylation changes on *FKBP5* (moderator of glucocorticoid activity) in Holocaust survivors, in 32 individuals and their 22 offspring, and eight controls and their nine offspring [12], showed significantly higher *FKBP5* intron 7 methylation levels in survivors, but lower levels in their offspring. The authors opined that this opposite methylation effect may be due to biological accommodation in children [12].

A follow up study, among children of Holocaust survivors showed lower methylation of *FKBP5* site 6 in children of Holocaust survivors compared to controls ($p=0.041$) [13]. Mother's exposure to the Holocaust was associated with statistically significant lower methylation ($p=0.043$), but father's exposure to the Holocaust was associated with lower methylation, but not statistically significant methylation in children compared to controls. A significantly lower methylation was found in Holocaust survival children whose mothers were exposed to the trauma in childhood as opposed to exposure later in life ($p=0.028$).

Could There be Potential Positive Aspects of Transgenerational Trauma?

At this time, we really don't know. However, post-traumatic growth and increased resilience have been seen with many individuals after trauma rather than disease and disability.

Early studies suggest that within a generation there can be epigenetic methylations effects associated with resilience after trauma. A pilot study ($N = 47$) explored the relationship between the stress genes nuclear receptor subfamily 3 group C member 1 (*NR3C1*) and FK06 binding protein 5 (*FKBP5*) with DNA methylation (from saliva sample) in regard to posttrauma responses including PTSD symptom severity, resilience, and post-traumatic growth (PTG). The study found initial evidence of a significant association of methylation of different *FKBP5* and *NR3C1* sites not only with PTSD symptom severity, but also with resilience and PTG. Opposite directions of methylation in *FKBP5* site cg07485685 occurred for PTSD symptom severity versus resilience [14] as measured by the Brief Resilience Scale [15]). Limitations of this study include the possibility of low generalizability due to low diversity of the sample and small sample size. Also, another limitation is the candidate gene cross-sectional design. Nonetheless, this study provides an interesting initial signal of possible epigenetic methylation associated with resilience and differential effects of PTSD versus resilience in terms of epigenetic methylation.

It is conceivable that there is also a subgroup or subgroups that might develop similar post-traumatic growth and increased resilience as a result of not only generational trauma but also transgenerational trauma. This could be due to some genetic and epigenetic protective factors. It is also possible that there is an interplay with psychological factors and life experience beyond the epigenetic contribution. On the other hand, the environmental contributions could be fully explained by the epigenetic factors.

If that is the case, it would be crucial to study the factors that differentiate the development of post-traumatic growth and resilience versus the factors that allow disease development and disability. This could have great social and cultural impacts.

CONCLUSION

The limited literature in humans suggests that children of parents who were exposed to extreme trauma have epigenetic methylation changes [10,12,13]. This risk of developing PTSD or other disorders including physical disorders risk could be passed from generation to generation. The environmental transgenerational effects that lead to changes in DNA methylation of offspring have also been demonstrated in animal models. As an example, dietary supplements during pregnancy were associated with increased methylation in mice (of the Agouti coat color gene)—causing permanent change in coat color [16,17]. Of course, environmental interventions are not limited to trauma and dietary supplements but could range to include others factors such as toxins or even pharmacological interventions [18].

In line with the well-established notion that glucocorticoids are stress hormones, many of the studies reviewed found that the glucocorticoid receptor (*NR3C1*) gene is associated with methylation changes. For instance, maternal exposure to intimate partner violence during pregnancy was associated with increased *NR3C1* DNA methylation in teenage children [19]. Maternal exposure to war violence or rape during pregnancy was associated with increased methylation in the *NR3C1* promoter region in newborns [20,21].

Some weaknesses of the current literature include both the limited number of studies, as well as the small sample sizes. Also, other confounding factors not accounted for in the studies may play a role.

Despite the limitations of the literature at present, there is accumulating evidence to at least suggest the epigenetic transgenerational transmission changes (of which DNA methylation is the most studied) from parents to children likely occur. This area merits replication in larger studies to examine the epigenetic effects transgenerationally. Other factors that the studies should consider we described previously [9].

Also, as discussed above, not all transgenerational effects are necessarily negative. It is conceivable that positive effects such as resilience could occur [14]. Similarly, while studying epigenetic alterations, it is not necessary that every alteration is associated with pathology. It could be that some reflect a compensatory mechanism or a protective factor. Thus, it is important in naturalistic and association studies among others to try to not only find a correlation, but also find whether this correlation (or even causation) represents a disease risk, a protective risk, or a compensatory factor.

I recommend that future studies focus not only on resilience as a result of within generational trauma, but also on transgenerational trauma. Such studies would be important for further understanding the various effects and outcomes of trauma across generations.

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