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Avenging Lamarck: the role of epigenetic in modulating reactions to traumatic events

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SUMMARY

Post Traumatic Growth and Post-Traumatic Stress disorder represent two parallel phenomena whose origin is a common ground, trauma. Following the Lamarck theory, recent epigenetic studies seem to confirm the importance of gene-environment interaction in determining different reactions to traumatic events that, according to the concept of Historical Trauma and Post-Traumatic Slave Syndrome, could interfere with the entire course of lives of a family and/or of a cultural group, becoming intergenerational. Recently, a growing field of research has focused on the associations between epigenome and mental illnesses, also including autism spectrum disorder (ASD), reporting a possible higher vulnerability to epigenetic alterations, in ASD subjects. Indeed, a greater neurobiological and genetic vulnerability to environment influences in association with the deficit in interaction and understanding of social stimuli make ASD subjects more easily exposed to trauma. On the other hand, these subjects, compared to neurotypical people, may more frequently develop positive reactions, thanks to divergent thinking that allows them to adopt a new point of view following stressful events. In this framework, the epigenome represents a new key to understand the impact on highly challenging events on illness trajectories and their role in mental disorders.

Key words: epigenetic, post-traumatic stress disorder, post traumatic growth, post traumatic slave syndrome, autism spectrum disorder

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Although the scientific literature of recent decades deeply focused on the negative consequences of trauma [1-5], recently a growing field of research paid attention to the possible positive outcomes of traumatic experiences that may or may not be favoured by personological traits and environmental conditions, thus introducing the concept of post-traumatic growth (PTG) [6-10]. PTG and post-traumatic stress disorder (PTSD) represent two parallel phenomena whose origin is a common ground, trauma [6-11]. In this perspective, the environment is highly involved by influencing the reaction to challenges and difficult situations, from which not only different psychological trajectories may develop for the subject, but also, as reported by some studies, endure across generations of families and populations [6,12-16]. Lamarck, an early transformation theory thinker, famously claimed that organisms' environment and habits could influence physiology, producing physical changes that could be inherited across generations [17]. This theory was at first criticized due to the intrinsic atheism of it, then partly accepted, and in the end the debate settled around Darwinian theories, as simple lamarkism was considered by early 20th century biologists as unprovable, absurd, or even dangerous [17,18], while aroused new interest in the 21st century being confirmed by new studies on DNA [14-19]. Anyway, since first studies on twins and families reported genetic underpinnings for the development or not of traumatic symptoms [14-19], some questions still remain unresolved: different reactions to trauma may run in families for genetic or environmental reasons? How important could be the environment impact on trauma reaction? How environment/gene interactions track different psychological trajectories starting from stressful life events? According to the concept of Historical Trauma, the environmental setting, in the frame of extreme and prolonged traumatic events, can determine intense emotional and psychological discomfort, often associated with prolonged grief [20-22]. In this perspective, traumatic experience could interfere with the entire course of lives of a family and/or of a cultural group, becoming intergenerational. In 2005, Joy the Gruy resumed the concept introducing the theory of post-traumatic slave syndrome (PTSS) [23]. Referring to the African-American community, the author described PTSS as a pattern of behaviours, beliefs and actions determined by a multigenerational trauma, resulting from centuries of slavery [12,13]. Since the Colonialism era, continuous oppression and institutionalized racism have determined the development of a symptomatology characterized by reduced self-esteem, hopelessness and self-destructive feelings, anger and aggressivity, as well as internalized racism leading to aversion towards the belonging group and its customs [13]. In this framework, it appears clear how traumatic experiences could be transmitted to further generations not present at the time of exposure, eventually inducing, as reported by a conspicuous field of biological researches, molecular adjustments through synaptic plasticity, oxytocin signalling, cholinergic synapse and inflammatory system alterations [24], that pass through generations [19-20,24]. Indeed, in extreme events' survivors' offspring, lower levels of cortisol have been associated with high risk of developing post-traumatic stress symptoms despite not having experienced the trauma [14-15,25]. Moreover, in these subjects the life expectancy was reduced by a factor of 2.23 times [19]. In this perspective, gene/environment interaction becomes extremely important, and epigenetics takes a central role. Human genome can be modified by external environment through DNA modification mechanisms, methylation among the most common [25].

According to early age adverse events (ACEs) theory, adverse environmental events suffered in childhood, such as neglect, physical and sexual abuse, maltreatments [26], may stably modify our DNA, making the subject more vulnerable to the development of psychiatric and neurological disorders in adulthood. Recently, few studies reported the discovery of Transport and Golgi Organization 6 Homolog (TANGO6) gene's methylation, that often seems to follow ACEs, being associated with an increased risk of developing post-traumatic stress symptoms and cognitive disorders [27,28]. It should also be noted how multiple ACEs' may assume later in life the appearance of a complex trauma that results in issues with emotional regulation, identity and attachment, ascribable to the symptomatic picture of PTSD complex [28-30]. This specific presentation may also explain the relatively low percentage of full-fledged PTSD diagnosis reported in young people with cumulative adverse early age events [28].

In recent years, a growing field of research has focused on the associations between epigenome and mental illnesses [31-33], including also autism spectrum disorder (ASD) [34-36]. Over the past 20 years, the prevalence of ASD in children has increased from 0.66% in 2002 to 1-2% in 2023 [36,37]. In this framework, some authors also suggested how this growth in prevalence may not be explained only by changes in diagnostic nosography or genetics. Recent studies in epigenetics have detected specific gene alterations as possible risk factors of ASD [36,38]. Indeed, while the epigenetic involvement in hippocampal plasticity, social and motivational behaviour, glucocorticoid metabolism and stress response still remains uncertain [34], subjects with ASD seem to have a general hypomethylation of DNA in the brain and blood cells compared to neurotypical subjects [36]. Moreover, some studies have shown altered DNA methylation of several ASD candidate genes, including the gene encoding the oxytocin receptor (OXTR), the RELN and SH3 And Multiple Ankyrin Repeat Domains 3 (SHANK3) genes, following exposure to environmental factors known as risk factors for ASD: nutritional (vitamin D and folate), or toxic ones (sodium valproate, bisphenol A) [38]. Moreover, decreased social experiences seem to predict an hypermethylation in OXTR causing a suppression in this gene expression and a decreasing in circulating oxytocin, which is involved in important social behaviors such as empathy, eye gaze and pair bonding, highly compromised in ASD [34]. Autistic subjects, therefore, seem to show a greater predisposition to altered methylation mechanisms and thus, possibly, to gene/environment interaction compared to other neuropsychiatric disorders [36,38]. It should be noted how a possible higher vulnerability to epigenetic alterations could explain the increased risk, for subjects in the autism spectrum, to develop post-traumatic stress symptoms more easily following exposure to high challenging situations. Starting from a greater neurobiological and genetic vulnerability to environment influences [36,38], the deficit in interaction and understanding of social stimuli, the difficulties in adapting to new contexts, often resulting in stressful events extremely difficult to mentalize, make ASD subjects more easily exposed to trauma [1-5]. Furthermore, the ruminative tendency of these subjects that exposes them to a continuous re-experiencing may result in PTSD [1-5]. On the other hand, on the eventual basis of an increased vulnerability to changes even from an epigenetic viewpoint, subjects with ASD, compared to neurotypical people, may more frequently develop after life events not only negative, but also positive reactions, such as PTG. In this framework, the exposure to a highly challenging events could lead, as a form of PTG, to gain a new point of view on reality and, in the context of neuroatypical subjects' divergent thinking, became an opportunity to develop hyper-adaptive ideas and skills that can determine the growth of individuals and society [2,5].

In this framework, cultural and environmental context, social support and personal resources promoting positive coping skills, favour the development of a PTG defined as "positive psychological changes experienced as a result of the struggle with traumas or highly demanding situations" [11]. The first study aiming to examine gene-environment interaction in the context of PTG identified a correlation between exposure to Hurricane Katrina and a component of the Regulator of G Protein Signalling 2 (RGS2) gene. Lower exposure in homozygous rs4606 (RGS2) correlated with lowest levels of PTG, while moderate and higher exposure correlated with the highest level of PTG [40]. Subsequently, few research focused on the changes that the environmental context could permanently make on the genome. In epigenetic terms, a possible correlation has been identified between methylation of FKBP Prolyl Isomerase 5 (FKBP5) and nuclear receptor subfamily 3, group C, member 1's (NR3C1) different sites and three different possible reactions to trauma: PTSD, resilience, PTG. Indeed, greater severity of PTSD symptoms were reported to correlate with methylation of the NR3C1 site, while lower severity of PTSD has been associated with low methylation in two sites of FKBP5's untranslated region. Furthermore, lower PTG levels were significantly associated with hypermethylation of a non-promoter NR3C1 region and hypomethylation of a NR3C1 promoter, while lower resilience levels were significantly associated with methylation of three NR3C1 sites [41]. Focusing on resilience outcome, this can be affected by epigenetic in three ways: epigenetic inheritance, the environment's influence and, finally, protective aspects during exposure to adverse events. In the latter case positive environmental aspects such as parental care, healthy diet, cognitive stimulation, exercise, physical and social contact seem to decrease the methylation of bone derived neurotrophic factor (BDNF) and N3CR1, while increasing tumor necrosis factor (TNF) methylation, which would favour a better resilience [42]. In this perspective, recent proteomics studies seem to confirm the presence of protein sites related to the development of PTSD [43-46] encouraging future research investigating the role of proteomics in PTG trajectories.

In conclusion, we think that the role of gene/environment interaction in determining the development of different trauma reactions' strategies should be further investigated. While the importance of environment in maintaining traumatic events across future generations has been highlighted by some authors, end even the possible persistence of a complex PTSD across family and entire populations [12-13,29-30], a small but substantial group of studies focused on the role of traumatic settings to leave stable fingerprints on DNA and to address various trajectories as trauma reactions [14-15,19-25]. The epigenome, therefore, represents a new key to understand the impact on highly challenging events [26-28] on illness trajectories and their role in mental disorders [31-36,38].

Conflicts of interest statement

The authors declare no conflict of interest.

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Authors' contributions

Conceptualization, L.D, B.C.; methodology, L.D., B.C.; investigation, C.B., B.C.; resources, L.D., B.C., C.B..; data curation, B.C., C.B.; writing – original draft preparation, C.B.; writing – review and editing, L.D., B.C., S.P.; visualization, L.D. B.C.; supervision, L.D., B.C., S.P. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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