No Geiger Counter for Holocaust Radioactivity: Possible or Impossible Biomarkers of Holocaust Traumatization?

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ABSTRACT

For many years, transgenerational transmission of trauma used to be explained with learning theories or in psychoanalytic terms as "radioactive identification." At that time, nobody believed that a trauma of a parent could also leave physical "scars" on the child. During the last decade, however, significant progress in neuroscience has begun to uncover the biological mysteries of hereditary memory. This biological line of research assumes that exposure to "Holocaust radiation" might be highly toxic for a developing embryo. Despite this progress, however, there is still no radiation detection instrument, such as the Geiger counter for "Holocaust radioactivity." This paper discusses the possible use of biomarkers to measure Holocaust traumatization. Because of the many obstacles in this line of biological research, we are still unable to confirm that the traumatization of the first generation "lingered on" as a result of a germline transmission of epigenetic information between generations. Thus it seems that the theory of a specific genetic predisposition for Holocaust traumatization still needs to be supplemented by a more integrative bio-psycho-social explanatory model.

Transgenerational transmission of Holocaust trauma (TTT) from traumatized parents to their offspring has been a focus of interest for many years. Numerous publications have suggested what was transmitted (or not), how this transmission may have occurred and when it may take place (during which critical periods of development and under which conditions) (1). The question is no longer if children of traumatized parents suffer from psychological disorders or not, but who. It is now generally accepted that only particular parents transmit various influences to certain individual children under specific circumstances and at different critical time periods.

For example, parents with some kind of stress disorder may transmit their emotional burden to sensitive children if an extra-family support network is lacking. Such children may then continue to carry an "allostatic overload" (2) that they inherited from their parents and may suffer from "transgenerational stress disorder," a subtype of generalized anxiety disorder, or "secondary traumatization."

Studies on the etiology of TTT, however, are less conclusive. Most likely there is a combination of psychosocial learning factors and gene-environment interaction in its development and a combination of nurture and nature. But the biological part of this assumption has not yet been verified by sufficient empirical data. The present paper discusses the possible use of biomarkers to gain such data.

BIOMARKERS

For many years, TTT used to be explained with learning theories or in psychoanalytic terms (3) as "radioactive identification." At that time, nobody believed that a trauma of a parent can also leave physical "scars" on the child. Neither was it assumed that such "radioactivity" could be as hazardous as ionizing radiation and that it could cause actual physical damage to the body of the children. During the last decade, however, significant progress in cognitive neuroscience, molecular biology and epigenetics have begun to uncover the biological mysteries and cellular basis of hereditary memory (4, 5). This biological line of research assumes that exposure to "Holocaust radiation" may be highly toxic for a developing embryo (6) and that it may enter into a cell membrane and modify biomolecules in the cytoplasm of the first generation which may

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cause epi-mutations in the gametes of the child (7-9). Such defective developmental programming may have serious consequences for the formation of vulnerability and resilience and lead to mental disorders throughout the life in the child (10).

Despite this progress, however, there is still no radiation detection instrument, such as the Geiger counter for Holocaust radioactivity. Neither has thermal biophoton emission, which reveals information about the health of cells under stress in living organisms (11), been used for this purpose on human subjects. As a result, we cannot (yet?) get direct access to the biological footprints of inherited implicit memories of fear, nor directly study the epigenetic "switches" that control human fear responses (12). Most importantly, we still cannot directly study the physical representations of fear memories (engrams) in human beings to determine if they are based on current experiences or if they may somehow be traces of repressed memories of traumatized parents (13). Research on TTT is therefore still based only on subjective client self-reports rather than on any specific psychobiological measures or "biomarkers" that objectively measures cellular, biochemical or molecular alterations in human tissues, cells or fluids (14, 15). Similarly, PTSD is also lacking any specific and cost efficient biomarkers (16). In fact, psychiatry as a whole has not identified valid clinically biomarkers for most mental disorders (17).

Finding such biomarkers would not only facilitate the diagnosis of children of survivors, but also potentially help explain the biological etiology of TTT. Primarily, it would verify the repeated observation from anecdotal clinical reports and cohort studies that the physical "scars" within the mind and body of survivors in the first generation may be present also in the offspring. By observing the manifestation of Holocaust traumatization in the brain and periphery with actual biomarkers in the first affected generation (F0) and then detecting the same biomarkers also in the second generation (F1), we would have actual evidence of transmitted trauma over the generation barrier (18, 19). To prove that such an influence was inherited and not only a result of psychosocial factors, we would thereafter ideally need to show that the same biomarker also appears in the third (F2), fourth (F3) and perhaps in future generations. Only then would we be able to confirm that the traumatization "lingered on" and was a result of a germline transmission of epigenetic information between generations in the absence of direct exposure (20). Anything less than this would leave TTT as an assumption at best or a myth at worst (21-23).

POSSIBLE BIOMARKERS OF HOLOCAUST TRAUMA

Since all traumatization involves some form of adaptation to stress, possible biomarkers of TTT may be found within any or all of the physiological systems that regulate stress. Most research on biological TTT has therefore focused on the activity of the various systems within the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic adreno-medullary (SAM) axis and the limbic system. These systems are all central to threat assessment within the brain and body through complex interactions among the nervous, endocrine and immune systems in which receptors on critical cells send and receive information to their subsequent programming effects (24). A large number of studies (25-27) have investigated the relevant biomarkers within any or all of these (1) neuroendocrine (28) (2) neuroanatomical (29) and (3) epigenetic systems (30-32). If the "scar" was caused by HPA-dysregulation, it would be measured by the level of cortisol in the saliva of the second generation (33). Children of Holocaust survivors with PTSD were found to have significantly lower cortisol, but better cortisol suppression in their blood, than offspring of survivors without PTSD (34). If the "scar" was caused by a hyperactive Amygdala (35) or by a weakened medial prefrontal cortex (36) it would be measured in the brain abnormalities of an fMRI scan. If the "scar" was explained in epigenetic terms it would be measured in alterations of the DNA methylation around the glucocorticoid receptor gene in the hippocampus or in the estrogen receptor in diverse brain regions (37). In one recent study, Holocaust survivors and their offspring had methylation changes on the same site in a functional intronic region of the FKBP5 gene, but in the opposite direction (38). In addition, biomarkers have been studied within many other biological systems, such as oxytocin, p11, mRNA and telomere shortening. For example, a recent study in Israel found that individuals after war captivity who suffered from depression but not from PTSD had decreased telomere length (39).

However, while all these studies may have found significant findings on one or the other physiological correlate measured, none have yet proven to be clinically useful or sufficiently valid as a definite biomarker of traumatization. First, within neuroendocrinology, there is disagreement regarding baseline levels of cortisol observed in people with PTSD (40) and cortisol responses show large intra- and inter-individual variability (41). Second, there is no consensus as to what has gone wrong within the brain as a result of abnormal fear learning, exaggerated threat detection, and in the regulation of emotion/cognition (42). As a

result, there are currently no state-of-the-art neuroimaging technologies of the brain that are clinically useful for establishing a reliable diagnosis of mood disorders (43, 44). In fact, brain imaging plays no accepted role in psychiatric diagnosis beyond ruling out medical factors such as tumors or traumatic brain injuries (45). Finally, within epigenetic studies, the findings are inconclusive since they are based mostly on animal studies (46) that are difficult to translate to human subjects because responses to psychological trauma in humans are fundamentally more complex than in animals (47, 48). In addition, such studies on humans still struggle with methodological difficulties and ethical constraints (21) and require information across multiple generations. Some of these difficulties may be illustrated in the (first?) human epigenetic study of TTT mentioned above (49). Most of what we know about TTT in humans is therefore based on retrospective cohort studies (e.g., 50) that suffer from selection bias and confounding factors. While neurobiological laboratories all over the world are struggling to overcome these obstacles, large-scale genome- and epigenome-wide association studies are also conducted (51). One such effort is the Research Domain Criteria (RDoC) project (52) that was created in order to discover the underlying neurobiological and bio-behavioral mechanisms of mental disorders. So far, however, a recent review of its core findings in neurobiological PTSD research found that it had not yet produced substantial, new knowledge on the pathobiology of this disorder, nor had any drug that specifically target PTSD core symptoms progressed to clinical use (53, 54). As of this writing, the RDoC has not yet made a significant impact on the diagnostic system used within psychiatry as a whole (55).

CONCLUSION

We still do not have any valid and clinically applicable biomarkers for Holocaust trauma and there is no *tangible* evidence for the epigenetic inheritance of phenotypes in the etiology of TTT. As a consequence, we still cannot prove that massive stress exposure in parents can in fact influence PTSD risk also in their children.

Finding valid biomarkers of Holocaust traumatization (HT) is obviously a challenging task. Obstacles are not only caused by methodological constraints, but also because HT cannot simply be regarded as one specific and persistent disorder detached from the human mind. It has also become increasingly clear that the difficulties in finding biomarkers are caused by the fact that such traumatization (1) cannot be easily measured in human beings; (2) is not clearly identified; (3) tends to vary between individuals and populations; (4) is not constant over time; and (5) may be the result of a failure to regain physiological homeostasis rather than a simple physiological response to stress (56). This compels us to take a fresh look at our basic assumptions (57). Perhaps the theory of a specific genetic predisposition for Holocaust traumatization is fundamentally flawed. If so, the search for specific biomarkers, like the search for the Holy Grail (58), might lead to a blind alley (59, 60). And, if so, there will be a need to develop a more integrative bio-psycho-social explanatory model to the study of traumatization and its possible transmission than pure biological reductionism.

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