

Epigenetic transgenerational transmission of Holocaust trauma: A Review

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Abstract

Transgenerational transmission of trauma (TTT) renders some children of survivors vulnerable to stress while others become more resilient. TTT was previously assumed to be caused primarily by environmental factors, such as the parents' child-rearing behavior. Recent research findings, reviewed in this paper, suggest that it may also be inherited through epigenetic mechanisms. New data indicate that the glucocorticoid receptor gene may cause the stress hormones of the child to become allostatic rather than resilient. Six clinical case anecdotes on suicidality, depression and PTSD, as well as on certain olfactory, cardiac and pulmonary problems, are presented to illustrate such possible epigenetic transgenerational transmission of Holocaust trauma. Further studies may justify the introduction of a new diagnostic entity -- *transgenerational stress disorder* -- with immediate relevance for the assessment, prevention, and treatment of the offspring of many kinds of trauma survivors.

Epigenetic transgenerational transmission of Holocaust trauma

Seventy years after the end of World War II, children of Holocaust survivors are now middle-aged or older, becoming parents and grandparents themselves. While some were able to transform the legacy of the Holocaust into post-traumatic growth, others are still struggling with the effects of the war as if they were disposed to suffer the curse of Holocaust trauma. These more vulnerable sons and daughters of survivors have Holocaust associations throughout their lives. About a third of them suffer from manifest psychopathology when a new trauma awakens the old one. During these periods, they have nightmares and flashbacks of things they never experienced. Daily events remind them of the horrors of the war and the agony their parents suffered. More than half a century after World War 2, there is a prevailing sense of catastrophic expectancy. It has become an automatic response among the Jews in Israel and elsewhere as shown in a recent study of Israeli offspring who were more preoccupied with the Iranian nuclear threat than others (Shrira, 2015).

Since even simple organisms learn fundamental survival skills and pass these on to their offspring, it's not surprising that life-changing experiences in humans, which result in knowledge useful for survival, would be passed on to future generations. Children of survivors are thus molded by the war experiences of their parents, especially since these experiences were extremely negative, uncontrollable and sudden (Carlson & Dalenberg, 2000) and induced intense fear, helplessness, or horror. Essentially, *Transgenerational Transmission of Trauma* (TTT) may be understood as a kind of vicarious encounter with death.

All famines, wars, persecutions and mass murder, which left a deep and enduring trace in the body of the first generation, may be assumed to leave some kind of scar also upon

successive generations. Holocaust survivors narrowly escaped mortal threat and survived against all odds. Many suffer from lifelong, sporadic and debilitating posttraumatic stress disorder (PTSD) (Barak & Szor, 2000; Dasberg, 1987; Kellermann, 2009) which they transmitted to their offspring. Indeed, there is a strong relationship between parental PTSD and PTSD in offspring. Apparently, the more a person experienced traumatic events, the more he or she suffered from PTSD (Hong & Efferth, 2015; Neuner et al., 2004; Schoedl et al., 2014) and the more this disposition is passed on to the offspring. Research has shown that parental Holocaust exposure is a strong predictor of lifetime emotional disorders in offspring (Bowers & Yehuda, 2015; Lambert, Holzer & Hasbun, 2014; Yahyavi, Zarghami & Marwah, 2013; Yehuda, Halligan & Bierer, 2001; Yehuda, Halligan & Bierer, 2002). A large number of studies show how parental adaptive and pathological fear may be transmitted to their offspring, such as in PTSD (Bosquet et al., 2011; Reul, 2014; Roth, 2014; True et al., 1993; Yehuda et al., 2008).

Transgenerational Epigenetic Inheritance

Earlier explanations of such manifestations of TTT assumed that they were caused primarily by environmental factors, such as the parents' child-rearing behavior (Kellermann, 2001). For many years, the prevalent notion was that children who had grown up with traumatized parents had learned to become fearful as well. New research, however, shows that transgenerational effects may be inherited also through epigenetic mechanisms (Bohacek & Mansuy, 2013; Ennis, 2014; Harper, 2005; Kellermann, 2013; Thomson, 2015; Yehuda & Bierer, 2009; Zannas, Petronis, 2010; Provençal, & Binder, 2014; Provençal & Binder, 2015a). An increasing number of studies are trying to validate this claim and the term transgenerational epigenetic inheritance - TEI – has been coined to depict it (Choi & Mango, 2014).

Within such a biological framework, the traumatic memories of the parents are transmitted through epigenetic marks; the changes in gene functioning or to the DNA environment that affects the way the DNA is read into RNA, and then how RNA is expressed into a protein. This theory suggests that children of survivors are tainted with a chemical marking upon their chromosomes similar to the numbers tattooed on their parents' forearms.

Epigenetics integrates both hereditary and environmental factors, which adds a new and more comprehensive psychobiological dimension to TTT. Not only can epigenetic measures explain how an adverse social environment gets 'under the skin' of the survivors of trauma (Toyokawa et al., 2012), but also why a latent predisposition *sometimes* becomes manifest under stress in their children (Zovkic et al., 2013). After all, every person has a unique variation of the human genome and there are often multiple factors that influence the likelihood of developing PTSD.

This new epigenetic paradigm (Moore, 2015) assumes that biological and psychosocial factors are in close interaction with one another (Crews et al., 2014; Hofer, 2014). Trying to find the multiple hereditary and environmental causes of TTT, however, is a daunting task; the assumed risk factors include not only epigenetic factors, but also personality traits and social support, and traumatic experiences of the children themselves during their lives. It is difficult to disentangle effects that reflect TEI from early rearing influences and subtle attachment patterns experienced because of having trauma-exposed and/or symptomatic

parents. It is precisely because of this complexity that epigenetics makes so much sense as a suitable explanation for TTT.

“Faulty” Programming

TEI can be metaphorically described in computer terminology. It is as if the child was born, not only with the parents’ hardware (DNA), but also with traces of their old, and infected “glucocorticoid programming” software (Seckl & Meaney, 2006). Even though the computer was reformatted (or reprogrammed) at conception, some traces of the old program remains. At fertilization, the germ cells were supposed to have been wiped clean of any chemical modifications to DNA. No memories were supposed to slip through the generation barrier. Research from the last decade, however, has found evidence for what clinicians have long observed, but were unable to verify. Some DNA methylation can escape the ‘reset’ mechanism or ‘reprogramming’ in human germ cells (Surani, 2001; Tang et al., 2015) and this may explain why it’s possible that some memories can reappear in children of survivors.

Like a binary computer program that uses encoded switches with either 1 or 0, epigenetic programming (or re-programming) may activate or suppress specific electrochemical signals, or proteins, to either initiate or shut down the action potential of neurons. If these mechanisms have been compromised in the parents and then inherited by the children, there will be a kind of software bug in the nervous and endocrine systems and produces an incorrect functioning of the ‘program’. When this happens, the body will function as if it was infected by a computer virus that caused it to behave irrationally and send faulty instructions to and from the brain. In other words, the epigenetic marks will change the transcription potential of the genes and give them flawed instructions on certain cues. It may appear as a subtle ‘somatic marker’ (Damasio, 1994) or a ‘gut feeling’, for example instructing a child of Holocaust survivor not to leave food on the plate because ‘then and there, they died from starvation’ (Bygren et al., 2014). This example highlights the interconnectedness of body and mind and the two-way communication between the gastrointestinal system and the brain, which are all signs of the malicious ‘Holocaust Virus’ in epigenetic TTT.

All such computer malware develop slowly over a long period and the overt signs may emerge only after several years. It is observed repeatedly in the survivors themselves, in their children and even in their grandchildren seventy years after the end of the war. When it has taken root, it will linger and stay active for a lifetime, leading to pathological stress, panic attacks and even to complex PTSD (Danielson, Hankin & Badanes, 2015). The symptoms seem to be caused by long-term changes in the brain chemistry as confirmed in many studies (Perry, 1999; Roberts et al., 2012; Thakur et al., 2015). If no help is received, the ripple effects may produce chaos in the delicate inner hormonal balance of the entire body and cause it to crash or freeze.

It may sound too simplistic to explain the often complex hereditary vulnerability to PTSD in children of survivors as a software bug within a computer program. In reality, the biological effects of parental trauma upon children are surely more complex. But epigenetics provides a useful new psycho-biological paradigm for TTT. First and foremost, it has kicked off new

research as shown in the explosion of studies on epigenetics during the last decade (Burggren & Crews, 2014; Lim & Brunet, 2013; Rodgers & Bale, 2015).

Research on Epigenetics

Within the past few years, several exhaustive reviews have been published with summaries of the recent findings. Such reviews have been written, for example on fear memory and biomarkers (Maddox, Schafe & Ressler, 2013), learned fear (Zovkic & Sweatt, 2013), neural fear network and PTSD (Wilker & Kolassa, 2013), early life stress (Provençal & Binder, 2015b), epigenetic risk factors in PTSD and depression (Raabe & Spengler, 2013), transgenerational epigenetics and psychiatric disorders (Franklin, 2014) and on the inheritance of learned behaviors (Dias et al., 2015). These reviews have summarized significant advances in cognitive neuroscience and they have begun to unravel the biological mysteries and cellular basis of transmitted trauma. They suggest that there might indeed be a biological basis for the long-term emotional effects of trauma, including its transgenerational transmission on later generations.

The Cross-Disorder Group of the Psychiatric Genomics Consortium (2013) found that most psychiatric disorders are moderately to highly heritable. Specifically, they concluded that exposure to stress, particularly in early life, has both acute and lasting epigenetic effects. In fact, such stress may even influence cognitive functions and behavior, as well as the risk for suicide and psychiatric disorders across the lifespan and also unto future generations (Griffiths & Hunter, 2014). It is now largely accepted that early-life stress produces changes in the brain and periphery that can ultimately influence behavior through epigenetic changes, such as DNA methylation, histone modification and microRNA processing (Bale, 2015; Blaze, Asok & Roth, 2015).

Studies on traumatized mice have demonstrated how unpredictable maternal separation can induce depressive-like behaviors, not only in the first generation, but also in their offspring (Debiec & Sullivan, 2014; Franklin et al., 2010). In addition, lab mice trained to fear a particular smell transmitted this fear to their unborn sons and grandsons through a mechanism in their sperm (Callaway, 2013; LeRoux, 2013). Many similar studies have shown that animals can inherit a memory of their ancestors' traumas, and respond as if they had lived the events themselves (Dias & Ressler, 2014). Parental traumatic experience may induce neuro-anatomical adaptations and related cue-specific behavioral predispositions in offspring and thus, "the experiences of a parent, even before conceiving, markedly influence both structure and function in the nervous system of subsequent generations" (Gallagher, 2013).

Maternal Transmission

The embryo and the fetus during its various periods of development in the womb have been of particular interest when trying to explain such transgenerational effects. A comprehensive overview of such transgenerational epigenetic programming (Babenko, Kovalchuk & Metz (2015) suggest that stress-induced epigenetic signatures are indeed transmitted to the next generation. Based on existing evidence, prenatal stress, through epigenetic alterations, becomes one of the most powerful influences on mental health in later life.

What babies comprehend in utero will affect what they remember after they're born and that information will prepare them for the world outside the womb. Every meaningful experience—whether joyous or painful—is stored in memory and has a lasting impact on a baby's developing nervous system (Weaver et al., 2004). Studies on different populations have confirmed these observations and validated them with data on how conditions in the womb affect the health of a person not only as a fetus but well into adulthood (Li, Beard & Jaenisch, 1993; Lillycrop et al., 2007). The epigenetic effects are profound since various types of cells, including neural cells, differentiate during embryogenesis (Sakashita et al., 2001; Takizawa et al., 2001). These effects are particularly visible during the last trimester of pregnancy when babies begin to engage many of their senses and learn about the world (Yehuda et al., 2005). When this period is influenced by severe stress in the mother, the epigenetic changes produced by fetal programming may last throughout life and can be passed on to future generations (Drake & Walker, 2004; Gluckman et al., 2007; Hazani & Shasha, 2008; Onoye et al., 2013; St Clair et al., 2005).

TEI is more likely to occur during particular times in child development. The earliest stages of life, beginning well before birth and immediately after are moments of maximal plasticity (Burggren & Crews, 2014). When investigating the epigenetic effects on children of Holocaust survivors, we therefore need to take the neurochemical responses to external environmental exposures into account both during pregnancy and after birth. Such investigations focus on the unfolding of the fetus and the maturation of the toddler and in particular how pregnancy in times of hunger and stress may have affected the health of the offspring (Heijmans et al., 2008). This effect was observed not only in the immediate postnatal period but throughout their adult lives (Sperling, Kreil, & Biermann, 2012). For example, childbearing women during the war in the ghettos and camps responded to the emotional shock of persecution and the prolonged starvation with various hormonal disturbances, such as the cessation of menstruation, hair loss, and irregularities in heart function and the nervous system (Nachimovsky, 1948; Preiss, 2009). After the war, mothers in DP-camps became pregnant while they were still recuperating from starvation, typhus, TB or other illnesses. The long-term epigenetic effects of such exposure to early-life stress on the offspring were profound (Provençal & Binder, 2015a; Yao et al., 2014). Such harmful influence was observed already in 1948 by a gynecologist in Munich who found a high percentage of congenital malformations in the newborn babies (Eitinger, 1993). It was as if these mothers were symbolically feeding their babies with war-tainted milk, if they had any milk at all.

Paternal Transmission of RNA

While maternal nutrition and metabolism are obvious determinants of the health of adult offspring (Tollefsbol, 2014), recent reports also describe adverse effects on offspring associated with the father's diet, showing non-genetic inheritance of paternal experience. These results were interpreted as “you are what your dad ate” (Ferguson-Smith & Patti, 2011).

Sperm may also contribute to TTT since it can carry RNA (Hosken & Hodgson, 2014). Sharma (2014) suggested that extracellular mRNAs and proteins provide the much-needed continuum inclusive of epigenetic inheritance. An imbalance in sperm microRNAs may also

be a key factor through which trauma can be passed on. Mansuy and her team (Gapp et al., 2014) identified short RNA molecules as a key component of these processes. These RNAs are synthesized from genetic information (DNA) by enzymes that read specific sections of the DNA (genes) and use them as a template to produce corresponding RNAs (ETH Zurich, 2014).

Transmission of HPA Dysregulation

Considering that hormones (signaling molecules) regulate the proteins that control the body's stress-sensing system, they have been a major focus of research in transgenerational PTSD. According to Jablonka & Raz (2009), "the involvement of hormones in the induction of heritable epigenetic variations is no longer a mere speculation: several of the mammalian examples suggest that changes in hormonal stimuli induce heritable epigenetic changes" (p. 159). During acute stress, the hypothalamic-pituitary-adrenal axis (HPA axis) is activated (Hulme, 2011). Corticotropin-releasing hormone (CRH) is secreted from the hypothalamus under the influence of serotonin from the Amygdala. CRH stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH), which then prompts the adrenal glands to increase the production of glucocorticoids. This releases the stress hormone cortisol, which stimulates noradrenaline to activate the fight-flight response. Cortisol serves to stop many metabolic, neuronal defensive and immune reactions and energy can be mobilized to cope with the stressor. Through these chemicals, the HPA-axis controls reactions to stressful situations, triggering several physiological changes that prime the body for action (Meewisse et al., 2007). The more stressed a person is, the more CRH is secreted, leading to increased ACTH, and higher levels of cortisol. When cortisol activates the fight and flight stress response, it also sends a signal back to the hypothalamus to inhibit CRH production and the pituitary gland to inhibit ACTH. In this feedback loop, cortisol will reduce norepinephrine activity, gradually calming the person down and creating a mutually balanced system (Engelmann, Landgraf & Wotjak, 2004; Miller, Chen & Zhou, 2007). In some people who have experienced trauma, however, this system doesn't function as it should.

Rachel Yehuda and her team from the Traumatic Stress Studies Division at the Mount Sinai School of Medicine have investigated such HPA-axis dysregulation in trauma survivors for many years (Yehuda, 2005). People with PTSD seem to have higher corticotrophin-releasing factor (CRF) levels, blunted adrenocorticotrophic hormone response and low levels of cortisol. Apparently, low cortisol levels have been found in saliva, urine, and blood in many, but not all, populations with PTSD (de Kloet et al., 2006; Heim, Ehlert & Helhammer, 2000; Meewisse et al., 2007). Children of Holocaust survivors with PTSD also have significantly lower levels of cortisol, but better cortisol suppression in their blood than offspring of survivors without PTSD (Yehuda et al., 2007; Yehuda, 2009). Such HPA axis dysregulation leads to an inability to produce enough adrenal cortex hormones in response to stress and is seen in populations who have struggled for generations to cope with trauma. It gives rise to a kind of exhaustion, or 'adrenal fatigue', similar to secondary adrenal insufficiency (Neary & Nieman, 2010). It's as if these children continued the struggle for survival of their parents, until their resources were depleted. They seem to have been 'programmed' by excessive glucocorticoids to be either predisposed or protected from PTSD (Seckl & Meaney, 2006).

Transmission of Brain Functioning

The epigenetic machinery in the brain is both complex and intertwined and it's difficult to disentangle brain-region and cell-type specific epigenetic codes in a given environmental condition (Graff, Kim, Dobbin, & Tsai, 2011). Nevertheless, neuroimaging studies have shown that the amygdala, the hippocampus, and the prefrontal cortex all play a part in stress and PTSD (McEwen, et al., 2015). For example, according to the "glucocorticoid cascade hypothesis" (Sapolsky, Krey & McEwen, 1986), chronic stress may cause smaller hippocampal and prefrontal cortex volume, deficits in declarative (conscious) memory and some amnesia (Baker et al., 2005; Bremner et al., 1995; Samuelson, 2011). Stress hormones triggered by way of the HPA-axis are encoded by the basolateral area of the amygdala (BLA). This makes the person respond emotionally to anything that unconsciously is associated with the event (Bokkon et al., 2014; LaBar & Cabeza, 2006; McGaugh, 2000). Functioning independently of the hippocampus, the BLA thus conserved the emotional trauma overload while repressing the cognitive recollections of the event, as also seen in offspring of mothers who survived the Tutsi genocide in Rwanda (Perroud et al., 2014; Roth, Neuner & Elbert, 2014).

Increased activity of the amygdala-HPA axis produced by experimental manipulation represents several of the physiological signs of stress-related psychiatric disorders in humans (Gillespie et al., 2009; Lee et al., 2013). The activation of both amygdala and hippocampus and the interaction between them may be what gives emotionally based memories their distinctiveness (Richter-Levin & Akirav, 2000). Infusion of glucocorticoids in the hippocampus after fear conditioning induces PTSD-like memory impairments and an altered pattern of neural activation in the hippocampal-amygdala circuit (Kaouane et al., 2012). The hyperactive amygdala-mediated fear response to danger and the weakened ability of the medial prefrontal cortex to regulate these responses are some of the common responses to trauma (Yehuda & LeDoux, 2007).

Candidate Genes

Many years of research has shown that changes in gene expression happens when a memory is formed and stored (Roth, 2014). Even though there are many difficulties in identifying candidate genes implicated in psychiatric disease (Burmeister, McInnis, & Zollner, 2008), there has been some progress in finding neurobiological alterations to important components of the stress response system (Skelton et al., 2012). Specifically, epigenetic changes have been found in different gene locations involved in the regulation of the HPA axis (Voisey, Young, Lawford, & Morris, 2014). Wilker et al., (2014) concluded that an epigenetic modification of the glucocorticoid receptor gene promoter is linked to inter-individual and gender-specific differences in memory functions and PTSD risk. The glucocorticoid receptor (GR) gene in the hippocampus was found to be critical for negative feedback in the stress response (Champagne, 2013) and for increased corticotropin-releasing hormone (CRH). Findings have indicated polymorphisms (phenotypical aberrations) within two genes, FKBP5 and CRHR1 (Binder et al., 2008) that regulate HPA axis function when the child is also exposed to child maltreatment (Klengel et al., 2013). Significant associations were also found with a variable number tandem repeat (VNTR) polymorphism (Segman & Shalev, 2003; Yehuda & LeDoux, 2007). Other genes, such as the PRKCA were found to lead to improved memory, and therefore also to increased risk of

PTSD (de Quervain et al., 2012). In addition, increased DNA methylation at the NGFI-A binding site of the NR3C1 promoter was associated with reduced PTSD risks in male survivors of the Rwandan genocide (Vukojevic et al., 2014).

Recent Advances

There have been recent advances in this line of research. Daskalakis & Yehuda (2014) looked at methylation of the exon 1F promoter of the glucocorticoid receptor (GR-1F) gene (NR3C1), the most studied genomic region in human stress-related diseases. In order to demonstrate alterations of GR-1F promoter methylation in relation to parental PTSD and neuroendocrine outcomes, Yehuda et al., (2014a) sought to identify effects of parental Holocaust exposure and PTSD on GR-1F promoter methylation to discover epigenetic marks connected to glucocorticoid dysregulation (Bader et al., 2014; Bierer et al., 2014; Lehrner et al., 2014) in this population at risk for PTSD. They found that paternal PTSD, only in the absence of maternal PTSD, was associated with higher levels of GR-1F promoter methylation, while offspring with both maternal and paternal PTSD showed the least level of methylation.

In August 2015, Yehuda and co-workers (Yehuda, et al., 2015) published the first findings of epigenetic TTT in humans in both Holocaust survivor parents and their offspring. Holocaust exposure had an effect on *FKBP5* methylation both in parents and in their offspring, a correlation not found in the control group and their children. Even if this study had a small sample size and can be criticized for other methodological problems, it presents a first glimpse of a possible epigenetic inheritance in this population. The findings, which echo those of Klengel et al. (2013), suggest that methylation of the *FKBP5* gene in the parent may indeed be inherited. If this happens, the glucocorticoid receptor gene may be silenced, making the stress hormone of the child allostatic rather than resilient (McEwen, 2000; Oken, Chamine & Wakeland, 2014). Thus, some vulnerable children of survivors may become predisposed to stress while others will be more resilient.

Critique of Epigenetic TTT

Despite this large body of research, the jury is still out on whether transgenerational epigenetic inheritance is possible in humans. It is still disputed in many quarters (Daxinger & Whitelaw, 2010; Grossniklaus et al., 2013; Qiu, 2006) on the ground that it is guided more by hype and hope (Albert, 2010) than on objective evidence. Available data is based mostly on animal models, while neurobiological findings on humans are still insufficient (Heard & Martienssen, 2014). A reason for this is that “controlled studies [on humans] are neither feasible nor ethical and phenotypic as well as biological data across several generations are lacking” (Dias et al., 2015, p. 105). But even if we had more such data, it would be very difficult (if not impossible) to clearly separate the influence of biological heredity from parental upbringing in humans.

Therapists have suspected for long that the risk for psychopathology in children of survivors may be a multigenerational phenomenon (Klengel, Dias & Ressler, 2015). The severity and persistence of mental problems in this population could not stem only from the psychosocial environment (e.g. parents talked too much or too little about the war). There had to be more to TTT and the possibility of parents actually being harmed by the war in a

neurobiological manner which their children might have inherited, was always at the back of their minds. When the first studies on epigenetic transgenerational trauma were published (Yehuda, Halligan, & Bierer, 2001), it therefore sounded very likely to therapists working with these populations. It explained not only why some children became more vulnerable while others remained resilient, but also why so many still suffer from the effects of the war. The latest finding – that there might be an epigenetic modification of the glucocorticoid receptor gene in the traumatized parent which was then transmitted to the child (Meaney & Szyf, 2005) – resonate well with clinical experience. Learning that children of trauma survivors may have had a ‘defective’ or methylated *glucocorticoid receptor gene* ever since they were born also make sense to those children of survivors who have been preoccupied by Holocaust associations for most of their lives. It may especially help those previously bewildered by their lifelong difficulties in coping with stress to realize that there is an actual hereditary disposition to their difficulties.

Case Anecdotes

To illustrate some of these difficulties and put them in a relevant parent-child context, I will here present six case scenarios taken from clinical practice. These cases suggest that suicidality, depression and PTSD, as well as certain psychosomatic olfactory, cardiac and pulmonary manifestations, may have an epigenetic source based on specific parental Holocaust trauma,

(1) Transmission of suicidality

Mrs. U from Poland was six years old during the war. She remembers being trapped in their burning house, surrounded by Nazi soldiers who shot anyone who tried to get out. The family members hid in the cellar, lying on the floor while hearing shots fired and barking dogs. Mrs. U saw some of her family members being burned alive. Somehow she survived and when it was all over, she could escape to the forest where she was hiding for three years with the constant fear of being caught. After the war, she was sent to Israel with other orphans. Because of her traumatic wartime experiences, the overwhelming fear, powerlessness and loss of control had become a permanent learning experience she could not overcome. Despite this, she married and gave birth to two girls, one of whom suffered from depression in young adulthood and later committed suicide. Did the daughter inherit hypermethylation of the ribosomal RNA gene promoter from her mother (McGowan et al., 2008)? Specifically, was there an alteration in the CRHT1 gene: a marker found for suicidal susceptibility (Wasserman et al., 2008; Niculescu et al., 2015)?

(2) Transmission of depression

Anna was only 12 years old during the mass killing of the Einsatzgruppen - the paramilitary death squads of Nazi Germany. She watched her family being shot one after the other and thrown into an open trench. Anna was holding her baby sister and trying to calm her as she was waiting for her turn. The Nazi soldier, who tried to kill both of them with one bullet, shot the baby in the head and pushed both in the trench full of bodies. Anna had not been hit and crawled out from the open grave at night. A farmer found her, took care of her and she survived the war. Many years later, Anna gave birth to a daughter and named her after her baby sister. Anna was symbolically born from a grave and her daughter became a

'memorial candle' (Wardi, 1992), suffering from clinical depression for most of her life. Was there an epigenetic transmission of depression (Sun, Kennedy & Nestler, 2013)? Specifically, would there be similarities in diminished hippocampal activation on a functional magnetic resonance imaging (fMRI) during a memory task (Milne, MacQueen & Hall, 2012)?

(3) Olfactory transmission

A man forced to work in the crematoria in Auschwitz was exposed to the smell of burned cadavers for almost a year. During this gruesome labor, he saw the corpse of his wife and contemplated giving up. But with a lifelong sense of guilt, he decided to live and survived the war. He preferred not talk to anyone about his experiences, shut down his emotional life, remarried and gave birth to a child. When he was attending barbecue parties, however, and smelled burned meat, he would get severe panic attacks. Many years later, this symptom also appeared in his son. Might there have been a transgenerational epigenetic transmission from father to son? Had exposure to stress during the war affected the miRNA germ cells in the sperm of the father and were these passed on to his son via olfactory neural pathways, as suggested in research on the neural basis for a strong "odor-emotional memory" (Dias, & Ressler, 2014; Tong, Peace & Cleland, 2014).

(4) Cardiac disease transmission

A child of camp survivors shared that she could not tolerate cold weather and had to move to a warmer place. She said that her heart goes into spasm when she got frozen; a medical condition called 'vasospastic cardiac disease' which may be caused by epigenetic regulatory mechanisms (Schleithoff et al., 2012). Was it possible that she had inherited this disease from her parents who had endured the extreme cold weather in the camp and during the Death March? Would a comparison of blood or saliva samples offer concrete, physical proof of epigenetic transmission?

(5) Transmission of dyspnea and pulmonary hypertension

A Hungarian Jewish woman was sent to be exterminated in Auschwitz but was taken out of the gas chamber because there was no more Zyklon B available. She somehow survived the war and gave birth to a daughter called Michelle. Many years later Michelle was interviewed and exclaimed: "When I go to work in the morning and see so many cars and exhaust fumes, I tell myself, don't breathe! I remember that this is how they would gas people . . . and I think about the camps. There is not one day that I don't think about those things. They cross my mind twenty times a day, a hundred times a day!" (Gottschalk, 2003, p. 355).

Were her mother's experiences passed down to her daughter through transgenerational epigenetic transmission? Could the mother's childhood trauma have affected selective histone deacetylase inhibitors and targeted DNA methyltransferases and did they cause pulmonary hypertension in the daughter (Saco et al., 2014)? Was mother's anxiety so intense at the time of near death that a torrent of hormones flowed into every cell of her body, including her egg cells and hijacked her brain's epigenetic machinery? Did this cause the Amygdala fear response threshold to violate its rules of evolutionary conservation by an overload of adrenaline? Had the daughter inherited a specific epigenetic modification which

made her susceptible to anxiety throughout her life? If so, could this be the reason for her thinking about the war all the time? Could it work like this for other children of Holocaust survivors?

(6) Transmission of susceptibility to PTSD in the military

The father was a well-functioning survivor of the Holocaust but had never talked about his experiences. His eldest son suffered PTSD when fighting in one of the wars in Israel and was dismissed from active duty. His condition became chronic, and he was unable to function adequately for the rest of his life, receiving a disability pension from the Department of Veterans Affairs. Was there a prior susceptibility to PTSD, which could be traced back to his father's war experiences? Could his predisposition be detected in a test of the SNPs in a specific gene? Would it be visible on a brain scan, showing damage in the hippocampus? Should all soldiers be tested for susceptibility to PTSD before being enlisted (Boks et al, 2015; Dekel, Mandl & Solomon, 2013; Neylan, Schadt & Yehuda, 2014; Sipahi et al., 2014; Yehuda et al., 2014b)?

Discussion

These examples represent only a tiny part of all the possible epigenetic transmission scenarios involved in TTT. They were chosen because of the extreme strain imposed on the parents and their possible transgenerational epigenetic effects on the offspring (Rudan, 2010). Many more can be found in the clinical setting and they all pose urgent questions about epigenetic transgenerational transmission with concrete testable hypotheses for further investigation.

Clearly, many unanswered questions remain regarding the exact mechanisms of how posttraumatic stress may be transmitted from generation to generation (Dias et al., 2015). For example, how exactly did the Holocaust trauma enter into the mature sexual reproductive cells of a traumatized parent? For how many generations do the biological heredity and/or the psychosocial transmission continue? Do they become fixed or can they be reversed? Most importantly; what causes some children to develop resilience while others remain vulnerable to stress? With significant advances in neuroscience, cell biology and molecular genetics, these questions are beginning to be answered.

Future studies on gene-environment interaction will surely provide additional understanding of both the biomarkers and the psychosocial origins of PTSD and TTT. Since TTT tends to be highly volatile, future research should focus on the variability of the nervous and endocrine systems in both parents and children, and also between children. Case-dependent studies on actual parent-child combinations, rather than on the correlations of both populations at large, may determine the risk factors in operation for certain individuals with specific genetic vulnerability (Daskalakis et al, 2013).

The findings of such research may lead to the introduction of a new diagnostic entity -- *transgenerational stress disorder* -- as a separate subtype of PTSD, distinct from secondary PTSD, with immediate relevance for the assessment, prevention, and treatment of children of Holocaust survivors.

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