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The Search for Biomarkers of Holocaust Trauma

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Abstract

Despite significant progress in basic neuroscience research of stress and PTSD, no definite biological pathways of traumatization have been identified. As a result, the biological part of transgenerational transmission of Holocaust traumatization (HT) cannot be verified. Why has it been so difficult to find biomarkers of HT? The present paper tries to answer this question with the help of a discussion of the various obstacles in this line of research. Such obstacles are not only caused by methodological constraints, but also because HT cannot simply be regarded as one specific and persistent disorder, which are detached from the human mind. It has also become increasingly clear that the difficulties in finding biomarkers are caused by the fact that HT (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. Such methodological, conceptual, diversity, dynamic and adjustment factors have all contributed to the difficulties in finding biomarkers of HT and they have made this kind of psychophysical research extremely complex. It is concluded that a more integrative bio-psycho-social explanatory model to the study of traumatization remains more viable than the pure neurobiological one.

Keywords

Traumatization; PTSD; Holocaust

Introduction

Psychological effects of the Holocaust on survivors and their families have been well documented for over half a century. Holocaust trauma (HT) is perhaps the most investigated of all kinds of traumatization and it is sometimes presented as a prototype for different kinds of post-traumatic disorders. Most studies are based on descriptive, epidemiological and correlational data. During the last decades, however, findings from psycho Neuro-endocrinology raised expectations of finding psychophysiological data of such traumatization and a search begun for possible biomarkers [1] of HT which would be relevant also for other stress-related disorders.

A basic assumption in this research was that the emotional suffering of people who had experienced adverse events would remain in the survivor's body [2], like scars formed during the healing of damaged skin. If the whereabouts in the body were found, where such emotional scars were manifested, specific remedies could be developed. Since the autonomic nervous system controls the delicate balance between "fight-flight" and "rest-digest", scientists asked if such biomarkers might be located within the autonomic nervous system and the hypothalamus [3]. If so, might it also be connected to a dysregulation of the HPA-axis [4,5] Did it involve stress hormones [6-8], such as adrenaline, cortisol, and norepinephrine [9] ? Could it be observed in the brain [10], and if so, would it engage neural circuits in the Amygdala [11], the Hippocampus [12] and/or perhaps in the pre-frontal cortex [13]? How would such a traumatization activate or inhibit neurotransmitters, such as epinephrine/norepinephrine, acetylcholine, dopamine [14] and/or serotonin [15]? Was glucocorticoid programming involved [16-18]? Did the traumatization affect epigenetic control [19-22]? Or, was there perhaps a more complex interaction between these different systems [23-26]? A better knowledge of the molecular pathways [27-29] involved in the interaction between the mind, body and environment would perhaps suggest new ways to diagnose and treat the emotional scars of traumatization through psychopharmacology, or measure the physiological effects of psychotherapy, meditation and life style changes [30].

But despite the tremendous progress in basic neuroscience research of stress and PTSD, no definite biological pathways of HT have been clearly identified [31]. In fact, psychiatric disorders in general cannot be fully distinguished by any specific biological markers [32] and we are still far from producing tests that can be routinely used in their diagnosis and treatment [33]. When considering the variability of findings and the complex interplay of the commonly studied markers of the endocrine and immune systems pre-, peri- and post-trauma with other factors, the current clinical applications remains limited [34]. On the whole, there is a lack of progress in new treatments that were assumed to come from this new knowledge [35].

Why has it been so difficult to find biomarkers of HT? Are the attempts to find biological signs of traumatization a futile search for a Holy Grail that does not exist [36]? In order to answer these questions, I will revisit some basic assumptions in biological psychiatry and discuss them from the point of view of Holocaust traumatization. It is my hope that a discussion of the obstacles involved in this line of research may provide a more balanced view of studies within the field which might help to decide where to go from here.

Which are the fundamental obstacles in this line of psychobiological research? Apparently, the unresolved problems which have hindered progress may be found within neuroscience itself [37-45]. These problems are not only caused by conceptual difficulties and methodological constraints, but also because HT cannot simply be regarded as one specific and persistent disorder, which are detached from the human mind. It has become increasingly clear that the difficulties in finding biomarkers are caused by the fact that HT [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. These problematic factors will be further discussed below within the context of HT, but they are relevant also to other stress-related disorders, such as PTSD.

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Methodological factors

The first, and most obvious, obstacle to finding biomarkers of HT is based on methodological constraints. While significant advances have been made in the neurobiology of stress, most new knowledge is still based on translational animal research. Relevant experimental data on living human beings are scarce, since it is obviously unethical to experimentally study the biological scars in traumatized people. It's true that traumatized people may be genetically similar to animals and that they may have felt like animals in a cage. But we would literally have to use 'Mengele methods' to achieve valid anatomic, metabolic, and cellular data from traumatized human beings who are still alive. It's also true that some of the stress responses of human beings may look like those observed in animals; such as the classical fear-conditioning responses 'freeze', 'panic' and 'blacking out', observed in people who were tortured, raped and almost killed. They bring to mind the many testimonies of traumatized Holocaust survivors who were exposed to extreme malnutrition, beatings, and other forms of abuse.

But even though persecuted Jews during the war were symbolically portrayed as such [46], their diverse responses cannot actually be compared to those observed in mice [47]. Animals are poor models for traumatized human beings [48] because they 'get lost in translation' [49] even in clinical trials of cancer treatment. In stress research, a laboratory rat's response to inescapable shock mimics only the fight/flight processes in the limbic system, while leaving the more 'sophisticated' rational mind of the hippocampus and pre-frontal cortex largely unobserved. What is found in such experiments will therefore highlight only the primitive mechanisms of instinctual fear and possibly some parts of implicit or associative memory while the neural substrates and signaling pathways required for more complex processes, such as problem solving, planning and decision-making, would go largely unobserved. Considering these limitations, there is a need for more specific human fear conditioning models for drug discovery in the future [50].

Comparing the neurobiology of Holocaust survivors with the behavior of electrocuted, drowning and tortured mice do not resemble the unique human reactions to the atrocities of the 2nd World War. Even well-conceived animal experiments cannot reproduce reliable equivalents of such human diverse and ingenious coping strategies. For example, when watching documentaries of the Eichmann trial in Jerusalem from 1960-61 and listening to witness accounts of the conditions in the various camps, one wonders how the survivors could look so composed after all they had endured, only fifteen years earlier. They talked about experiencing persecution, torture and hunger of enormous proportions. But they had not died and they were able to describe what had happened to them. What was their secret of survival? One such witness gave the following account: "The first thing we did was to learn about the place. Where do you get beaten? Where do you get shot? Where do you get soup? How do you keep some bread for tomorrow? What do they want us to do in order to keep us alive? How can the guards be outsmarted? Who can be of help? Who are my fellow companions? What would be the meaning of survival? Is it all worth it?"

These are all highly complex cognitive and emotional survival strategies and not only primitive fight-flight mechanisms. They include finding a meaning in survival through remembering the past and anticipating the future [51], maintaining dignity [52], and purposeful inventiveness [53]. Some survivors also made use of active imagery, mindfulness and daydreaming.

It may be tempting to describe such strategies in terms of their biological functions. But even if some physiological processes may be identified in such studies, they will probably not come close to encompass the total experience of HT. Neither can the vicissitudes of courage and free will be reduced to neural circuits in the brain. The vast variety of cognitive and emotional strategies employed are simply too complex, too interconnected and too dependent of a multitude of psychosocial factors to be condensed into biological correlates. Moreover, the engrams [54,55] of 'memories of fear' which may be captured in translational animal studies utilizing optogenetics [56], currently cannot add much to our understanding of HT in human beings. Even if human information processing might be based on electrical and/or chemic currents passing through channels and neurotransmitters in the brain, it doesn't capture the very essence of human consciousness and free will. The human mind doesn't work [only] as electronic circuits within a computer and as a result, much of this data remains irrelevant. Traumatization in human beings is much more complex than the primitive mechanisms of stress observed in tortured animals [57,58]. As a result, the psychiatric domains will remain unique to humans [59] and perhaps this is a major reason for why so few neuroscientific discoveries have been implemented in the diagnosis and treatment of traumatized people [60].

Valid comprehensive neurobiological data must of course be based on data on human beings rather than on animals. However, while such data will be more relevant and valid, it doesn't mean that it will be easier to interpret. Ex post facto correlational studies with representative cohorts also have their own inherent weaknesses. For example, in comparison to causal data from experimental animal studies, they may be influenced by a lack of randomization of subjects which makes it difficult to isolate confounding factors. Correlation obviously does not prove causality and, as a result, there may be other plausible explanations for the 'significant' variances found. In the search for the biomarkers of PTSD, five different possible explanations for an observed association between a given biological abnormality and PTSD were listed [61]. First, an abnormality may be an antecedent risk factor for exposure to a traumatic event that could then cause PTSD. Second, an abnormality may be an antecedent vulnerability factor for developing PTSD upon exposure to a traumatic event. Third, an abnormality may be the consequence of exposure to the traumatic event alone, in which case it would be found in both PTSD and non-PTSD trauma survivors equally but not in unexposed persons. Fourth, the abnormality may be a manifestation or product of the PTSD, that is, a PTSD sign. Finally, the abnormality may be the product of a sequel or complication of PTSD.

Additional errors may originate from the research methods themselves. Most data on stress is based on retrospective self-reports, such as the Stressful Life Events Screening Questionnaire and similar symptom inventories [62]. But even though such measures are complemented with and/or validated by a clinician administered PTSD scale [63,64], they still depend on the awareness and willingness of the subjects to report on symptoms, which is not always the case. Subjects may not recognize the link between their symptoms and an experienced traumatic event, they may be unwilling to disclose the event, or what they reveal may be obscured by depression, substance abuse, or other comorbidities [65]. Such self-reports will therefore remain inherently biased.

Despite these methodological obstacles, however, there is remarkable progress in the field. Since the initial work of Selye [66], the study of physiological stress has continued uninterrupted and

produced significant results [3,67]. There is no doubt that we now understand a great deal about how people cope with an adverse environment and especially how various physiological mechanisms work together to bring about either stress or an inner balance.

Future prospective epidemiological studies may help to minimize the above mentioned sources of error [68]. Perhaps a combination of qualitative and quantitative research methods [69] may contribute additional understanding to cognitive neuroscience data? Most importantly, however, is that data from intrusive animal studies, such as optogenetics, neuromodulation and electrophysiology, sooner or later must be shown to be translatable also to humans. Possibly, non-intrusive imaging methods [70,71], such as MRI, fMRI, MRS, along with CT and PET [72-74] can be of value in detecting structural abnormalities and pathological conditions which may produce anatomical biomarkers of traumatization. But there will probably be a need for even more sophisticated technologies which can measure the nervous system at a cellular or molecular level. This may take some time, because while the human brain only weighs on average 1.5 kg, it contains approximately 100 billion neurons [75].

Ultimately, the challenge of finding biomarker of HT will rest on psychophysiological measurement: What exactly do we attempt to measure? How can individual differences be measured? How can dynamic manifestations be measured? How do we measure something that is continually adjusting to inner and outer influences? These questions will be further discussed below within the context of searching for biomarkers of HT.

Definition factors

The second obstacle to finding biomarkers of HT is based on conceptual issues. What are we actually talking about when we say that we search for the biomarkers of HT? It sounds simple enough. But it is not. As long as we have not defined exactly what we mean by 'Holocaust traumatization', it is not evident what we are studying. As a matter of fact, investigators cannot even agree on a satisfactory definition of psychological stress despite a century of research on its various aspects [76]. We clearly need a more sophisticated characterization of the subject of investigation because as long as we don't know what we are looking for, how do we know if we have found it?

We obviously don't study the event itself: the war and the persecution. Definitions based on the tragic narratives and recollections of the survivors – while important in themselves – will not produce the expected results. Descriptions of the disturbing feelings from then and there are equally insufficient. What we are interested in are the biological correlates of the enduring 'extremely negative, uncontrollable and sudden responses' [77] which appear in the here and now, even a long time after the original event. Simply put, what we want to study is the "accumulated residue of emotional pain suffered in one's past" [78].

Since these disturbing responses are triggered when the experience is recalled, traumatic memories must be one of the core features in the biomarkers of HT. A conceptual problem with such memories of fear [79], however, is that there is often a paradoxical co-existence in traumatized people of declarative amnesia of the disturbing event together with sensory intrusive thoughts [80-82] of certain details of the event [83]. Some of the most painful parts of the event might not have been processed on a symbolic level, as described in the rich literature on PTSD [84]. In fact, dissociation at the moment of the trauma has been long recognized as the single most important predictor for developing PTSD [85,86]. After all, there may be other parts of the event that were simply not registered at all, since 'the mind is not a video recorder' [87]. Thus, when we are asking survivors about their 'traumatic memories of fear', it is not obvious if we are studying the accumulated residue of emotional pain that are remembered, forgotten, repressed, dissociated or simply not registered at all.

This conceptual difficulty becomes especially relevant when considering the recent introduction of a vast range of powerful new devices in cognitive neuroscience that aims to investigate 'engrams' or the physical representations of memories [88] at the cellular and neuronal circuit level. For example, during a fearful event, some specific memory molecules within a handful of neurons may become excitable and are then recruited to encode the memory by the brain [89] to create persistent increases in synaptic strength, known as long-term potentiation [LTP]. But in human beings it is difficult to determine if such biophysical and biochemical changes in the brain occur as a result of normal memory processing or as a result of dissociation, repression or simple forgetting.

In addition to the difficulties of defining traumatic memories, there is little agreement regarding other, more general features of psychological trauma. While the characteristic responses to life-threatening events have been extensively investigated for more than a century [90], no single classification can fully and adequately delineate the various features of this experience. The eloquent analyses of psychological 'trauma' by Freud before and after WW1 [91], and later by Kardiner and Spiegel [92] on traumatic neurosis following WW2, cannot be regarded as sufficiently precise from a conceptual point of view. Ambiguities remain, even after the launch of post-traumatic stress disorder [PTSD] in 1980 because it has become increasingly recognized that a great number of patients do not present demarcated symptoms of re-experiencing, avoidance and hyper-arousal, while still reporting emotional pain from their past suffering. In reality, there is often a variety of different somatic, emotional, cognitive, and interpersonal complaints after the adverse event. As a result of such conceptual ambiguity, there has been a gradual expansion of post-traumatic categories, such as normal stress responses, acute stress disorders, uncomplicated PTSD, comorbid PTSD, late-onset PTSD, or complex PTSD, which made the original diagnosis of PTSD less discrete than originally intended. New types of post-traumatic disorders were gradually suggested, delineating post-trauma after sudden loss, separation, dental care, car-accidents, abortion, etc. People with multiple traumas throughout their lifetime would be labeled as having 'complex trauma' [93] or 'cumulative trauma' [94].

When new findings were reported that only those who were maltreated early in life would later develop PTSD [95], things became even more complicated, indicating that even if the disorder was clinically homogeneous, it was etiologically heterogeneous [96]. The gradual expansion of PTSD, referred to as 'criterion creep' [97], has become a conceptual shortcoming that hinders progress in its psychobiological study. If we also assume that different neural modifications underlie PTSD after different traumatic events [98], and if its pathophysiology stems from multiple neurobiological systems [99], it makes the research of neurobiological correlates very challenging.

An additional reason for the complex definition of PTSD lies in the answer to the question of susceptibility [100]. On the basis of accounts from torture victims, who asserted that 'everyone has a breaking point', we would conclude that anyone can get PTSD.

Therefore, all human beings will be damaged in one way or another if the stressful event is sufficiently severe, regardless of their vulnerability or resilience. But there is obviously no general consensus of such a 'sufficiently severe' breaking point. Since adverse events are intrinsic parts of life, anyone who experienced an event that was subjectively perceived as overwhelming, and thereafter had some characteristic signs of hyperarousal, nightmares and flashbacks, would then be qualified as being a trauma survivor. It might also include a sensitive child who experienced the death of a pet and thereafter suffered from sleeping problems with nightmares about the pet.

These widening conceptualizations raised doubts regarding the syndrome validity of the DSM-IV criteria for PTSD [87]; leading to suggestions that PTSD may not be a distinct syndrome [101]. Rather than being a single, well-defined disorder [93,102] it should be understood within a spectrum of conditions, similar to the autism spectrum, or the ADHD spectrum.

Another suggestion in how to minimize the conceptual vagueness of PTSD, as well as other mental disorders, comes from proponents of biological psychiatry. The 'Research Domain Criteria' [RDoC] was created [103] to produce a new diagnostic system based on their underlying neurobiological and bio-behavioral mechanisms, rather than on the phenomenology of clinical observations. However, while the RDoC may indeed be useful for research purposes, it has not yet made a significant impact on the diagnostic system used within psychiatry because of the conceptual, methodological, Neuro-ethical, and social issues involved [104] and a strict neurobiological view of mental disorders would probably be considered by clinicians to be too narrow and too 'impoverished' [105] for their purposes. Most importantly, no sustainable biomarkers have yet been found for the accumulated residues of emotional pain suffered in one's past because while it is easy to observe physiological signs of acute stress disorders [ASD], none have been clearly identified for PTSD with symptoms lasting for more than one month. In ASD, the neural, hormonal, visceral, and muscular changes in the body have been well described for a long time and the biological correlates within these physiological systems will also be more easily detected. But for PTSD, such observable physiological measures cannot be clearly and easily identified. As a result, the diagnosis PTSD is presently lacking any reliable, specific and cost efficient biomarkers [71,106,107].

The conceptual difficulties in the definition of HT are similar to those of PTSD and make the search for biomarkers very challenging. Any narrow definition of Holocaust traumatization that is based only on biomarkers will become conceptually flawed and clinically irrelevant if it does not also include the influence of psychological and social processes in the later developments of psychopathology and recovery. The conceptualizations of HT which evolved over the years reflected such a development and encompassed those who suffered from [1] severe mental disease; [2] Holocaust traumatization; [3] chronic traumatization; [4] late-onset traumatization; [5] resilience; [6] complex traumatization; and [7] a combination of anxiety symptoms with complicated bereavement and grief with depressive features [108]. Furthermore, when acknowledging the fact that many survivors presented a high degree of 'subjective well-being' [109], three waves of resilience research in Holocaust survivors evolved [110,111]. This research focused first on traits and environmental characteristics that enabled people to overcome adversity, then on processes related to stress and coping and finally on how people grow and are transformed by adverse events. It was based on the efforts of survivors to cope with their feelings after the war, and their use of defensive strategies which cannot be simply categorized as maladaptive 'traumatization' effects.

These conceptual developments demonstrate the controversial nature of the mental health of Holocaust survivors, suggesting that there is a largely paradoxical combination of co-existing vulnerability and resilience apparent in this population. Even if some studies, such as [112], found that Holocaust survivors suffered from substantially more posttraumatic stress symptoms, no single diagnostic label – including PTSD - can be considered suitable to describe the complex constellation of adaptive and maladaptive coping strategies in this population. While the diagnosis of PTSD has been frequently used within the field of legal medicine to justify reparations for their suffering, these four letters do not even come close to encompass the accumulated residue of emotional pain that they suffered and cannot be the single basis for future neurobiological studies of HT.

Nonetheless, we must acknowledge that such accumulated residues of emotional pain from the war evidently remain with the survivors for the rest of their lives. Denying this would be comparable to denying the existence of the Holocaust itself. The massive traumatization suffered during the war undoubtedly left a lasting impact on how the mind and the body dealt with the hardships in life. It will be the task of future research to find the stored psychophysical residues of these lasting effects.

Diversity factors

The third obstacle to finding biomarkers of HT stems from the heterogeneity of Holocaust-exposed survivors. Studies have identified individual differences in pre-war personality make-up [113] and in their post-war readjustment [114,115]. The most apparent difference concerns their different war experiences. While we may assume that everybody endured extreme hardships during the war, their individual experiences of escape, deportation, ghetto, camps, hunger, torture, forced labor, hiding, defensive activities, death marches, emigration, etc. obviously made a large difference, especially in terms of their severity and duration. Numerous documentaries and personal witness accounts have illustrated how these different war experiences diversely affected how each person endured the war. If we neglect this fact, our perspective will become a 'depersonalized' approach [116]. Different people obviously react in uniquely original ways to the same experience [117] and it is challenging to find uniform biological correlates for all diverse idiosyncratic responses.

What we can do at best is to include an assessment of those individual differences that we believe are relevant, and to try to minimize the influence of the possible 'confounding factors' as much as possible [118,119]. For the purpose of studying the biomarkers of HT, demographic data, such as gender [120,121] and age at the time of the stressful event – with or without cellular/epigenetic age [122] should obviously be collected. But there are also other variables, such as cognitive abilities, personality, social attitudes, psychological interests, psychopathology, previous emotional disability, cumulative life-time stress, cultural and religious background, the availability of social support, physical condition and health, intelligence, occupation and personal strengths which may also be assumed to have affected how each person endured the war and which therefore also are important to control. Many of these variables have been linked to variations in how each person was able to survive in the first place. In addition, socio-demographic factors, such as level of education, ethnicity, income and disability may also be significant determinants of how each survivor recuperated after the war.

Finally, personality factors, including identity, temperament, attitudes and cognitive memory processing are all important sources of variability in survivors of trauma [23]. For example, different levels of identification with 'victimhood' have been shown to have a profound influence on how each person dealt with his or her traumatic past. Those who kept their resentment and anger for having been 'wronged' may have more difficulties than those who were able to get over their sense of powerlessness. According to theory of shattered assumptions [123], these more fortunate individuals at one point or another started to redefine themselves as 'survivors' of a past injustices [124], rather than as defenseless victims in a malicious world. Some also adopted a self-distanced, rather than a self-immersed perspective [125], which helped them come to terms with the negative aftereffects of the war. Such 'cognitive self-appraisals' are often overlooked in traumatization research [126], even though they clearly have a significant impact on how people cope with adverse events. Individuals with a tendency to endorse negative thoughts and beliefs about the traumatic event [127,128] will be more at risk for PTSD than those with a more positive outlook on life.

A general assessment of mental health, including a measure of severity and comorbidity, will also be important in any HT study. Such an assessment will include survivors who had psychiatric problems before the war, those who developed problems as a result of the war, and those who developed problems as a result of trying to cope with their debilitating symptoms. A precise delineation between these groups, however, is never an easy task since they tend to melt into one another. For example, in the population of Holocaust survivors who remained chronically hospitalized in psychiatric institutions in Israel for most of their lives, it was never easy to clearly distinguish between their psychotic disorders and their residual symptoms of PTSD [129,130]. Without taking such individual diversity into consideration, including information about the family history of schizophrenia in each patient, one would mistakenly conclude that the psychiatric symptoms were caused only by the war experiences.

There might also be a great variety of intrinsic cognitive, affective and pathophysiological variations in how each person responds to stress. For example, in a recent review of the pathophysiology of PTSD [99], it was suggested that post-traumatic responses to adverse events may not present with the same constellation of symptoms in each afflicted person, and that the initial presentation of the disorder was often confounded by other psychiatric comorbidities [105]. In fact, trauma-exposed individuals in general are known to be inherently heterogeneous [131] and people with PTSD often suffer from many comorbid psychiatric disorders [132]. Holocaust survivors with more severe PTSD also had more cumulative lifetime stress and physical illness [133]. Since the current diagnostic definitions of psychiatric disorders accentuate reliability at the cost of clinical validity in heterogeneous populations with comorbid conditions, they are likely to yield false results when searching for biomarkers of mental disorders [34].

As a result of such individual variation in stress responses, researchers should focus more on specific individual vulnerability than on trying to determine the general features of the population as a whole. This has become especially important when trying to explain why only a minority of survivors develop stress-related pathologies after a stressful event. What made them more susceptible to stress, while others were more resilient? While female gender, lower social economic status, lack of social support, premorbid personality characteristics and preexisting anxiety or depressive disorders are examples of factors that have been found to increase the risk for PTSD [60], younger age at the time of the trauma seems to make most difference in this traumatization process [134]. Since traumatic experiences at different phases of development evidently produce distinct effects, it has been repeatedly shown [134-136] that the most important individual difference when it comes to traumatization seems to be various adverse childhood experiences [ACE] [117,137,138]. This includes early life stress [ELS], childhood trauma and abuse [CA], childhood maltreatment [CM] and damaging attachment-style [AS] [139]. Whether inflicted passively through neglect or actively through abuse, these childhood experiences have been found to be prevailing risk factors to various kinds of symptom developments [140,141] and make a huge difference in how each individual survivor responded on a long-term basis to the adverse events of the war [142–144]. Adult survivors who were sufficiently nurtured as infants seemed more able to withstand adversity than those without early bonding [145]. Any study of biomarkers of HT should therefore aim to include some assessment of such ACE.

The vast diversity described above makes research on the psychophysiology of individual differences extremely difficult [119]. Obviously, it also creates a huge challenge in developing a biomarker-based diagnosis of PTSD [45]. Even though demographic and environmental factors, personality and psychiatric history, dissociation, cognitive and biological systems, and genetic or familial risk are increasingly studied together [146], many studies still lack a sufficient control of confounding factors based on such individual diversity.

Since people utilize individual stress-inhibitory neural pathways to properly tune and terminate their stress responses [147], there is a need for a more personalized approach [6,148]. Such an approach would emphasize within-individual [as opposed to group average] symptom clusters, for example on the basis of human genetic diversity [149]. An accurate inference of these individual differences may require more sophisticated designs than the classical estimates of mean effects [150]. Advances in human genome science and molecular innovations in neuroscience have also encouraged the pharmaceutical industry to focus beyond broad spectrum population therapeutics to more personalized medicine in the neuropsychiatric field [151]. Even though there are still many challenges in such 'genomic' medicine, the opportunities are gaining momentum [152].

Dynamic factors

The fourth obstacle to finding biomarkers of HT is that survivors have changed over time and are no longer influenced only by the effects of the war. After all, the war happened more than seventy years ago and so much has happened ever since. Survivors have experienced a variety of additional distressful events and have adjusted to a multitude of new circumstances in life. Both mitigating and aggravating new experienced have continued to influence them. Thus it is important to consider that not only the original stressful events, but also later environmental challenges play an important role in modulating individual vulnerability to illness [12]. This lack of constancy becomes a fundamental problem in any search for biomarkers because there is not only a gradual change in the presenting symptoms, but also in new coping mechanisms which probably will alter the underlying biological correlates as well.

The time gap between an adverse event and the measured response is therefore an essential factor in all traumatization research. But, as we have already mentioned above, it's clearly difficult to exactly

differentiate between 'acute', 'recurrent', 'delayed' and 'chronic' stress. The 'one-month' criterion added in the DSM-III for PTSD remains an arbitrary delineation, not only for clinical, but also for research purposes. There is no other mental disorder that includes such a time factor and puts so much emphasis on time. But fundamental questions remain regarding such a time factor; How long time does it take for a specific body and mind to recuperate after an adverse event? How long time should it take to mourn? What can be regarded as a 'normal' process of physiological and mental recuperation? These are still open questions which are difficult to answer.

While physical wounds have a well-defined course of healing, emotional wounds do not. In physical wounds, there is an initial immune response causing the wound to become inflamed. New cells form over the wound and scar tissue forms to heal the wound. If such physical wounds take more than a few weeks to heal, there may be an infection which requires medical treatment. But emotional wounds like traumatization do not have a well-defined course and there may not even be a healing-process in the physical sense. Rather, it can be described as a vague and multifaceted cognitive and emotional process of coming to terms with a new reality. It may take one month, a year, ten years or an entire life-time to reconcile oneself with the consequences of the event and learn to live with it. For some people, this process may get stuck, and time may even make things worse. From what we have learned from traumatized Holocaust survivors, it's obviously not true that 'time heals all wounds.' Even when such wounds become gradually less painful, they may never completely disappear. How can such processes be defined in medical terms? How can they be measured with a biomarker?

The absence of a well-defined course of healing is especially true for HT. This may be clearly seen in the rich literature on the psychological effects of HT which were observed among survivors ten [153,154], twenty [155-157], thirty [158], forty [159,160], fifty [161-163], sixty [164], or seventy [165,166] years after the war [108]. The differences in observed symptomatology over the years as shown in the above studies provide a reliable indication of the survivors' development, growth and post-war adjustment.

Immediately after the war, survivors embarked on a long journey of recuperation. Similar to a musical symphony, their lives passed through different phases. Although there might have been a kind of Leitmotif or a Haunting Melody [167] with reminiscence from the past trauma that run through their entire lives, they also had new good and bad experiences. Despite occasional 'hang-ups' with frightening recollections and intrusive flashbacks, most survivors were able to focus on the present for longer periods of time and gradually put the past behind them. Earlier regarded simply as either powerless victims or heroic resistance fighters, many transformed their social identity from persecuted Jews to empowered survivors. As a result, they are today viewed in a more differentiated manner, as multi-faceted individuals who cope with their ageing similar to others [168-171]. Despite their earlier traumatization, many have reached some level of inner balance and they function well most of the time.

During their long journey of transformation, each survivor chose a different personal path of healing. They either learned from others, or found it within themselves; some from religion, or from friends and family. New corrective experiences in their environments had a reparative effect, which somehow corrected the earlier destructive ones. While searching for how to bring some balance to body, mind and spirit, they not only engaged in excessive work and repression of the past [111]. Many also utilized various kinds of professional help and received supportive or transformative post-traumatic therapy or psychiatric medications when things got too difficult. Therefore, when we observe the survivor today, we will not find the same survivor as the one in 1945. It's obviously not the same mind, and it's not the same body.

Apparently, there is also a relatively small group of Holocaust survivors who are stuck in the past. This clinical population of survivors includes those who suffer from more or less chronic PTSD and also those who suffer from 'late' or 'delayed' onset PTSD' [172]. For them, it's as if time stopped and they are re-living experiences from the past 'like a broken record that is spinning around and around' [173]. However, even among this clinical population, the characteristic symptoms of HT cannot be regarded as sufficiently stable and constant to be assessed in a reliable way. As found also in the fluctuating path of PTSD, different symptoms show different trajectories of change with age. For example, as survivors grow older there will be less dissociation [62].

If the symptoms change, the underlying biological correlates will probably also change. Psychophysiological measures are 'state-dependent', which means that they are influenced by the emotional state of a person when the measurement is done. How can reliable biomarkers of HT be found, if they have transformed into something else or if they are no longer there? How can biomarkers, which by definition were caused by adverse environmental events, remain sufficiently constant, robust and enduring to be measured in a favorable environment many years after the actual event? How can they account for all the changes at each stage of development? Even if there might have been some tangible biomarker present at one time or another after the war, these neurobiological processes in the brain and the periphery might not be observed at a later date of observation.

Several questions regarding the dynamic nature of traumatization become particularly relevant when considering the recent studies on epigenetics. The very definition of epigenetic methylation markers as continually changing raises several questions of their robustness. How can epigenetic alterations over the course of a lifetime reflect different environmental exposures [122] ? Was the finding of methylation in the FKBP5-gene [174] a temporary 'state' or a stable 'trait'? Does the plasticity of epigenetic factors [175] compel us to reevaluate earlier psychophysiological findings? In addition, should we not take into account a 'normal' shortening of the telomere [176-178] when considering how the body deals with stress in different ages? Is it not likely that the reconsolidation and the dynamic nature of memory [179] will also alter the underlying cellular and molecular correlates [29]?

All these questions reflect the fluctuations which occur on a continual basis as the organism tries to adjust to a new environment. Especially in response to new experiences, we may expect that there will be a rebalancing of the HPA-axis and a regeneration of the neurons in the brain as a result of Neuro-modulation and Neuro-plasticity [180]. New synaptic connections are formed and reorganized [181] all the time, with the Amygdala constantly preparing for emergency events [182]. Brain circuits are plastic and remodeled by stress to change the balance between anxiety, mood control, memory, and decision making [183]. As the glucocorticoid receptor gene tries to adapt, new epigenetic methylation marks on specific locations of cells will be added. As a result, specific neuroendocrine, neuroanatomical, and epigenetic signs, found during the lives of traumatized people,

may not be an actual physical representation of the traumatic event itself. The original signs of HT may have been erased, like footprints in the sand that disappears with every new wave of experience. What we might see when looking at, for example cortisol, the Amygdala or the glucocorticoid receptor gene NR3C1, will therefore be only a shadow of the previous event.

Obviously, nothing in the universe remains the same. Nevertheless, change can be lawful, rather than capricious. Change can be regulated within a dynamic harmony that tries to keep the various physical mechanisms in equilibrium. Instead of searching for static biomarkers of HT, perhaps we need to focus on the dynamic processes of change involved? This may require looking at HT from a different long-term perspective of 'long-term adaptation in slow motion', or as 'short-term evolution in fast forward'? Such a perspective will take into account 'evolvability, phenotypic plasticity, epigenetic inheritance, complexity theory, and the theory of evolution in highly dimensional adaptive landscapes' [184]. These inherent self-repairing processes obviously make the search for 'relatively stable' biomarkers more difficult and they will also involve complex homeostatic and adjustment mechanisms.

Adjustment factors.

The fifth obstacle to finding biomarkers of HT stems from the apparent contradictory nature of stress responses. What we attempt to study is not a simple stimulus → response process (adverse event → traumatic stress), but a much more complicated process of mediation within the body and mind that attempts to overcome the inner disequilibrium created by any adverse event (adverse event → traumatic stress ← readjustment). In such a study, we are not (only) interested in the high stress levels (heartbeat, sweat etc.) in themselves, but the regulatory mechanisms employed in trying to regain an inner balance at the time of the adverse event and later, as expressed in many different physiological systems. First, within the endocrine regulatory system, abnormalities in the negative feedback to the hypothalamic-pituitary-adrenal [HPA] axis [185] will be of more interest than the expression of stress hormones themselves. Second, within the neuroanatomical regulatory system, the input from structures like the prefrontal cortex and hippocampus will be more important than the immediate activities within the Amygdala to provide negative regulation to the HPA axis, since they may promote a termination of the stress response [5]. Third, within the regulatory immune system, some signs of psychological distress may in fact be attempts of the body to protect itself from foreign substances [186,187]. Finally, within epigenetic regulatory systems, the balance of histone methylation regulated by histone methyltransferases, and histone demethylation regulated by histone demethylases, will be more important than looking at only one or the other form of gene expression [188]. In addition, executive self-regulating feedback loops, both within the brain and between the brain and the body, would also be active within such a regulatory system. Searching for biomarkers of HT within such a complex multilevel system [189] is therefore a big challenge.

This obstacle is based on the concept of 'homeostasis' [190] which assumes that all organisms must maintain a complex and dynamic equilibrium which is relatively stable while being challenged by internal or external adverse forces. Maintenance of such a balance depends on the tight orchestration of factors involved in the response to stress and its recovery [4]. To achieve such as state, it has to maintain an inner equilibrium, such as a stable body temperature, even when it is hot inside or cold outside. The 'thermostatic' system is regulated by both negative and positive feedback, as well as by feed forward mechanisms. These 'control mechanisms' can sense an internal change and activate physiological processes that reverse, or negate that change. All these mechanisms are of course important when trying to study the biomarkers of HT. But we have more questions, than answers regarding how they function in survivors of adverse events.

In normal circumstances, the hypothalamus is the thermostat that keeps everything in balance (within specific boundaries). But what happens when there is excessive stress (sleep deprivation, starvation, excessive temperature changes, a constant threat of annihilation, etc.) on virtually all bodily functions, such as during the Holocaust? Did it lead to a permanent damage to the inner 'thermostat' of the survivors? Did this regulatory system gradually adjust to the constant threats or was it damaged? Can this be a reason for why there is a dysregulation of the 'feed forward' mechanism that is supposed to help the body respond to a control signal in anticipation of a future change? Can this be a reason for why some survivors remain constantly alert and prepared for a future catastrophe? If such regulatory functions of the homeostatic system were destroyed, how can they be measured, and possibly fixed?

The regulating mechanism is well understood in a simple thermostat. But there is still insufficient understanding of how it actually functions within the body. A simple thermostat needs a sensor to detect changes in the condition to be regulated, an effector mechanism that can vary that condition; and a negative feedback connection between the two. If stress is detected in humans, the effect mechanism should increase the levels of glucocorticoids to calm the system. But instead there is a paradoxical decrease in glucocorticoids [191-193], which indicate that there might be another 'mediating function' in between. There have been several attempts to explain this mediating function. For example, those stress-induced increases in glucocorticoid levels may protect not against the source of stress itself but rather against the body's normal ways to deal with stress [194]. Even though more needs to be figured out regarding the 'stress thermostat', changes of the HPA-axis after acute stress seem to play a key role in the production of stress-associated pathologies [195,196]. Only few studies have been published on such effects in Holocaust survivors. For example, low urinary cortisol excretion was found in Holocaust survivors with posttraumatic stress disorder [197], and cortisol levels were significantly lower at awakening, and in the evening in Holocaust survivors with PTSD [198]. Perhaps such dysregulation of the HPA-axis contributed to the finding [68] that survivors were significantly more likely than non-survivors to suffer from dyslipidemia [more triglycerides, cholesterol and/or fat phospholipids in the blood], or from hypertension, diabetes mellitus, vascular disease and metabolic syndrome, as well as from obesity? But there seems to a lot that we still do not understand about the stress regulation in this and other traumatized populations [199].

Perhaps a reason for the slow progress in finding biomarkers within a homeostatic system of adaptation and evolution is that the biological correlates do not remain sufficiently 'robust' [200]? Essential variables must remain within a range, or within a 'viability zone' of lower and upper bounds [201] to be reliably measured. When adverse events occur, the physiological system will attempt to cope with the changes within such a viability zone, without 'breaking' [202]. Perhaps this is how it functions in general systems of stress? Does the body in fact maintain a constant internal environment

also from a psychological point of view? Should it? Should neural activation and inhibition be self-regulating in the same way as the thermostat? Or should there be a preparatory effect of baseline and stress-induced corticosterone levels which can increase the threshold of severity necessary for subsequent stimuli to become stressors [203]? Can the 'base-levels' of what it means to be calm be similarly measured in various people with different experiences? Are there 'normal' physiological base-level of stress? Is the corticoid repression gene inherently programmed to secrete the exact amount of cortisol to bring any psychological system into balance? Is there a universal 'viability zone' for such systems? Are the 'breaking-points' within such a stress-system similar in different people and can they really explain why some individuals develop PTSD while others do not? How do we know if higher corticotrophin-releasing factor (CRF) levels, blunted adrenocorticotropic hormone [ADCH] responses and low levels of cortisol may be a sign of illness rather than a sign of adaptive coping? Is long-lasting hormonal alterations to extreme stress in humans normative or maladaptive [204]? Apparently, as long as we do not know what should be expected within a specific environment, we cannot differentiate the good from the bad [205]. Where biology draws the line between these two; positive, motivating stress and negative, energetically costly stress, is an enduring evolutionary conundrum [206].

The capacity of stress to cumulatively damage aging tissue has been referred to as the 'Glucocorticoid Cascade Hypothesis' [67]. It was explained as an inability to terminate the secretion of adrenocortical stress hormones, glucocorticoids, at the end of stress. This hormonal excess may be due to degenerative changes in a region of the brain which normally inhibits glucocorticoid release; the degeneration, in turn, is caused by cumulative exposure to glucocorticoids. Together, these effects would form a feed-forward cascade with potentially serious patho-physiological consequences in the aged subject. When conditions place the organism under great strain for a long time, such as during the Holocaust, the homeostasis mechanism would no longer operate smoothly. It could even become a kind of an 'adaptation disease [66]. The assumption was that when there is additional stress on an already depleted and 'tired' mechanism, it would somehow push the physiological system away from its baseline state toward a lower utility state [207]. It has been proposed that "Master homeostatic regulators that circulate and operate throughout the organism, such as stress hormones [e.g., glucocorticoids] and immune mediators [e.g., cytokines], are at the crossroads of peripheral and central susceptibility pathways and represent promising functional biomarkers of stress-response and target for novel therapeutics" [208].

Chronic HT and PTSD may represent such a situation where there has been a failure of the body to return to its pre-stress baseline. Insufficient cortisol available to regulate the system would then cause a kind of 'adrenal fatigue' and a feeling that 'enough is enough'. During the Holocaust, the concentration camp inmate who resigned to his approaching death because of such exhaustion was called Muselmann. It is plausible that individuals, who nevertheless survived after having been in this state of collapse for some time, may have caused a dysregulation of the HPA-axis and developed an inability to produce enough adrenal cortex hormones in response to stress as a result. But there is still no agreement as to what 'normal' glucocorticoid levels should be when a person is coping with extreme stress and it is therefore impossible to test this assumption. Apparently, there is not even a consensus as to how to interpret the earlier findings of glucocorticoid pathways of traumatization [45]. Cortisol levels therefore cannot be a reliable biomarker for HT, because, the findings of low cortisol levels has been both counterintuitive and not uniformly reproducible [209].

Many of these questions have been raised throughout the history of stress-research. In an attempt to resolve the dilemma of 'flexible' homeostasis, the term 'hetero-stasis' was suggested by [210] to define the process by which a new steady state was achieved through adaptive mechanisms. It was perhaps a precursor for 'allostatic' [211], and the 'end of stress as we know it' [212]? Allostatic load did not only emphasize the accumulated 'wear and tear' of stress on the body, but also a kind of predictive regulation of internal sensations [213]. But if the biomarkers of HT are located within such an 'allostatic load', they will still be difficult to measure because we still cannot predict how the regulatory mechanisms within the autonomic nervous system, the HPA-axis, the endocrine system, and the immune system actually work in humans who endured stress for a long time. As a result, findings of higher or lower levels of various measures cannot be reliably interpreted as signs of short-term adaptive effects or as maladaptive long term 'allostatic load'. This makes the search in itself a contra-intuitive process. Stress cannot be simply understood as symptoms of illness, but possibly also as attempts to regain homeostasis, and therefore as a kind of indicator of a healing process.

Surviving the war obviously necessitated a constant effort to adapt to the extraordinary challenging environment of persecution. It did not only make survivors more vulnerable, but also more resilient. This has been gradually more accepted in the research on traumatization, and it has changed the focus from searching for vulnerability markers to resilience markers [214]. Such resilience seems to be more than just the 'flip side' of a risk factor because it was assumed to include characteristics that also protect a person against the development of psychopathology in the face of stress [215].

As a result of this change in focus, post-traumatic stress responses can now be regarded, not only as something pathological, but also as 'normal responses to an abnormal situation'. Instead of asking why survivors become anxious, we now ask ask why they were unable to reinstate a normal state of resilience. Some neuroscientists have even started to search for the neuroendocrine markers which are associated with a resilient phenotype, focusing on the 'psychobiology and molecular genetics of resilience' [27]. Despite all these developments, however, it is still difficult to measure the survival advantages of the more resilient survivors [216], and it will probably remain a challenge to study the multisystem concept of allostatic load for a long time [217-219].

Conclusion

Various methodological, conceptual, diversity, dynamic and adjustment factors have all contribute to the difficulties in finding biomarkers of HT and they make this kind of psychophysical research extremely complex.

What can be done in order to make progress? From a methodological point of view, further epidemiological studies may help to identify risk factors for traumatization. Possibly, cognitive neuroscience data from animal studies could be combined with qualitative and quantitative studies on human beings through new non-intrusive brain-imaging methodology. From a conceptual point of view, the future psychophysiological study of HT would benefit from a more exact and simple definition of traumatization, such as 'accumulated residues of emotional pain from the past',

rather than as [simply] PTSD. The focus of such future studies may be the physiological residues of the learned fears (in engrams, endo-phenotypes, glucocorticoid receptor genes, etc.) which may have caused the automatic reactions to threatening stimuli. From a diversity point of view, there is a need for a more personalized approach which emphasizes within-individual (as opposed to group average) symptom clusters. From a dynamic point of view, there is a need to look at HT from a long-term developmental perspective which takes into account the continuing changes which occur in a person's life after the traumatic event. From the point of view of adjustment, signs of traumatization should be evaluated not only as maladaptive, but also as possible normal responses to abnormal situations within a homeostatic system of adaptation and evolution. All these recommendations together suggest that we still need a more integrative bio-psycho-social explanatory model to the study of traumatization than pure biological reductionism.

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