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Bouncing Back

Trauma and the HPA-axis in Healthy Adults

PHD SUMMARY

COACTION PUBLISHING

Bouncing back - trauma and the HPA-axis in healthy adults

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Background: Dysregulation of the hypothalamic–pituitary–adrenal (HPA)-axis is thought to underlie stress-related psychiatric disorders such as posttraumatic stress disorder (PTSD). Some studies have reported HPA-axis dysregulation in trauma-exposed (TE) adults in the absence of psychiatric morbidity. In this dissertation we set out to unravel part of the mechanism that underlies the complex relations between trauma exposure, stress regulation, and psychopathology.

Method: Mentally healthy TE subjects were compared with non-trauma-exposed (NE) healthy controls. To distinguish between the potential effects of childhood trauma and adulthood trauma, we included women exposed to childhood trauma as well as men who were exposed to trauma during adulthood. Basal HPA-axis functioning was assessed with salivary cortisol samples. HPA-axis reactivity was assessed with the dexamethasone/corticotropin-releasing hormone (Dex/CRH) test.

Results: The results show that childhood trauma exposure is associated with an attenuated cortisol response after the Dex/CRH challenge test in women. In contrast, trauma exposure during adulthood was not associated with alterations in HPA-axis regulation after the Dex/CRH test. Neither childhood trauma nor adulthood trauma were associated with basal HPA-axis functioning.

Conclusion: Childhood trauma rather than adulthood trauma may chronically affect HPA-axis functioning. Since the association between adulthood trauma and resilience to psychopathology cannot be explained by HPA-axis functioning alone, other factors must play a role.

Keywords: *HPA-axis*; *cortisol*; *trauma*; *childhood trauma*; *adults*; *resilience*

Mentor: Prof.dr. F.G. Zitman (Leiden University Medical Center, department of Psychiatry).
Thesis defended in Leiden, the Netherlands, November 30, 2010.
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Exposure to traumatic events is often thought to be associated with an increased vulnerability to develop psychiatric disorders such as posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). However, the majority of trauma-exposed individuals (TE) do not develop a psychopathology. Epidemiological studies on PTSD show a widely diverging range of lifetime prevalence of PTSD after trauma exposure of 3–10% in adult populations, depending on the type of trauma, time of trauma exposure, and gender (Breslau et al., 1998; Bronner et al., 2009; de Vries & Olff, 2009; Frans, Rimmo, Aberg, & Fredrikson, 2005; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). The lifetime prevalence of psychiatric disorders after childhood trauma exposure is reported to be much higher. Over 39% of the females and 29% of the males from a large cohort who reported sustained childhood sexual abuse, subsequently developed PTSD in adulthood (Molnar, Buka, & Kessler, 2001).

The main question we wanted to answer in this dissertation was whether exposure to psychological trauma leads to hypothalamic–pituitary–adrenal (HPA)-axis dysregulation independent from current or lifetime axis-I psychiatric disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (Fig. 1). In addition, we tried to identify the roles of trauma type and time of trauma exposure during the lifespan in the putative HPA-axis dysregulation.

Citation: European Journal of Psychotraumatology Supplement 1, 2010, **1:** 5844 - DOI: 10.3402/ejpt.v1i0.5844
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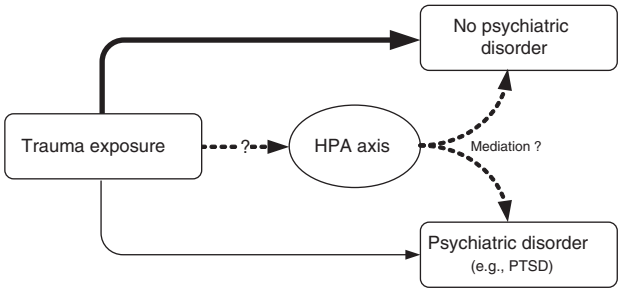

Fig. 1. Established and hypothesized relationships between trauma exposure, the putative mediating role of the HPA-axis, and subsequent trauma-related psychiatric disorders. The first question marks represent the primary hypothesis of this dissertation. The line drawn between 'Trauma exposure' and 'No psychiatric disorder' is made thicker than the one between 'Trauma exposure' and 'Psychiatric disorder' to visualize that the former relationship occurs more frequently than the latter.

To answer our research questions, we designed the empirical studies presented in this dissertation. In addition, we performed a meta-analysis on studies that examined trauma-exposure during adulthood, HPA-axis regulation and PTSD.

Summary of major findings

The first study of this dissertation (Chapter 2) concentrated on trauma exposure in childhood. Early in life, the HPA-axis is in development and trauma exposure during childhood is thought to have profound effects on HPA-axis regulation. These effects may be evident even throughout adulthood and in the absence of psychiatric morbidity. In this chapter, we explored the influence of exposure to childhood trauma on HPA-axis regulation in a group of women without present and lifetime psychiatric disorders, and compared them with women without a history of childhood trauma. The results of this study support the hypothesis that HPA-axis regulation is durably changed by exposure to sustained childhood trauma, as we found a blunted cortisol and adrenocorticotropic hormone (ACTH) response to the dexamethasone/corticotropin-releasing hormone (Dex/CRH) challenge test. These findings are largely consistent with several lines of evidence, which comprise animal studies (de Kloet, Sibug, Helmerhorst, & Schmidt, 2005; Sanchez, Ladd, & Plotsky, 2001; Sapolsky & Meaney, 1986; Suchecki, Rosenfeld, & Levine, 1993). However, causal inference cannot be asserted based on our cross-sectional analysis. Therefore, an alternative interpretation of the results is that higher resilience against psychopathology explains why the women in our study had not developed psychiatric illnesses following childhood trauma exposure. The salivary cortisol responses to awakening, as well as the cortisol levels over the rest of the day, were not (lastingly) altered by childhood trauma exposure (Fig. 2).

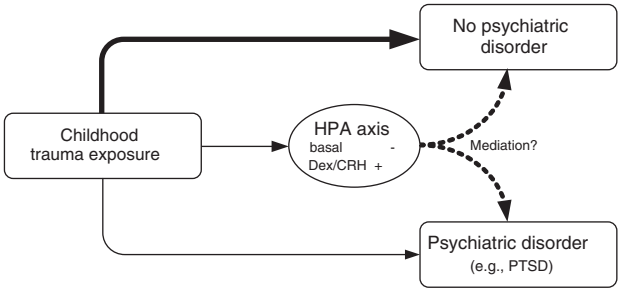

Fig. 2. Established relationship between childhood trauma exposure and HPA-axis regulation. No effect of childhood trauma exposure on basal HPA-axis regulation was found; a blunted cortisol and ACTH response to the Dex/CRH challenge test were found in trauma-exposed (TE) women.

In Chapter 3, we described the mental health of a large group of Dutch peacekeeping veterans 10–25 years after deployment to Lebanon and former Yugoslavia, and its association with deployment-related trauma exposure. We found that 10–25 years post-deployment, Dutch peacekeeping veterans did not show more psychological distress than the general Dutch population as assessed with the Brief Symptom Inventory (BSI). In addition, we did not find a significant association between past trauma exposure (10–25 years ago) and current psychological distress. Moreover, trauma exposure explained only 9% of the variance in psychological distress. From these findings, we concluded that even though military peacekeeping operations may have a strong impact on the lives of soldiers, trauma exposure in this group of veterans did not seem to be related to current psychological distress. In other words, exposure to traumatic events often occurs during deployment, but this did not cause sustained psychological distress in the majority of the Dutch peacekeepers.

In Chapter 4 the relationship between past trauma exposure (as described above) and current HPA-axis regulation in a group of peacekeeping veterans without current or lifetime DSM-IV axis I psychiatric disorders was explored. The HPA-axis was tested through basal salivary cortisol over the day as well as with the Dex/CRH challenge test. In contrast to our hypothesis that trauma exposure during adulthood would be associated with altered HPA-axis functioning, we did not find evidence of HPA-axis alterations. However, as HPA-axis regulation in military personnel may well be different than that of non-military controls due to e.g., chronic stress during deployment, military training, or personality structure, we also compared peacekeeping veterans with civilian non-trauma-exposed controls (NE) without current and lifetime psychiatric morbidity. Again, no differences were found. From these results we concluded that deployment-related trauma exposure in male peacekeeping veterans is unrelated to long term HPA-axis alterations (Fig. 3).

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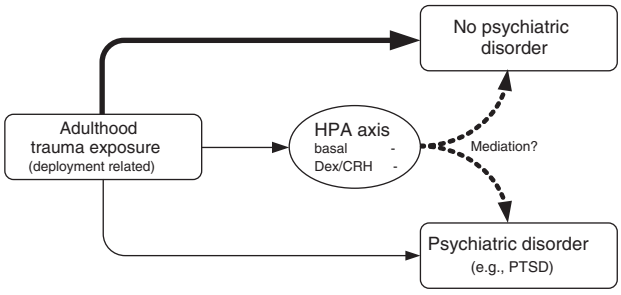

Fig. 3. Established relationship between deployment-related trauma exposure and HPA-axis regulation. No effect of deployment-related trauma exposure on HPA-axis regulation was found.

In Chapter 5, we studied the effect of work-related trauma exposure on HPA-axis regulation in Dutch railway personnel. Train drivers and conductors in The Netherlands are frequently exposed to severely stressful and traumatic events during the course of their daily work. Verbal and physical aggression as well as "person-under-train" accidents and near-accidents occur on a regular basis for many of the men and women. In this study, we compared TE male train drivers and conductors without current and lifetime DSM-IV axis I psychiatric disorders with NE controls, also without psychiatric disorders. In support of our hypothesis that trauma exposure during adulthood is associated with HPA-axis dysregulation, we found a blunted salivary cortisol response to awakening in the TE subjects. However, no effect was found in HPA-axis reactivity during the Dex/CRH test. These results support the idea that trauma exposure during adulthood is associated with subtle basal HPA-axis alterations, even in the absence of psychiatric morbidity (Fig. 4).

The results from the studies on the effect of adulthood trauma on HPA-axis regulation in this dissertation are mixed. In order to describe and summarize all current evidence on the association between trauma exposure during adulthood and HPA-axis regulation in our and other studies that included TE healthy individuals as well as NE healthy controls and PTSD patients, we performed two meta-analyses on 37 eligible studies published between 1995 and 2010 (Chapter 6). In the first meta-analysis, the TE subjects were compared with NE control subjects (including 21 studies) and, in the second meta-analysis, TE subjects were compared with PTSD patients (including 34 studies). The results clearly show that trauma exposure during adulthood is not associated with basal HPA-axis dysregulation. In addition, no evidence was found for an association of PTSD with basal HPA-axis regulation. In subgroup analyses, however, we found increased cortisol suppression after dexamethasone in TE subjects. Mechanisms that have been proposed to explain the enhanced cortisol suppression in response to dexamethasone are an up-regulation of pituitary glucocorticoid receptors or glucocorticoid receptor sensitivity, resulting in an increased negative feedback sensitivity in TE individuals. As the results of the DST in TE subjects and NE controls were based on only five publications, more studies on this topic are needed.

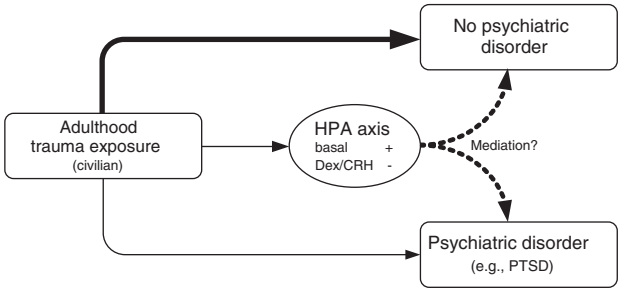

Fig. 4. Established relationship between civilian trauma exposure during adulthood and HPA-axis regulation. Lower basal cortisol levels were found in TE individuals compared to NE individuals. No differences were found on the cortisol and ACTH response to the Dex/CRH.

General discussion

The findings of the studies presented in this dissertation add to the literature on the association of trauma exposure and HPA-axis functioning in several ways. First, in the design of our studies, we focused on TE individuals without current or lifetime psychiatric disorders and compared them with a non-psychiatric NE control group. In most studies on the association between trauma exposure, PTSD, and HPA-axis regulation, PTSD patients were compared with individuals without psychiatric disorders. This precludes the possibility to distinguish between effects of psychiatric symptoms or trauma exposure *per se* (Lindley, Carlson, & Benoit, 2004; Muhtz, Wester, Yassouridis, Wiedemann, & Kellner, 2008; Simeon et al., 2007).

Second, although the issue of trauma exposure in control subjects is important, many studies did not address this issue. Some studies screened their eligible control subjects on trauma exposure (either during childhood, adulthood or both), and included only NE controls (Lindley et al., 2004; Muhtz et al., 2008; Simeon et al., 2007). Occasionally, TE controls with a comparable type of trauma-exposure, e.g., military veterans with deployment related trauma exposure, were included (de Kloet et al., 2007, 2008; Golier, Schmeidler, Legge, & Yehuda, 2007). Often, however, the presence or absence of trauma exposure in non-psychiatric controls was not taken into account (Baker et al., 2005; Smith et al., 1989; Yehuda, Golier, Halligan, Meaney, & Bierer, 2004; Yehuda et al., 1993). These different ways of selecting and handling trauma exposure in control groups between studies makes comparison and interpreting the mixed

results difficult. This was a major reason for conducting a meta-analysis on studies investigating trauma exposure and HPA-axis regulation in TE and NE subjects without psychiatric disorders. To study the additional effect of PTSD, we also carried out a meta-analysis on studies investigating PTSD patients and TE subjects.

In the following sections, we will discuss the findings from this dissertation within a broader perspective of vulnerability and resilience. Furthermore, we will discuss our experiences in relation to the inclusion of the TE participants. Finally, we will discuss future perspectives.

Exposure to childhood trauma

Consistent with our hypothesis and with findings from previous studies, we found a blunted cortisol and ACTH response to the Dex/CRH challenge test in mentally healthy adult women with a history of moderate to severe childhood trauma exposure.

Preclinical studies have shown that in rodents, very early in life, a time window exists during which low basal levels of corticosterone (with the same role in rodents as cortisol in humans) and hypo-responsiveness of the HPA-axis are crucial for the normal development of the brain circuitry (de Kloet et al., 2005). This window of vulnerability is known as the stress hypo-responsive period (SHRP), and prolonged activation of the HPA-axis is only resorted to under severe physiological and psychological stress (Sapolsky & Meaney, 1986). The SHRP in rats is sustained by specific components of maternal care: licking and grooming, and delivery of milk to the pup (Suchecki et al., 1993). Manipulations that alter the licking and grooming (maternal separation) result in long-term alterations in HPA-axis regulation and in emotional behaviour (Sanchez et al., 2001). Similar findings on variations in maternal behaviour during infancy have been reported in non-human primate studies (Coplan et al., 1996). Mothers of infant bonnet macaques were exposed to different foraging demands over 12 weeks. Mothers with low foraging demands (LFD) could obtain food without effort, whereas mothers with constantly high foraging demand (HFD) had to complete a daily task to obtain their food. In the variable foraging demand (VFD) condition, the mothers were exposed to unpredictable conditions with respect to food access, resulting in diminished perception of security and a reduction of maternal care of the infants. As adults, the VFD-reared macaques exhibited more trait anxiety than the LFD and HFD- reared macaques. In addition, dysregulation of the HPA-axis was reported, in particular, increased corticotropin releasing factor concentrations and decreased adrenal activity (Coplan et al., 1996).

In humans, during the first year of life, the HPA-axis also seems to have a hypo-responsive period. Several studies have shown that HPA-axis activity in early human development is under strong psychosocial regulation and that a healthy attachment style is an important protective factor from developing poor HPA-axis regulation (Gunnar & Donzella, 2002). Children who received insensitive, unresponsive care were more susceptible to cortisol elevations after a stressor than children who were securely attached to a caregiver (Tarullo & Gunnar, 2006).

The fact that the women in our study were exposed to sexual and physical abuse as well as physical and emotional neglect during a time in their lives when HPA-axis regulation was vulnerable to change, may, therefore, explain our findings of a blunted cortisol response to stress in this group.

Our findings suggest that exposure to traumatic events during childhood alters the regulation of the HPA-axis. This in turn may be a vulnerability factor for the development of psychiatric disorders.

Exposure to adulthood trauma

The results in our studies on military veterans differ from those on civilian subjects, suggesting that trauma exposure affects military personnel in other ways than it does civilian railway personnel, or, alternatively, that military personnel have a different level of HPA-axis-related resilience on average than civilian railway personnel. There may be several explanations for the findings of a blunted cortisol response in train drivers and conductors and no dysregulation in military veterans. An important purpose of military training is to let the soldiers get used to stressful circumstances and to 'keep their cool' in times of danger. This training may very well accommodate HPA-axis regulation during and after stress. Another explanation may be that people who are drawn to choosing a profession in which they are confronted with higher levels of stress and, potentially, even trauma, may have different personality structures (as well as HPA-axis set points) than people who do not make this choice. As PTSD was first diagnosed in combat veterans, it seems indicated to investigate HPA-axis regulation after trauma exposure in military veterans. However, this rather obvious choice has some pitfalls: there is a good chance that other factors – such as personality, trained adaptation to stress, and resilience – play a significant role in regulation of the HPA-axis in military personnel.

Another explanation for the blunted cortisol response to awakening we observed in TE railway personnel may be the fact that 25% of these men were working irregular shifts as opposed to none of the NE civilian controls. As the effect of working irregular shifts on HPA-axis regulation is not well known (Boquet et al., 2004; Griefahn & Robens, 2008; Kudielka, Buchtal, Uhde, & Wust, 2007), we did not make this an exclusion criterion. It may however be possible that working irregular shifts has a dysregulating effect on the circadian rhythm, and therefore on the circadian cortisol release.

Citation: European Journal of Psychotraumatology 2010, **1**: 5844 - DOI: 10.3402/ejpt.v1i0.5844

A third explanation for the difference in findings in the two groups may be the fact that railway personnel are still functioning in the environment where the traumatic events took place (in the trains, on the platforms), perhaps resulting in an increased fight-or-flight readiness, a normal response after stress.

The types of adult trauma and time since trauma may have different effects on HPA-axis regulation. These differences, however, may well be indissociable from the effects of personality traits and lifestyle factors. Therefore, we would recommend studying the effect of trauma exposure in large cohorts of individuals from the general population.

Vulnerability and resilience

The most important psychosocial risk factors for the development of psychiatric disorders such as PTSD after trauma exposure are a history of psychopathology, prior trauma, trauma severity, a family history of psychiatric disorders, a lack of social support, and additional life stress (Brewin, Andrews, & Valentine, 2000; Ozer, Best, & Lipsey, 2003). In addition, we know that trauma exposure during childhood increases the vulnerability to the development of PTSD and MDD in adulthood, especially in women (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Kessler, Davis, & Kendler, 1997; Kessler et al., 1995).

The presence of risk factors does not necessarily mean that a person will develop a psychiatric disorder after exposure to trauma. Also, the absence of risk factors does not automatically imply that a person is not susceptible to the development of psychiatric disorders after trauma. The currently known risk factors can only explain a portion of the risk for PTSD in TE populations. Both risk and resilience factors are closely related and may reflect twin sides of adaptation to trauma (Agaibi & Wilson, 2005).

In the studies described in this dissertation, we selected the participants who were likely to have high resilience against trauma-related psychopathology, as we only included individuals with multiple trauma exposure, without a history of psychiatric disorders as assessed with the Mini International Neuropsychiatric Interview (M.I.N.I.) (Van Vliet & de Beurs, 2007) and without current psychological complaints as assessed with the BSI (de Beurs & Zitman, 2006). All participants scored well below the cut-off for psychopathological caseness on the BSI. By selecting the TE participants in this way, we were able to study the effect of trauma exposure *per se* on HPA-axis regulation.

The relationship between HPA-axis regulation and resilience remains complex (Fig. 5). Most studies on resilience after trauma exposure have relied on assessments of people after the traumatic event has occurred. Determination of true resilience factors would require

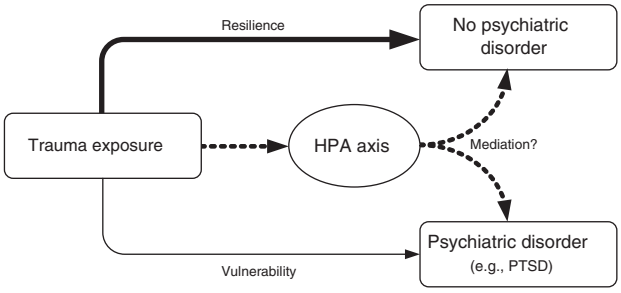

Fig. 5. Schematic outline of trauma exposure, HPA-axis regulation, resilience, and vulnerability for developing psychiatric disorders, and the mediating role of the HPA-axis.

prospective studies in which these factors are assessed prior to the onset of a trauma (Hoge, Austin, & Pollack, 2007). As far as we are aware, a large prospective study is currently carried out amongst Dutch military men and women who have been deployed to Afghanistan between 2005 and 2008 (PRISMO). All participants were assessed on psychological- and HPA-axis functioning prior to, during and directly after deployment, as well as during follow-up assessments after 6 months and 1, 2, 5, and 10 years. This study will provide more information on resilience to the development of PTSD and other stress-related psychiatric disorders.

Alternatively, study designs with twins could help unravel the genetic and environmental factors involved in vulnerability and resilience. Twin research to date suggests that (1) exposure to assaultive trauma is moderately heritable whereas exposure to non-assaultive trauma is not, (2) PTSD symptoms are moderately heritable, and (3) comorbidity of PTSD with other disorders may be partly due to shared genetic and environmental influences (Afifi, Asmundson, Taylor, & Jang, 2010).

Recruitment of the trauma-exposed (TE) participants

As in many studies, recruitment of the participants was a major task and more difficult than expected. We sought to include healthy individuals with a history of exposure to psychological trauma in childhood as well as in adulthood. First, we set out to recruit healthy individuals with a history of childhood trauma exposure. An advertisement was placed in a well read Dutch women's magazine (*Libelle*). We asked for TE as well as NE individuals without current or lifetime psychiatric disorders. The response was somewhat disappointing: 42 women and six men responded to the advertisement. All the women were screened for eligibility. Almost half of them were not eligible because of nightshift work, current stress or medical issues such as thyroid problems. Another 11 women declined participation. As a result, the final sample size of the TE group was small ($n = 10$).

At the same time as recruiting individuals with a history of childhood trauma exposure, we placed an interview and an advertisement in the most read nationwide newspaper (*De Telegraaf*) to recruit individuals with a history of trauma exposure during adulthood and without current or lifetime psychiatric disorders. The response was unsatisfactory as well; a mere 50 individuals (the majority of whom were women) responded.

There may be several explanations for the disappointing response. First, the most likely explanation may be that well-functioning TE individuals are more inclined to forget the negative impact of the traumatic event (Engelhard, Hout, & McNally, 2008), and as a result, do not remember the event as being traumatic (i.e., bias for not remembering traumatic events), and, therefore, do not recognise themselves in the description of the advertisement. Second, TE individuals may not want to be reminded of their traumatic experience. A final explanation may be that participation in the study required too much time and effort (as it included CRH infusion and blood sampling), especially considering the fact that we only wanted to include healthy people, who generally have other obligations and limited time. Of the people who did respond to our advertisement, many were not eligible to participate because they were (again or still) going through a stressful period (e.g., divorce, illness of partner or child) or they were using medication that interfered with HPA-axis regulation.

The next step in recruiting the necessary individuals for our study was to approach organizations through which large numbers of TE healthy people could be reached. First, we contacted the Dutch Veterans Institute, where we found veterans with and without deployment related trauma exposure. Second, we contacted the NS ('Nederlandse Spoorwegen' [Dutch Railways]), the main Dutch railway company, to find TE train drivers and conductors. During inclusion of the railway personnel, we discovered that some of the men (as not enough women were eligible) worked irregular shifts, either morning shifts, day shifts or evening shifts. None worked night shifts. To obtain a well-matched control group, we hoped to include train drivers and conductors without exposure to traumatic events. Unfortunately, due to reasons unknown to us, the Dutch railway company did not give us permission to contact NE healthy train drivers and conductors and, therefore, we had to include a sample of NE men from the general community, who were not working in irregular shifts.

Recruiting TE individuals without psychiatric disorders also was a challenge. Recruitment through advertisements may have given rise to self-selection bias. Those who chose to respond to the advertisements might have had more close relatives with PTSD or trauma exposure, specific personality traits, or other unmeasured characteristics that may have confounded associations. Recruitment of participants among specific groups with a high incidence of trauma exposure may have led to a confounding influence of personality traits or other lifestyle factors that are relevant to these specific groups. However, an advantage of contacting and selecting potentially eligible participants instead of having them respond to an advertisement is that self-selection bias plays a lesser role.

Conclusions

The overall conclusion of this dissertation is that trauma-exposure during childhood is associated with an attenuated cortisol response after the Dex/CRH challenge test in women. Basal HPA-axis regulation was not association with childhood trauma.

In contrast, trauma exposure during adulthood was not associated with alterations in HPA-axis regulation after the Dex/CRH test. We did, however, find a blunted salivary cortisol response to awakening in male railway personnel compared to unexposed controls.

Even though our results on childhood trauma exposure are based on just one study, pre-clinical studies using rodents and non-human primates have given us more understanding of the neuroendocrine consequences of early life stress and indicate that HPA-axis response to stress may be influenced by early adversity (Shea, Walsh, MacMillan, & Steiner, 2005). Also, recent studies support our findings (Carpenter et al., 2007; Elzinga et al., 2008; Meinlschmidt & Heim, 2005) of lower cortisol levels in TE subjects compared to NE controls with respect to childhood trauma.

Similar to the results of our two empirical studies on trauma exposure during adulthood, the literature on adulthood trauma exposure and its association with HPA-axis regulation and PTSD is inconsistent. This inconsistency may, for one, be the result of some studies including TE control subjects whereas other studies included NE control subjects, and still other studies included both TE and NE controls. To explore the complex and subtle relationship between trauma exposure and HPA-axis regulation further, we carried out two meta-analyses. We focussed exclusively on adult trauma exposure and not childhood trauma in these meta-analyses, because: (1) adulthood trauma exposure may differently impact the HPA-axis than childhood trauma exposure, (2) there are many groups of people who are at risk for trauma exposure during adulthood (e.g., military personnel, police officers, fire-fighters, rescue workers, health care workers), and 3) less is known about adulthood trauma.

Based on the results from our meta-analyses of studies examining trauma exposure during adulthood and HPA-axis regulation in individuals with and without PTSD, we concluded that basal HPA-axis dysregulation in TE

Citation: European Journal of Psychotraumatology 2010, **1**: 5844 - DOI: 10.3402/ejpt.v1i0.5844

adults is neither associated with trauma exposure nor with PTSD symptomatology. Cortisol suppression after dexamethasone, however, was higher in TE healthy individuals compared to NE healthy controls. This suggests that trauma exposure during adulthood may be associated with more delicate neuroendocrine HPA-axis dysregulation involving the hypothalamic-pituitary feedback system. Because the findings on the dexamethasone suppression test (DST) were based on only 5 studies, they should be confirmed by future studies.

Fig. 6 illustrates the main conclusion of this dissertation. Resilience to psychiatric disorders after trauma exposure during childhood is associated with HPA-axis alterations that are demonstrable in adult women. Resilience and vulnerability to PTSD after trauma exposure during adulthood, however, were not clearly associated with HPA-axis alterations. This last observation is confirmed in our meta-analysis.

Even though our studies on trauma exposure during adulthood do not clearly show an association between trauma and HPA-axis regulation, studies assessing the effect of administering cortisol to patients post-trauma show that the development of subsequent PTSD can be influenced (Aerni et al., 2004; Schelling et al., 2001, Schelling et al., 2004). This forms another line of evidence that the (modulating) role of the HPA-axis is of importance.

Since the association between adulthood trauma and resilience cannot be explained by HPA-axis regulation, other factors must play a role. As described in the introduction of this dissertation, the autonomic nervous system (ANS) is another important part of the stress system, in addition to the HPA-axis. ANS functioning can be assessed in various ways with various outcome measures. The most studied outcome measures of the ANS are heart rate, blood pressure and skin conductivity. In addition, norepinephrine levels can be measured.

A recent study in patients with generalized social anxiety disorder (gSAD) showed that not cortisol but salivary alpha-amylase (sAA), a relatively new marker of autonomic activity, was found to be higher in basal, non-stimulated conditions, as well as after the DST (van Veen et al., 2008). The findings in this study suggest that in gSAD there is an increased activity of the ANS but not of the HPA-axis. This hyperactivity of the ANS is in line with the clinically observed somatic symptoms of hyper-arousal in gSAD such as trembling, blushing and perspiration.

As symptoms of chronic hyperarousal of the ANS often are present in PTSD, the ANS may play a role in resilience and vulnerability after trauma exposure. When an individual experiences a traumatic event, the brain activates the ANS to meet the threat of a traumatic event, which is a normal, healthy, adaptive survival response. Sometimes, however, the ANS continues to be chronically aroused even though the threat has passed and has been survived – a key symptom of PTSD. Also, in a study among depressed adult women with a history of childhood trauma, hyperreactivity of the ANS was reported (Heim et al., 2000). The assessment of the ANS in studies investigating the relation between trauma exposure and the resilience or vulnerability to psychopathology may provide new information on why some people develop psychiatric disorders and others do not.

Beside the ANS, psychological factors are clearly of importance in resilience and vulnerability. The experience of a traumatic event may disrupt major beliefs regarding personal invulnerability, benevolence of the world, meaning, self-worth, and relations with others. An individual may feel vigilant, depressed, powerless, vulnerable or guilty about not being able to change the situation, and

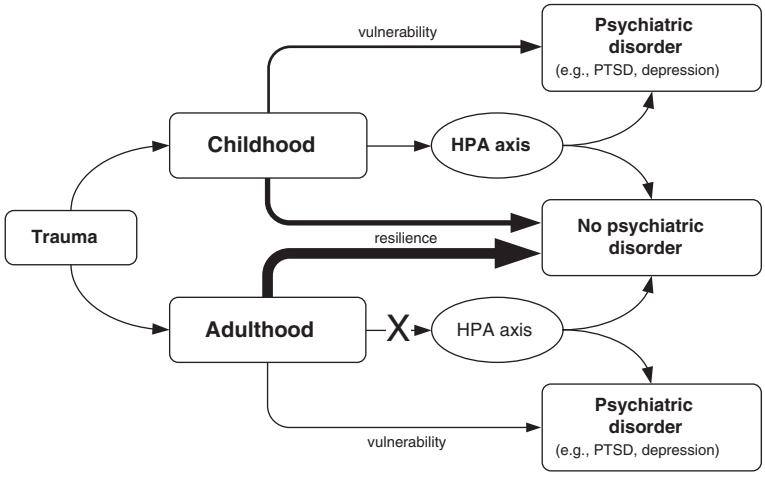

Fig. 6. The association between childhood trauma exposure, resilience and vulnerability in which the HPA-axis plays a mediating role, and the association between adulthood trauma exposure and resilience and vulnerability without the mediating role of the HPA-axis.

these feelings may colour the way the individual sees the world. This may increase vulnerability for psychiatric disorders such as PTSD and MDD.

Future perspectives

Based on the findings and conclusions from the studies that were presented in this dissertation, we suggest that it should become good practice to include a TE and/or a NE control group in studies examining psychiatric disorders and HPA-axis regulation. In studies examining the relationship between trauma exposure and stress regulation, adequate trauma assessment, not only of the TE subjects but also of the controls should take place. This trauma assessment should not only cover trauma exposure in adulthood but more importantly, also trauma exposure during childhood. Even though this dissertation mainly refers to PTSD, trauma assessment during childhood as well as during adulthood should also be carried out in studies involving MDD and HPA-axis regulation.

Also, a meta-analysis on the effects of childhood trauma exposure on HPA-axis regulation in healthy individuals is needed to confirm the findings we presented in chapter 2.

Furthermore, in future studies on trauma exposure, stress regulation, and psychopathology, it is important not to focus solely on the HPA-axis but to shift attention to other principal stress-axes (e.g., the ANS) and their interaction with the HPA-axis to fully understand the neural effects of stress. As mentioned earlier, assessment of alpha-amylase may be studied as a marker of ANS functioning. Another example for further study is the neuropeptide oxytocin that plays a role in mediating social affiliation, attachment, social support, and maternal behaviour (Young & Wang, 2004). Oxytocin also has a protective effect against stress and anxiety, and may therefore increase resilience to psychiatric disorders. A preliminary association has been found between decreased oxytocin concentrations and trauma exposure in childhood, suggesting that oxytocin may somehow be involved in the mechanism translating early adversity into adult vulnerability to stress and disease, including depression and anxiety disorders (Heim et al., 2009).

As far as psychological factors are concerned, enhancing resilience in individuals at risk of trauma exposure as well as in TE individuals by focusing on interpersonal factors such as attachment and interpersonal relationships may prove to be a valuable addition to the exposure techniques that are widely used as treatment for PTSD (Markowitz, Milrod, Bleiberg, & Marshall, 2009).

It is important for future studies to assess HPA-axis functioning with uniform protocols (e.g. cortisol sampling at specific time points and over more than one day) and also to use the same outcome measures and statistical analysis techniques (e.g. Area under the Curve, GLM repeated measurements). Well-adopted guidelines should be developed on data sampling and analysis. In addition, because of the issue of compliance to the salivary cortisol sampling procedure, cortisol sampling monitoring devices should be developed and used.

In addition to all the cross-sectional studies that have been discussed in this dissertation, prospective (longitudinal) studies, for instance in groups of people with a high risk of trauma exposure, will lead to more understanding of the relationship between trauma exposure, psychiatric disorders and stress regulation.

Finally, an increasing number of studies on the influence of genetics and epigenetics on the development of psychiatric disorders and resilience after trauma exposure are being published. On the one hand, genetic factors can influence the risk of exposure to some forms of trauma, perhaps through individual differences in personality that influence environmental choices (Stein, Jang, Taylor, Vernon, & Livesley, 2002). On the other hand, animal studies show that neglect and exposure to stressors may alter gene expression in the brain, leading to increased stress and anxiety in rats (Francis & Meaney, 1999). In general, future research involving genetics may deepen our understanding of the complex links among genes, brain, cognition, emotion, and the environment.

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Citation: European Journal of Psychotraumatology 2010, **1**: 5844 - DOI: 10.3402/ejpt.v1i0.5844

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Citation: European Journal of Psychotraumatology 2010, **1**: 5844 - DOI: 10.3402/ejpt.v1i0.5844