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Differential activation of the renin-angiotensin-aldosterone-system in response to childhood and adulthood trauma

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ABSTRACT

Objective: Previous evidence suggested lasting and cumulative effects of traumatization on the renin-angiotensin-aldosterone-system (RAAS). However, it is unclear whether traumas during childhood and those experienced in adulthood differentially impact the RAAS. In this study, we sought to investigate main and putative interactive effects of childhood and adulthood trauma on RAAS functioning.

Methods: Plasma concentrations of renin and aldosterone were measured in a general population sample (n = 2016). Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ), adulthood trauma was measured using the PTSD module of the Structured Clinical Interview of the DSM-IV. Linear regression models were calculated to assess the relations between childhood or adulthood traumatization with renin and aldosterone concentrations.

Results: Exposure to (ß = 0.094; p = 0.01), severity of childhood trauma (ß = 0.004; p = 0.01) were associated with increased aldosterone, but not renin levels. Results were carried by all dimensions of abuse, while childhood neglect was not associated with altered RAAS activity. In contrast, adulthood traumas (ß = 0.113; p < 0.01) were significantly associated with increased renin concentrations. Subjects with PTSD (renin: ß = 0.345; p = 0.01; aldosterone: ß = 0.232; p = 0.04) and those who had been exposed to both childhood and adulthood trauma showed increases in renin (ß = 0.180; p < 0.01) and aldosterone (ß = 0.340; p < 0.01) levels.

Discussion: These findings indicate that trauma is associated with differential alterations of the RAAS depending on the time of traumatization. Moreover, exposure to childhood or adulthood trauma may act synergistically on the RAAS, resulting in severe dysregulation of the RAAS. The results contribute to explain associations between trauma and enhanced risk for physical disease.

1. Introduction

Exposure to traumatic events during childhood or adulthood is associated with a wide range of physical health conditions and particularly cardiovascular disease (Baker et al., 2009; Goodwin and Stein, 2004). For example, Dong et al. found a dose-response relationship between the number of traumatic events during childhood and ischemic heart disease (Dong et al., 2004). Results from Stein et al. showed an increased risk for hypertension in subjects with two or more childhood traumas (Stein et al., 2010). Regarding adulthood trauma, findings from general population samples showed increased rates particularly of cardiovascular disease in individuals with a history of traumatic events in their adulthoods (Glaesmer et al., 2011; Spitzer et al., 2009).

While the mechanism underlying these associations is not

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completely understood, previous findings have suggested that dysregulation of different neuroendocrine systems may be involved. Given the important role of the hypothalamic-pituitary-adrenal (HPA-)axis and the sympathoadrenal-medullary (SAM-) system in the stress response, numerous studies have investigated the activation of these neuroendocrine systems in relation to traumatic stress. However, existing studies yielded inconsistent results. For example, in their study on women with a history of childhood sexual abuse, Heim et al. found increased activity of the HPA-axis and the SAM-system in response to acute stress (Heim et al., 2000). Goldman-Mellor et al. found blunted cortisol reactivity following acute cognitive stress in subjects who experienced childhood trauma and additional recurrent psychological distress. In contrast, subjects with childhood trauma, but only little or no later distress showed elevated baseline cortisol and prolonged responses (Goldman-Mellor et al., 2012). It has been suggested that the time period of traumatization may contribute to explain these inconsistencies with findings showing a dysregulated HPA-axis in individuals with a history of childhood trauma (Shea et al., 2005), while Klaassens et al. found no clear evidence for altered HPA-axis functioning in relation to adulthood trauma in their review and meta-analysis (Klaassens et al., 2012). Moreover, results from Kuhlman et al. indicated that HPA-axis functioning may vary depending on the type of childhood trauma (Kuhlman et al., 2015a, 2015b).Finally, there is some evidence suggesting interactive effects between childhood and adulthood trauma on HPA-axis activation: peak adrenocorticotropin (ACTH) levels in response to acute psychosocial stress have been shown to be highest in women with a history of childhood trauma and exposure to additional traumas during adulthood (Heim et al., 2002).

The renin-angiotensin-aldosterone-system (RAAS) closely interacts with the HPA-axis in the stress response. The RAAS is a key system involved in blood pressure regulation and its dysregulation is an important factor in the pathophysiology of cardiovascular disease (Ferrario and Strawn, 2006). Concentrations of renin and angiotensin II (ANG II), the main effector of the RAAS, are enhanced by sympathetic activation in response to acute and chronic stress (Yang et al., 1994). ANG II mediates the release of cortisol and aldosterone from the adrenal cortex under conditions of acute stress. In contrast, aldosterone levels were found to be diminished under conditions of chronic stress due to suppressed release of ACTH and downregulated adrenal ANG II receptors (Aguilera, 1993; Miller et al., 2007). In summary, a history of childhood as well as adulthood trauma both represent conditions of chronic stress leading to an altered metabolism of the HPA-axis and the SAM-system. Considering the close relationship of these neuroendocrine systems with the RAAS, these previous results indicate that traumatized subjects may exhibit a dysregulated RAAS with increased renin and diminished aldosterone levels.

In fact, there is growing evidence suggesting that the RAAS is also implicated in the endocrine responses to traumatic stress and the pathophysiology of trauma-related disorders like PTSD. For instance, in animal studies blockade of AT_1-receptors in fear training reduced the acquisition of fear, indicating that renin and ANG II may mediate the effects of threatening events on fear memory. More specifically, increased renin and ANG II levels in response to fear or stress related SAM-system activation may contribute to fear acquisition and deficits in extinction of trauma-related memories, which have been described as key mechanisms in the development of PTSD. (Blechert et al., 2007; Wessa and Flor, 2007). In support of this concept, Khoury et al. reported that intake of Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARBs), but not of other antihypertensive drugs, was associated with reduced PTSD symptoms (Khoury et al., 2012). Marvar et al. found that inhibition of type 1 angiotensin (AT_1) receptors enhances fear extinction in mice showing anxious behavior after cue fear conditioning (Marvar et al., 2014). More recently, Nylocks et al. demonstrated that a common polymorphism within the ACE gene was associated with PTSD symptoms and that this polymorphism modified the effects of ACE-I and ARBs on PTSD diagnosis (Nylocks et al., 2015). Regarding fear acquisition, Hurt et al. investigated auditory fear conditioning in a mouse strain with deletion of the AT_1-receptor gene from corticotropin-releasing factor (CRF) expressing cells which are known to be involved in fear processing (Hurt et al., 2015). The authors found reduced anxiety-like behavior in knock-out mice compared to wild-type mice suggesting that (a) ANG II and its AT_1-receptor are not only involved in impaired fear extinction but also in conditioned fear acquisition and that (b) specifically cells implicated in the HPA-axis regulation influence fear acquisition. Given that CRF is released in response to stress and that activation of the CRF receptor leads to anxiety-like responses, these results indicate that the RAAS and the HPA-axis interact in their effects on altered fear memory formation in PTSD. In a small case-series, Houlihan et al. found increased renin, but lowered aldosterone levels in six patients with combat-related PTSD (Houlihan, 2013). In a recent paper of our working group, we identified associations between the number of traumatic events and increased levels of renin, but not aldosterone in a community-based cohort (Terock et al., 2018), suggesting that traumatic stress has lasting and cumulative effects on RAAS activity. Moreover, we found that PTSD was associated with increased levels of renin over and above the trauma-load, supporting the concept of a role of renin in the pathogenesis of PTSD. However, results were mainly derived from data on adulthood trauma, while the role of childhood traumatization on RAAS activity still remains to be clarified.

In detail, we tested the hypothesis that both (i) childhood and adulthood trauma were each associated with enhanced renin and diminished aldosterone levels and that (ii) childhood and adulthood trauma interact such that individuals who had been exposed to both showed the highest levels of renin but the lowest levels of aldosterone.

2. Methods and materials

2.1. Study population

The present analyses are based on data from the Study of Health in Pomerania (SHIP), a population-based project in northeast Germany. SHIP is based on a representative sample from the general population including adult men and women aged 20–79 years. Baseline examinations were performed between 1997 and 2001 and included 4308 participants. The first five year follow-up (SHIP-1) was conducted between 2002 and 2006 with 3300 participants being re-examined. Between 2007 and 2010 a psychometric assessment, named “Life-Events and Gene-Environment Interaction in Depression” (SHIP-LEGEND), was performed in consenting SHIP-0 participants as an add-on study. All participants of SHIP-0 still alive in 2006 (N = 3669) were invited and 2400 agreed to participate in SHIP-LEGEND. In the present study, we included 2302 SHIP-LEGEND participants who also underwent the SHIP-1 examinations. From these subjects, we excluded all those with missing information on exposure, outcome or confounding variables, with high renin or aldosterone concentrations above 500 ng/l (> 99.9th percentile), and all pregnant women (n = 286). Our final analytic sample comprised 2016 subjects. We further excluded 33 subjects with PTSD for additional sensitivity analyses, ultimately leading to a sample of 1983 subjects. Fig. 1 provides a detailed overview of the selection process and composition of our analytic sample.

SHIP-LEGEND included a diagnostic interview for mental disorders based on Diagnostic and Statistical Manual for Mental Disorders (IV edition) diagnostic criteria. Sociodemographic and clinical information were assessed by a computer-assisted face-to-face-interview or self-report instruments. For psychometric assessments, various established and validated self-report questionnaires as well as a newly developed interview on 80 positive and negative life events were applied. Details on the SHIP cohorts including sampling and study design can be found elsewhere (Völzke et al., 2011). All investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. The survey and study methods of

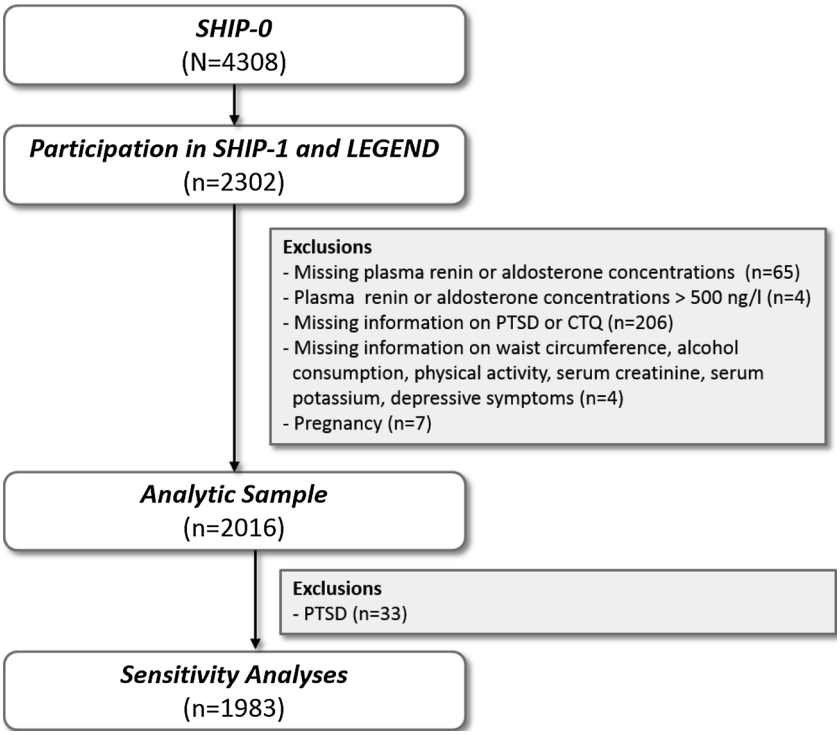

Fig. 1. Selection of the study population.

both the studies were approved by the institutional review boards of the University of Greifswald.

2.2. Interview and physical examinations

The SHIP-1 study program included a large range of standardized medical examinations and a computer-assisted personal interview. Socio-demographic characteristics as well as information on behavioral risk factors, including alcohol consumption and physical activity, were collected. Physical activity was dichotomized based on self-report. Subjects were asked whether they performed any physical activity. When subjects answered affirmatively, they were classified as "physically active", all other subjects as "physically inactive". Alcohol consumption was determined in terms of drinking behavior in the previous month. To obtain the daily intake of pure alcohol (g/day), the average consumption of beer, wine, and spirits was calculated: (number of days on which alcohol was consumed) × (average number of alcoholic beverages consumed on these days)/30. The result was multiplied by a standard alcohol content of 4.8% for beer, 11.0% for wine, and 33.0% for spirits (Baumeister et al., 2005; Völzke et al., 2015).

Moreover, participants were asked to bring all medication taken in the last seven days prior to the examination. The drugs were categorized according to the anatomical-therapeutic-chemical (ATC) classification code. Antihypertensives (ATC C02), diuretics (ATC C03), beta blockers (ATC C07), calcium channel blockers (ATC C08), ACE-I (ATC C09A, C09B), and ARBs (ATC C09C, C09D) were classified as altering renin or aldosterone concentrations. Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the subject standing comfortably with weight distributed evenly on both feet. Laboratory analyses

Non-fasting venous blood samples were obtained between 8:00 a.m. and 7:59 p.m. from the SHIP-1 participants following a standardized protocol. The majority of blood samples (82.6%) was taken before 2.00 p.m. Plasma renin concentrations and plasma aldosterone concentrations were measured in EDTA plasma by radioimmunometric procedures (renin, Renin III generation, Cisbio Bioassay, Bagnols-sur-Cèze Cedex, France; aldosterone, Coat-A-Count Aldosterone, Siemens Healthcare Diagnostics, Eschborn, Germany) as previously described (Hannemann et al., 2010). The serum potassium concentration was determined with indirect potentiometry with ion-selective electrodes using a Dimension RxL (Siemens Healthcare Diagnostics, Eschborn, Germany). Serum creatinine concentrations were determined with a modified kinetic Jaffé method (Siemens Dimension RxL; Siemens Healthcare Diagnostics, Eschborn, Germany). The eGFR was calculated using the four-variable Modification of Diet in Renal Disease formula.

2.3. Assessment of childhood trauma, PTSD, and depressive symptoms

The Childhood Trauma Questionnaire (CTQ) was used for self-report of childhood trauma including emotional, physical, and sexual abuse as well as emotional and physical neglect (Bernstein et al., 2003). It consists of 28 items that were rated on a five-point Likert scale from "never true" (= 1) to "very often true" (= 5). Depending on the scale sum score, participants were grouped into the severity categories "none", "mild", "moderate", and "severe". In accordance with the American CTQ-manual (Bernstein and Fink, 1998),we classified subjects having experienced at least mild forms of trauma as being traumatized (scale sum score ≥ 9 for emotional abuse, ≥ 8 for physical abuse, ≥ 6 for sexual abuse, ≥ 10 for emotional neglect, ≥ 8 for physical neglect). Factor structure and construct validity of the German version showed sufficient psychometric properties with some limitations due to the high inter-correlations of the different subscales and a weak internal consistency of the physical neglect subscale (Klinitzke et al., 2012).

The PTSD module of the Structured Clinical Interview for Diagnostic (SCID) and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) was applied for the assessment of adulthood traumatization and the occurrence of PTSD (First et al., 1997). First, subjects were asked if they had been exposed to one of the following events which are listed as traumatic events in the DSM-IV: combat or war-zone experience, physical assault, rape, childhood sexual abuse (not included in the present analyses), natural disaster, life-threatening illness, serious or nearly fatal accident, imprisonment and/or torture, sudden and unexpected

death of a loved one, as well as witnessing or learning about traumas to others. If the participant answered with "no" to each of these questions, the module was terminated. If a participant affirmed exposure to more than one traumatic event, the person was asked to identify the most distressing experience and to relate to this event when answering the subsequent questions. Subjects were then continuously asked about whether they experienced PTSD symptoms according to the DSM-IV in the interview. If the respondent did not pass the required diagnostic threshold (e. g. at least one re-experienced symptom), the interview was also terminated. In order to estimate the severity of traumatic stress, we also assessed the number of traumatic events. It has been found as a useful screening device with satisfactory sensitivity (66-%-76%) and specificity (67%–87%) for detecting traumas in samples of medical patients as well as healthy subjects (Elhai et al., 2008).

The screening questions of the Composite International Diagnostic Screener for mental disorders (CID-S) were applied for the assessment of co-existing depressive symptoms (Wittchen et al., 1999). The (CID-S) is an instrument specifically developed for the use in epidemiologic studies and showed satisfactory performance measures. Depression is assessed by two questions covering the dimensions "depressed mood" and "loss of interest". Participants were given the lifetime diagnosis of depression if at least one positive answer was given. Wittchen et al. found a combined sensitivity for the two questions of 62.6% for depressive disorders. However, more detailed analysis in the original investigation showed that primarily fairly short depressive episodes were not detected by the CID-S (Wittchen et al., 1999).

2.4. Statistical analyses

Selected health-related characteristics of the study participants are presented as medians with 1st - 3rd quartiles (continuous data) or proportions (categorical data). Group differences between participants without trauma, with childhood trauma, with adulthood trauma, and with childhood and adulthood trauma were tested for statistical significance with Chi-Squared (categorical data) or Kruskal-Wallis tests (continuous data). A value of $p < 0.05$ was considered statistically significant.

Multivariable linear regression models were calculated to assess the associations between the exposure variables: occurrence of childhood trauma, severity of childhood trauma, occurrence of adulthood trauma, adulthood trauma load, PTSD, combinations of childhood and adulthood trauma, and the two outcome variables: renin and aldosterone concentrations. Childhood trauma, adulthood trauma and PTSD were dichotomized and the category "no trauma" was set as reference in the respective models. The CTQ sum score was used as the measure of childhood trauma severity and a one-point-increase was modelled. The number of adulthood traumatic events was used as the measure of adult trauma load and entered the regression models as a continuous or categorized variable. This number ranged between zero and seven in the analytic sample (zero trauma n = 975; one trauma n = 692; two traumas n = 231; three traumas n = 79; four traumas n = 26; five traumas n = 11; six traumas n = 1; seven traumas n = 1). For the categorization, we allocated two to seven traumas to the category "two or more traumas" (n = 349) and set the category "zero trauma" as reference in the regression models. Combinations of childhood and adulthood trauma were defined as "no trauma", "childhood trauma", "adulthood trauma", and "childhood and adulthood trauma" and the category "no trauma" served as reference. Finally, we tested the putative interaction of childhood and adulthood trauma on their associations with renin and aldosterone concentrations. In further linear regression models, we examined the associations between the severities of the different categories of childhood trauma and renin or aldosterone concentrations. Emotional, physical and sexual abuse as well as emotional and physical neglect were categorized in "none", "mild", "moderate" and "severe", with "none" being used as the reference category. All models were adjusted for age, sex, alcohol consumption, physical activity, serum creatinine and potassium concentrations, depressive symptoms, intake of medication that alters renin or aldosterone concentrations and time of blood sampling. In addition, given that obesity is associated with hypertension (Hall et al., 2015) and enhanced sympathetic activation (Grassi Guido et al., 1995), we included waist circumference in the set of covariate in all models. Renin and aldosterone concentrations were log-transformed before being entered in the respective models. Effect size was estimated by Cohen's f2 in the regression analyses. Finally, we examined whether our results were stable after excluding all subjects with PTSD and therefore re-calculated all analyses in sensitivity analyses including 1983 participants.

All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Descriptive statistics

In our study population of 2016 adult subjects 40.7% (n = 820) reported no trauma, 7.7% (n = 155) reported an isolated childhood trauma, another 40.6% (n = 819) reported at least one adult trauma and 11.0% (n = 222) reported childhood and adulthood traumatization. The health-related characteristics of the subjects according to the four subgroups are given in Table 1. Subjects with isolated childhood trauma were more often female (p = 0.02), younger (p < 0.01), had a lower waist circumference (p = 0.02), took medication that altered renin or aldosterone concentrations less often (p < 0.01), and had lower renin concentrations (p = 0.04) than those with adult trauma, while aldosterone concentrations were comparable between the groups (p = 0.57). Subjects with childhood and adult trauma had higher renin

Table 1
Characteristics of the study population.

Characteristics	No Trauma (n = 820)	Childhood Trauma (n = 155)	Adulthood Trauma (n = 819)	Childhood and Adulthood Trauma (n = 222)	p
Female, %	52.1	58.1	47.7	55.9	0.03
Age, years	49.0 (39.0 - 60.0)	46.0 (38.0 - 58.0)	55.0 (44.0 - 67.0)	50.0 (40.0 - 61.0)	< 0.01
Waist circumference, cm	90.1 (81.2 - 100.1)	90.2 (77.0 - 102.8)	93.5 (83.5 - 102.5)	90.1 (79.6 - 100.8)	< 0.01
Physically inactive, %	56.5	54.2	55.1	56.3	0.92
Alcohol consumption, g/day	5.24 (1.86 - 14.17)	3.43 (1.31 - 12.43)	4.00 (1.05 - 12.43)	3.93 (1.31 - 13.40)	0.01
RAAS medication, %	30.4	24.5	43.2	33.8	< 0.01
Depressive Symptoms, %	11.5	23.9	20.2	31.1	< 0.01
PTSD, %	0.00	0.00	2.44	5.86	< 0.01
Creatinine, µmol/l	78.0 (67.5 - 88.0)	74.0 (66.0 - 85.0)	78.0 (68.0 - 90.0)	77.0 (67.0 - 87.0)	0.01
Potassium, mmol/l	4.30 (4.10 - 4.55)	4.30 (4.07 - 4.58)	4.30 (4.10 - 4.56)	4.30 (4.10 - 4.50)	0.45
Renin, ng/l	7.60 (4.80 - 12.15)	7.40 (5.00 - 11.70)	8.40 (5.10 - 13.90)	8.65 (5.60 - 14.60)	< 0.01
Aldosterone, ng/l	41.0 (27.0 - 60.5)	42.0 (27.0 - 63.0)	42.0 (26.0 - 62.0)	49.0 (27.0 - 76.0)	0.06

Data are median (1st-3rd quartile) or proportions. Group differences were tested with Chi-Squared or Kruskal-Wallis tests.
RAAS, renin-angiotensin-aldosterone system.

Table 2
Associations between childhood or adulthood trauma and the log-transformed plasma renin and plasma aldosterone concentration. Results from linear regression models adjusted for sex, age, waist circumference, alcohol consumption, physical activity, serum creatinine and potassium concentrations, depressive symptoms, intake of medication that alters renin or aldosterone concentrations and time of blood sampling.

Trauma		Outcome	ß-coefficient	stderr	df	t	p	Cohen's f^2
Childhood	Childhood trauma *(reference = no trauma)*	Renin	0.065	0.047	1	1.39	0.16	0.10
		Aldosterone	0.094	0.037	1	2.55	0.01	0.10
	CTQ sum score *(increase of 1 point)*	Renin	0.002	0.002	1	1.18	0.24	0.10
		Aldosterone	0.004	0.002	1	2.69	0.01	0.10
Adulthood	Adulthood trauma *(reference = no trauma)*	Renin	0.113	0.037	1	3.04	< 0.01	0.10
		Aldosterone	0.037	0.029	1	1.28	0.20	0.10
	Trauma load *(1 vs. no trauma)*	Renin	0.093	0.041	1	2.28	0.02	0.10
	Trauma load *(≥2 vs. no trauma)*		0.160	0.054	1	2.97	< 0.01	
	Continuous		0.056	0.020	1	2.82	< 0.01	0.10
	Trauma load *(1 vs. no trauma)*	Aldosterone	0.056	0.032	1	1.75	0.08	0.10
	Trauma load *(≥2 vs. no trauma)*		−0.007	0.042	1	−0.16	0.87	
	Continuous		0.003	0.016	1	0.21	0.83	0.10
Combinations of childhood and adulthood trauma	Childhood vs. no trauma	Renin	0.016	0.071	1	0.23	0.82	0.10
	Adulthood vs. no trauma		0.097	0.041	1	2.35	0.02	
	Child- & Adulthood vs. no trauma		0.180	0.062	1	2.91	< 0.01	
	Childhood vs. no trauma	Aldosterone	0.066	0.056	1	1.18	0.24	0.10
	Adulthood vs. no trauma		0.024	0.032	1	0.73	0.47	
	Child- & Adulthood vs. no trauma		0.34	0.049	1	2.73	< 0.01	
Trauma with PTSD	*(reference = no PTSD)*	Renin	0.354	0.145	1	2.45	0.01	0.10
		Aldosterone	0.232	0.114	1	2.03	0.04	0.10

CTQ, childhood trauma questionnaire; PTSD, post-traumatic stress disorder; stderr, standard error.
Statistically significant results printed in **bold**.

and aldosterone concentrations compared to subjects without trauma (both $p < 0.01$), had higher renin concentrations than subjects with isolated childhood trauma ($p = 0.02$) and higher aldosterone concentrations than subjects with isolated adulthood trauma ($p = 0.01$). Moreover, the highest proportion of subjects with depressive symptoms was observed among subjects with childhood and adulthood trauma (31.1%).

3.2. Associations of childhood or adulthood trauma with RAAS components

Multivariable linear regression analyses revealed increased aldosterone but not renin concentrations in subjects with childhood trauma. Moreover, a positive linear relationship between the severity of childhood trauma (CTQ sum score) with aldosterone but not renin levels became apparent (Table 2, Fig. 2). In contrast, adulthood traumatization and PTSD were associated with increased renin concentrations (adulthood trauma: ß = 0.113; SE = 0.037; $p < 0.01$; trauma with PTSD: ß = 0.354; SE = 0.145; $p = 0.01$) but not or only barely with aldosterone concentrations (adulthood trauma: ß = 0.037; SE = 0.029; $p = 0.20$; trauma with PTSD: ß = 0.232; SE = 0.114; $p = 0.04$) Further analyses revealed a dose-response relationship between adulthood trauma load and renin concentrations (Table 2, Fig. 3). Each additional trauma was associated with significantly increasing renin concentrations (ß = 0.056; SE = 0.020; $p < 0.01$), while aldosterone concentrations remained unchanged (ß = 0.003; SE = 0.016; $p = 0.83$).

Adulthood traumatization was related to significantly increased renin concentrations (ß = 0.097; SE = 0.041; $p = 0.02$) compared to non-traumatization. Moreover, subjects who had experienced both childhood and adulthood trauma, had, not only significantly increased renin concentrations (ß = 0.18; SE = 0.062; $p < 0.01$), but also significantly increased aldosterone concentrations (ß = 0.34; SE = 0.049; $p < 0.01$) when compared to those without trauma. Finally, the interaction term childhood*adulthood trauma was not significant, neither in the model for aldosterone ($p = 0.56$),nor in the model for renin ($p = 0.47$).

3.3. Associations of subscales of childhood trauma with RAAS components

In subscale analyses for childhood trauma, the association between childhood traumatization and increasing aldosterone concentrations was confirmed (Table 3). However, only the abuse categories (emotional abuse, physical abuse and sexual abuse) demonstrated

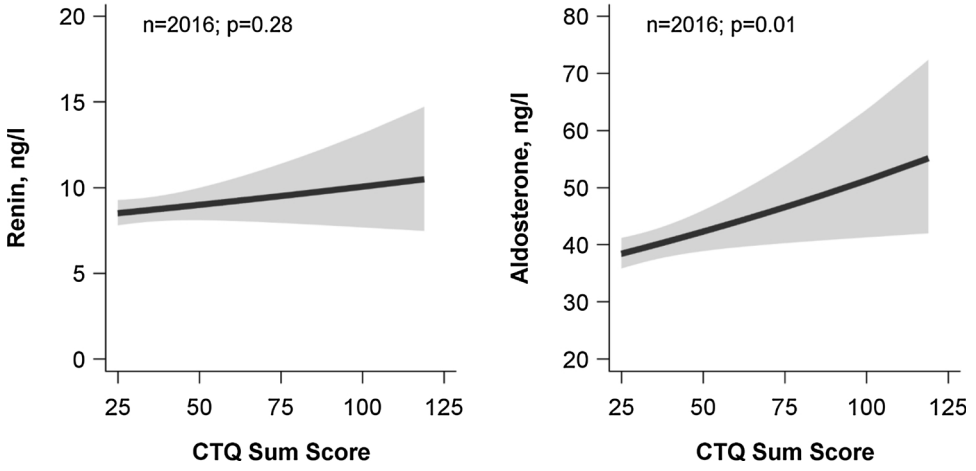

Fig. 2. Association between plasma renin or aldosterone concentrations and the childhood trauma questionnaire (CTQ) sum score. Estimated renin or aldosterone concentrations with 95% confidence intervals. Results from linear regression models adjusted for sex, age, waist circumference, alcohol consumption, physical activity, serum creatinine and potassium concentrations, depressive symptoms, intake of medication that alters renin or aldosterone concentrations, and time of blood sampling. Plasma renin and aldosterone concentrations were log-transformed before being entered in the regression models. The estimates were back-transformed to the original scale for visualization in the figure.

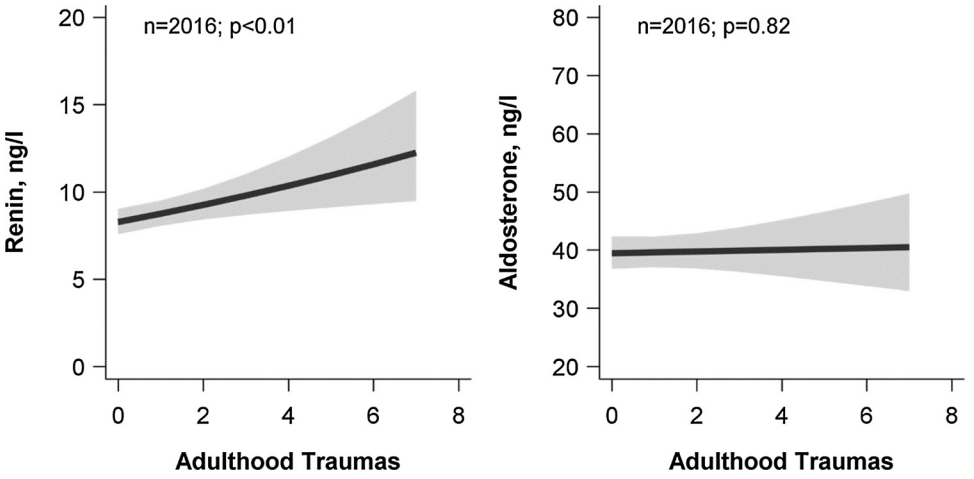

Fig. 3. Association between plasma renin or aldosterone concentrations and the number of adulthood traumas. Estimated renin or aldosterone concentrations with 95% confidence intervals. Results from linear regression models adjusted for sex, age, waist circumference, alcohol consumption, physical activity, serum creatinine and potassium concentrations, depressive symptoms,intake of medication that alters renin or aldosterone concentrations, and time of blood sampling. Plasma renin and aldosterone concentrations were log-transformed before being entered in the regression models. The estimates were back-transformed to the original scale for visualization in the figure.

statistically significant relations, while physical and emotional neglect were not associated with aldosterone concentrations. None of the abuse or neglect categories was related with renin concentrations.

3.4. Sensitivity analyses

In our sensitivity analyses that excluded subjects with PTSD, our main results were confirmed (data not shown). We found positive associations between childhood traumatization (ß = 0.088; SE = 0.037; p = 0.02) or CTQ sum score (ß = 0.004; SE = 0.002; p = 0.02) and aldosterone concentration. The relations between the subscales of childhood abuse and aldosterone were also largely confirmed. Thus, moderate (ß = 0.254; SE = 0.11; p = 0.02) and severe (ß = 0.244; SE = 0.118; p = 0.04) emotional abuse, moderate physical abuse (ß = 0.209; SE = 0.092; p = 0.02), as well as severe sexual abuse (ß = 0.370; SE = 0.166; p = 0.03) were significantly related to increased aldosterone concentrations. Severe sexual abuse was also related to increased renin concentrations (ß = 0.434; SE = 0.209; p = 0.04). Adulthood traumatization (ß = 0.108; SE = 0.037; p < 0.01) and trauma load (one vs. no trauma ß = 0.087; SE = 0.040; p = 0.03; two or more vs. no trauma ß = 0.159; SE = 0.054; p < 0.01) remained associated with renin concentrations and the combination of childhood and adult traumatization was related to increased aldosterone (ß = 0.120; SE = 0.05; p = 0.02) and renin concentrations (ß = 0.191; SE = 0.063; p < 0.01).

4. Discussion

The main finding of this study is that childhood and adulthood traumatization showed differential and additive effects on RAAS activity after statistical adjustment for behavioral and metabolic risk factors as well as major depressive disorder. Specifically, exposure to and severity of childhood traumatization was associated with increased levels of aldosterone, while exposure to traumatic events and the number of traumas during adulthood was positively associated with renin levels. Moreover, those subjects with a history of both childhood as well as adulthood trauma showed enhanced levels of aldosterone and, even more pronounced, renin levels. Finally, PTSD was found to be associated with enhanced levels of renin and aldosterone.

In this study, we chose to use a relatively mild definition of exposure to childhood trauma and to additionally evaluate effects of severity and subtypes of childhood trauma. Thus, finding statistically significant associations of trauma exposure with aldosterone levels suggests that mild traumatic stress with few or even one traumatic event during childhood may already result in long-term alterations of the RAAS. The association of childhood trauma severity with aldosterone levels was even more pronounced, showing that there is a dose-response relationship between the number of childhood traumatic events and

Table 3
Associations between severity of childhood traumatization and the log-transformed plasma renin and plasma aldosterone concentration. Results from linear regression models adjusted for sex, age, waist circumference, alcohol consumption, physical activity, serum creatinine and potassium concentrations, depressive symptoms,intake of medication that alters renin or aldosterone concentrations and time of blood sampling.

Childhood traumatization		Renin						Aldosterone					
(reference = none)		ß-coefficient	stderr	df	t	p	Cohen's f^2	ß-coefficient	stderr	df	t	p	Cohen's f^2
Emotional abuse	mild	0.099	0.068	1	1.45	0.15	0.10	0.078	0.054	1	1.45	0.15	0.10
	moderate	0.034	0.137	1	0.25	0.81		0.269	0.108	1	2.50	0.01	
	severe	0.215	0.148	1	1.45	0.15		0.244	0.116	1	2.10	0.04	
Physical abuse	mild	0.058	0.090	1	0.65	0.52	0.10	0.126	0.071	1	1.77	0.08	0.10
	moderate	−0.041	0.113	1	−0.36	0.72		0.239	0.089	1	2.68	< 0.01	
	severe	0.040	0.135	1	0.30	0.76		0.175	0.106	1	1.65	0.10	
Sexual abuse	mild	0.071	0.099	1	0.71	0.48	0.10	0.057	0.078	1	0.73	0.46	0.10
	moderate	0.080	0.119	1	0.67	0.50		−0.154	0.094	1	−1.65	0.10	
	severe	0.358	0.205	1	1.75	0.08		0.387	0.161	1	2.40	0.02	
Emotional neglect	mild	−0.032	0.043	1	−0.75	0.45	0.10	−0.052	0.034	1	−1.54	0.12	0.10
	moderate	−0.006	0.082	1	−0.08	0.94		0.061	0.065	1	0.94	0.35	
	severe	0.033	0.074	1	0.45	0.65		0.089	0.058	1	1.53	0.13	
Physical neglect	mild	−0.036	0.045	1	−0.80	0.42	0.10	0.030	0.036	1	0.83	0.41	0.10
	moderate	0.093	0.059	1	1.56	0.12		0.009	0.047	1	0.20	0.84	
	severe	0.135	0.089	1	1.51	0.13		0.075	0.070	1	1.07	0.29	

stderr, standard error.
Statistically significant results printed in **bold**.

aldosterone levels, similar to the relation of adulthood trauma and renin.

Finally, subgroup analyses revealed that the effects were carried by all abuse subscales, while emotional and physical neglect did not show significant associations with altered RAAS activity. This is remarkable since neglect, which was found to be the most prevalent form of childhood trauma in this sample (table S1) and other studies (e.g. Taillieu et al., 2016), showed strong correlations with all subscales of abuse (table S2), but still did not reach significance. Moreover, these results add to previous findings showing differential HPA-axis activity depending on the type of childhood trauma (Kuhlman et al., 2015a, 2015b) and may contribute to explain findings of specific associations of child abuse, but not neglect with increased risk for adult cardiovascular disease (Hosang et al., 2013). Also, they are in line with the notion of distinct neurobiological impacts of the childhood trauma subtypes (Nemeroff, 2016; Terock et al., 2016; Weltz et al., 2016). However, due to the cross-sectional design and the high correlation of all childhood trauma subtypes (table S2), these results must be regarded as preliminary. Longitudinal studies aiming to investigate the differential and putatively interactional effects of the different types of childhood trauma are necessary.

Our results extend previous findings of a dose-response relationship between traumatic events and renin concentrations (Terock et al., 2018). Finding elevated levels of aldosterone in response to childhood trauma, but not in response to adulthood trauma, is in line with results from previous studies showing that childhood and adulthood trauma may differentially impact HPA-axis activity (Meewisse et al., 2007; Rinne et al., 2002). More specifically, these studies provided some evidence for increased baseline cortisol levels in relation to childhood trauma, while no clear HPA-axis alterations were found in association with adulthood trauma (Goldman-Mellor et al., 2012; Klaassens et al., 2012). Previous results suggest that there are particularly sensitive periods in the early development of the HPA-axis, during which exposure to severe stressors leads to lasting disruptions in HPA-axis regulation (Levine, 2005). Kuhlman et al. investigated the age at first trauma exposure in relation to altered HPA-axis functioning in adolescents (Kuhlman et al., 2015a, 2015b). The authors found that only trauma during infancy was related to delayed cortisol recovery after acute stress, suggesting that particularly infancy, which is regarded as a period of transition to socially regulated HPA-axis function, may be critical for later HPA-axis regulation. Plasma concentrations of aldosterone are specifically linked to the HPA-axis given that ACTH is a potent stimulating factor for both the release of cortisol as well as aldosterone. Therefore, developmental alterations in the ACTH-mediated regulation of aldosterone synthesis and release may represent a mechanism underlying the relation of aldosterone levels and childhood trauma. This concept is supported by findings from animal and human studies showing that early adverse events severely impact the development of different neuroendocrine systems including the HPA-axis [for review (Meaney, 2001)) with evidence for a diminished negative feedback loop of the HPA-axis. (Ladd et al., 2004). In support of this concept, there is converging evidence for long-term effects of childhood trauma on the expression and epigenetic regulation of genes involved in the neuroendocrine stress response (for review: Raabe and Spengler, 2013). In particular, gene expression (McGowan et al., 2009) and methylation (Turecki and Meaney, 2016) of the glucocorticoid receptor were found to be specifically prone to the effects of childhood trauma. In contrast, results on the relation of later life chronic stress on glucocorticoid receptor regulation produced mixed results (Turecki and Meaney, 2016), suggesting a more specific role of early life stressors. Also, Heim et al. reported increased levels of corticotropin releasing factor (CRF), the stimulating agent for the release of ACTH, in association with childhood trauma (Heim et al., 2008, 2000). ANG II is another stimulating factor for aldosterone release via activation of adrenal AT_1 receptors. While chronic stress has been shown to downregulate adrenal AT_1 receptors (Aguilera, 1993), there is evidence from rodent studies showing sensitization of these receptors in response to maternal separation (Loria et al., 2011). Therefore, it can be speculated that childhood trauma may lead to an increased sensitivity of adrenal AT_1 receptors finally enhancing aldosterone release.

Exposure to adulthood trauma, the number of traumatic events and diagnosis of PTSD were found to be associated with increased renin levels. Although these findings have been reported in a previous paper of our working group (Terock et al., 2018), they are still noteworthy because these previous results were based on a different sample size and we previously had not differentiated between childhood and adulthood traumatization. Thus, finding our previous results generally confirmed provides further support for the observation of lasting and cumulative effects of traumatic events on renin activity and indicates that these effects can be attributed solely to the impact of traumatization in adulthood. Moreover, they support the concept that enhanced renin levels are involved in the pathophysiology of adult PTSD (Marvar et al., 2014; Nylocks et al., 2015). These effects may be mediated by the autonomic nervous system, an important effector for stress-induced renin-release, which has been found to show enhanced activity in relation to adulthood trauma (Murata et al., 1997) and chronic states of hyperarousal in PTSD (Cohen et al., 2000). However, it should be acknowledged that, in our sample, no participant with exposure to childhood but not adulthood trauma met the criteria for PTSD.

Additional sensitivity analyses after exclusion of all subjects suffering from PTSD slightly reduced the effect sizes, particularly for the relation of childhood trauma and aldosterone levels. However, main effects were still significant, which is remarkable with respect to previous findings showing that subjects with PTSD had the strongest RAAS dysregulation. Nevertheless, these results demonstrate that even the exposure to and the severity of traumatic events may independently impact RAAS regulation without clinical PTSD being present.

Some previous research demonstrated that childhood and adulthood traumatization interact in their neurobiological effects. For example, Heim et al. reported that childhood abuse and adulthood trauma independently and interactively predicted peak cortisol and ACTH responses with the interaction term being the most powerful predictor (Heim et al., 2002). While we did not detect interactive effects of childhood and adulthood trauma, our results showed that different components of the RAAS were altered when both types of trauma existed. Our findings indicate that different neuroendocrine pathways are activated specifically depending on the time of traumatization and that these mechanisms complement each other in their effects on the RAAS.

Considering these results from previous studies showing a dysregulation of the RAAS in response to trauma and PTSD and given the key role of the RAAS in the pathophysiology of cardiovascular disease, administration of ACE-I and ARBs may be particularly helpful in subjects with a trauma history. Elevated aldosterone in relation to childhood trauma may also contribute to explain findings of Dong et al. (2004) showing a dose-response relation between the number of childhood traumas and ischemic heart disease (Dong et al., 2004). With respect to findings pointing to a role of renin in the development of PTSD (Marvar et al., 2014; Nylocks et al., 2015), the use of ACE-I and ARBs may also be beneficial regarding prevention of or relief from PTSD symptomatology.

This study has several strengths including the large and well-characterized community-based cohort and adjustment for various metabolic, behavioral as well as clinical covariates. All of these covariates, apart from physical activity, showed a significant influence in the different models. The inclusion of these confounders, including sex and age, but also for example waist circumference, alcohol consumption, and depressive symptoms, helped us to generate robust estimates for the analyzed associations. However, some limitations should be acknowledged. First, childhood as well as adulthood trauma were assessed based on self-reported, retrospective information. While both applied instruments are widely used and well-established, the reliability of the obtained information has been called into question. Specifically,

subjects may prefer not to completely disclose traumatic events or have difficulties in recalling aspects of traumas (Edwards et al., 2001). Also, evidence from longitudinal studies indicated that participants tend to underestimate traumatic events particularly from childhood (Williams, 1995). Moreover, it should be recognized that the two instruments for measuring exposure to and severity of traumatic events show important differences in their conceptualization: The CTQ is a dimensional as well as a qualitative approach, as it measures the occurrence of different trauma types as well as their severity. In contrast, the trauma-list of the SCID only asks for the exposure to a variety of traumatic events, while no information is obtained about their frequency or severity. Therefore, our findings on dose-response relationships are limited in their comparability, particularly with respect to the assessment of adulthood trauma, as they do not necessarily reflect the individual trauma load in terms of severity and frequency a participant has been exposed to. Second, data on concentrations of ANG II, the key effector of the RAAS, were not available in this study. However, with respect to the strong functional connection between renin and ANG II, we believe that renin measures may represent a sufficient proxy for ANG II concentrations. Third, all participants were under regular medication, including antihypertensive drugs that may impact on renin or aldosterone concentrations. In order to sustain the statistical power of our sample, we decided not to exclude the subjects, but to adjust the analyses for the intake of such medication instead. Finally, although the results obtained in our different models are consistent and were confirmed in our sensitivity analyses, the reported effect sizes are rather small. Therefore, our findings demand replication by further epidemiological studies.

In conclusion, our study revealed altered RAAS activity in traumatized subjects with differential effects depending on the time of trauma exposure. Moreover, subjects with exposure to both childhood and adulthood trauma were found to be at specific risk for a severe dysregulation of the RAAS. Our results may contribute to clarify the relationship between traumatization and different physical as well as mental disorders. Additional studies are necessary to clarify the role of altered RAAS activity for the development of physical disorders and particularly cardiovascular disease in traumatized subjects.

Conflicts of interest

HJG has received travel grants and speakers honoraria from Fresenius Medical Care and Janssen Cilag. He has received research funding from the German Research Foundation (DFG), the German Ministry of Education and Research (BMBF), the DAMP Foundation, Fresenius Medical Care, the EU "Joint Program Neurodegenerative Disorders (JPND) and the European Social Fund (ESF)"

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JT, AH, MB, and HV declare there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.05.026.

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