



Sex differences in the association between basal serum cortisol concentrations and cortical thickness

Johanna Klinger-König^{a,*}, Stefan Frenzel^a, Anke Hannemann^{b,c}, Katharina Wittfeld^{a,d}, Robin Bülow^e, Nele Friedrich^{b,c}, Matthias Nauck^{b,c}, Henry Völzke^f, Hans J. Grabe^{a,d}

^a Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Germany

^b Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Germany

^c German Centre for Cardiovascular Research (DZHK), Partner Site Greifswald, University Medicine Greifswald, Germany

^d German Center for Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, Germany

^e Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Germany

^f Institute for Community Medicine, University Medicine Greifswald, Germany

ARTICLE INFO

Keywords:

Serum cortisol
Cortical thickness
Sex differences
HPA Axis
HPG Axis

ABSTRACT

Background: Basal cortisol concentrations vary between men and women. Likewise, previous findings suggest stress-related cortical thickness alterations. Thus, we aimed at elucidating sex differences in the association between serum cortisol concentrations and cortical thickness.

Methods: Data of 2594 participants (55.55% male; mean age = 53.55 years \pm 13.17 years) of the general population were used to investigate sex differences in basal serum cortisol concentrations and associations of serum cortisol concentrations with global and regional cortical thickness. The validity of the results was tested by including sex hormone concentrations as a biological and childhood maltreatment and depressive symptoms as a psychological confounder.

Results: Basal serum cortisol concentrations were higher in men than in women ($\beta = -0.158$, $t_{(2575)} = -6.852$, $p = 9.056e-12$). Sex differences in serum cortisol concentrations were diminished by including serum concentrations of testosterone, estrone, or estradiol in the models. In men but not in women, serum cortisol concentrations were inversely associated with the global cortical thickness (men: $\beta = -0.064$, $t_{(1412)} = -3.010$, $p = .003$; women: $\beta = -0.016$, $t_{(1131)} = -0.607$, $p = .544$). Additionally, these effects were observed in eleven cortical regions after adjusting for multiple testing. The associations were independent of childhood maltreatment and depressive symptoms.

Conclusion: Sex differences in serum cortisol concentrations and the association between serum cortisol concentrations and cortical thickness suggest important sex-specific effects of stress on the brain. Future studies should integrate the interaction between the hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-gonadal (HPG) axis in sex-stratified analyses.

1. Introduction

A major function of the hypothalamic-pituitary-adrenal axis (HPA axis) is to activate and regulate the cortisol secretion by the adrenal gland in response to stressful experiences. However, even in the absence of acute stress, cortisol secretion varies in a circadian rhythm (diurnal slope). A flatter diurnal slope was related to numerous mental and physical diseases such as major depression, inflammation, obesity, cancer and even mortality risk (Adam et al., 2017). Additionally, lower basal urinary, blood and saliva cortisol concentrations were associated

with traumatic experiences such as the holocaust or childhood maltreatment (Fogelman and Canli, 2018; Yehuda et al., 2009). According to Heim et al. (2008), the traumatic experiences might cause a higher sensitization of the HPA axis associated with lower basal cortisol concentrations which lead to a disinhibition of the stress response and thus an amplified stress reactivity indicated by higher cortisol concentrations during an acute stress response.

Under basal conditions, glucocorticoids as cortisol are binding to the mineralocorticoid receptor (MR) with a high affinity. Increasing glucocorticoid concentrations are related to a higher affinity for and stronger

* Corresponding author. Department of Psychiatry and Psychotherapy, Ellernholzstraße 1-2, D-17489, Greifswald, Germany.

E-mail address: johanna.klinger-koenig@med.uni-greifswald.de (J. Klinger-König).

<https://doi.org/10.1016/j.ynstr.2021.100416>

Received 10 August 2021; Received in revised form 1 October 2021; Accepted 1 November 2021

Available online 2 November 2021

2352-2895/© 2021 The Authors.

Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

activation of the glucocorticoid receptor (GR) (Joëls and de Kloet, 2017; Mifsud and Reul, 2018). Integrating the sensitization theory of Heim et al. (2008), chronic exposure to high cortisol concentrations might lead to long-term potentiation of the MR and GR systems which reduces basal cortisol concentrations. Simultaneously, the negative feedback to increased cortisol concentrations is slowed resulting in higher cortisol concentrations during an acute stress response (Deppermann et al., 2014; Pariante, 2006).

Accordingly, synaptic and morphological changes after chronic stress have been reported for several subcortical areas and the prefrontal cortex (Pittenger and Duman, 2008; Rajkowska, 2000). Chronic stress was related to a downregulation of the brain-derived neurotrophic factor (BDNF), a neurotrophin with synaptogenic properties (Jeanneteau and Chao, 2013). Further, neurotoxic effects of chronically high glucocorticoids are mediated by reduced GR activity, dendritic atrophy and neuronal loss (Rajkowska, 2000; Groeneweg et al., 2011; McEwen, 2004). In rats, the number of neurons in the forebrain was reduced after repeated injection of corticosterone (Alonso, 2000). In humans, increased cortisol concentrations in Cushing's syndrome patients were associated with global brain atrophy (Simmons et al., 2000; Patil et al., 2007; Gnjiđić et al., 2008). Similarly, a regional reduction of gray matter volume and cortical thickness in depressed patients was related to higher blood and saliva cortisol concentrations (Drevets, 2004; Liu et al., 2015; Lebedeva et al., 2018). Besides, reduced cortical thickness has been associated with childhood maltreatment (Kelly et al., 2013; Wang et al., 2016).

According to a review of Gray et al. (2017), sex differences in cortisol-associated structural brain changes were predominantly demonstrated in the hypothalamus, hippocampus, amygdala and prefrontal cortex of rodents. The authors concluded widespread neuronal effects of sex and stress hormones and suggested future studies to widen the range of researched brain regions, e.g. on cortical thickness (Gray et al., 2017). Stomby et al. (2016) reported small sex-dependent associations between area under curve saliva cortisol concentrations and cortical thickness of the caudal middle frontal gyrus and the right pars opercularis in 200 elderlies (>54 years). Although the interaction effects did not stand the adjustment for multiple testing, a positive association between cortisol concentrations and cortical thickness was observed in post-hoc analyses in healthy women but not in men (Stomby et al., 2016).

Sex differences in the associations between brain alterations and cortisol concentrations are likely to be explained by sex hormones, at least in part. The HPA axis interacts with the hypothalamic-pituitary-gonadal (HPG) axis, particularly by reducing the luteinizing hormone and via the activation of GR and estrogen receptors (Gray et al., 2017; Bourke et al., 2012; Juster et al., 2011). Thus, progesterone directly competes with cortisol for GR (Bourke et al., 2012). Estradiol inhibits the GR activation and decreases the GR expression (Gray et al., 2017). Further, estradiol was reported to increase the cortisol release via estrogen receptors in rats (Bourke et al., 2012; Weiser and Handa, 2009). In line, brain regions associated with the regulation of the HPA axis also have higher densities of estrogen receptors (Juster et al., 2011). Progesterone and estradiol are frequent compounds of oral contraceptives (OC) (Hertel et al., 2017; Eick et al., 2021). Accordingly, higher basal cortisol concentrations were reported in OC users (Hertel et al., 2017; Eick et al., 2021; Oinonen and Mazmanian, 2002). In free circulating women, higher basal cortisol concentrations were reported in the luteal phase, characterized by higher progesterone and estrogen concentrations, compared to the follicular phase (Baker and Driver, 2007; Genazzani et al., 1975; Shibui et al., 2000). Finally, after the administration of hydrocortisone, a decrease of testosterone concentrations, a precursor of estradiol, was already demonstrated in 1983 (Cumming et al., 1983). Later, various animal models also demonstrated inhibition of cortisol release by high testosterone concentrations (Bourke et al., 2012; Juster et al., 2011).

Although the interaction between the HPA and HPG axis was

discussed before (Gray et al., 2017; Bourke et al., 2012; Hertel et al., 2017; Baker and Driver, 2007; Cumming et al., 1983), sex hormone concentrations have rarely been included as potential confounders in previous work (Juster et al., 2011, 2016). Stalder et al. (2017) reported higher hair cortisol concentrations in men than in women. In contrast, Liu et al. (2017) did not support any sex differences of baseline saliva cortisol concentrations and even reported higher cortisol reactivity in men than women after a social stress test and during recovery. Integrating sex hormones, Juster et al. (2016) demonstrated flatter saliva diurnal slopes for men only when adjusting for testosterone and estrogen concentrations.

In the present study, data of 1441 men and 1153 women of the population-based Study of Health in Pomerania (SHIP) was used to investigate associations between basal serum cortisol concentrations and cortical thickness. According to previous reports, we expected an inverse association between serum cortisol concentrations and cortical thickness (Alonso, 2000; Simmons et al., 2000; Patil et al., 2007; Gnjiđić et al., 2008; Drevets, 2004; Liu et al., 2015; Lebedeva et al., 2018). Integrating the well-described interaction of the HPA and HPG axis (Gray et al., 2017; Bourke et al., 2012; Hertel et al., 2017; Baker and Driver, 2007; Cumming et al., 1983), we further expected sex differences in these cortisol-cortical thickness associations. Although the results of Stomby et al. (2017) (Stomby et al., 2016) were based on a smaller elderly sample, we assumed stronger associations between cortisol concentrations and cortical thickness in women. In support of the validity of the cortical thickness analyses in our sample, we aimed to replicate previously reported sex differences in our basal serum cortisol concentrations as well as inverse associations of the basal cortisol concentrations with depressive symptoms and childhood maltreatment (Fogelman and Canli, 2018; Heim et al., 2008). In a subsample (N = 720), the influence of serum concentrations of testosterone, estrone and estradiol on these sex differences was tested.

Previous studies investigating associations between cortisol concentrations and brain alterations were mostly based on animal models or patient samples (Alonso, 2000; Simmons et al., 2000; Patil et al., 2007; Gnjiđić et al., 2008; Drevets, 2004; Liu et al., 2015; Lebedeva et al., 2018; Gray et al., 2017). Further, particularly integrating potential sex differences, previous studies majorly focused on associations between cortisol concentrations and volumes of subcortical structures neglecting cortical structures (Gray et al., 2017). Developmental trajectories during childhood and adolescents (7–23 years) were reported to be sex-dependent in cortical surface and cortical volume but not in cortical thickness (Wierenga et al., 2014). However, sex-dependent developmental trajectories might impact sex-dependent associations between cortisol concentrations and cortical structure during adulthood. Although the interaction of the HPA and HPG axis is well-described, integrating sex hormones into the analyses of sex differences in cortisol concentrations was rarely done before (Juster et al., 2011, 2016). Therefore, our study aimed to close these gaps by researching sex differences between cortisol concentrations and cortical thickness in a large epidemiological sample. Whereas previous studies focused on animal models, patient samples and subcortical volumes without taking potential sex differences into account (Gnjiđić et al., 2008; Drevets, 2004; Gray et al., 2017), the present study was based on a large population-based sample focusing on sex-specific associations with cortical thickness. Rather than focusing on specific brain regions, we included the thickness of the whole neocortex aiming to extend previous results on GR-associated regions (Pittenger and Duman, 2008; Rajkowska, 2000; Alonso, 2000). The focus on sex differences particularly integrates the interaction of the HPA and HPG axis (Gray et al., 2017; Bourke et al., 2012; Hertel et al., 2017; Baker and Driver, 2007; Cumming et al., 1983). Thus, the study adds important information to the sex-specific neuroscience of stress in general and cortisol in particular.

2. Materials and methods

2.1. Study population

Data from the Study of Health in Pomerania (SHIP) (Völzke et al., 2011; John et al., 2001) was used. The SHIP baseline sample (SHIP-0: 1997–2001; N = 4308) was drawn from local registries in the north-east of Mecklenburg-West Pomerania in Germany. In parallel to the 10-years-follow-up (SHIP-2: 2008–2012; N = 2333), all participants included in SHIP-0 and still alive in 2006 were invited to take part in the Study of Life Events and Gene-Environment-Interaction in Depression (SHIP-LEGEND: 2007–2010; N = 2400), which aimed to phenotype psychiatric dimensions. From 2008 till 2012, examination in a second, independent cohort, drawn from local registries of the same local area (SHIP-TREND-0: 2008–2012; N = 4420), were performed (Völzke et al., 2011). Note that participants of SHIP and SHIP-TREND are not overlapping.

Subjects from SHIP-2 and SHIP-TREND-0 were invited to participate in whole-body magnetic resonance imaging (MRI). Head MRI was acquired from 1163 participants in SHIP-2 and 2154 participants in SHIP-TREND-0 that were free of any of the exclusion criteria for MRI scanning (e.g. cardiac pacemakers, pregnancy) (Hegenscheid et al., 2013). For 885 participants (491 men) in SHIP-2, cortical thickness, serum cortisol concentrations and covariates (see section 2.6) were available. Analogous data were available for 1709 participants (950 men) in SHIP-TREND-0.

The data collection in both cohorts as well as all statistical analyses were performed according to the Declaration of Helsinki, including written informed consent of all participants. All examinations and methods of the SHIP studies were approved by the institutional review board of the University Greifswald.

2.2. Interview and medical examination

During a computer-assisted face-to-face-interview, sociodemographic variables, smoking status (yes/no) and alcohol consumption were assessed. Alcohol consumption was defined as the average intake per day over the last 30 days (grams of ethanol per day) according to Baumeister et al. (2005). Participants were asked to report medication intake during the past week or to bring their packing containers or drug prescription sheet. Compounds were recorded and categorized according to the Anatomical Therapeutic Chemical (ATC) classification (ATC-Index, 2007). Participants reporting the use of sex hormones (ATC G03), locally applied contraception (ATC G02B) or corticosteroids for systemic use (ATC H02) were excluded from the analyses (SHIP-2: N = 126; SHIP-TREND-0: N = 270) as was one pregnant woman in SHIP-TREND-0. During a medical examination, body weight and height were measured with calibrated scales in light clothes. Height was measured to the nearest 1 cm. 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 participant standing on both feet. The waist-height-ratio (WHtR) was calculated as an estimate of central obesity and body fat (Swainson et al., 2017).

2.3. Psychometric data

Self-reporting questionnaires were handed over to the participants, including the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) in both cohorts, the Beck Depression Inventory-II (BDI-II) (Wintjen and Petermann, 2010) in SHIP-LEGEND and the Patient Health Questionnaire (PHQ-9) (Kroenke and Spitzer, 2002) in SHIP-TREND-0. The CTQ uses 28 items to assess childhood maltreatment on five subscales: emotional/physical/sexual abuse and emotional/physical neglect. According to Bernstein et al. (2003) (Bernstein et al., 2003), childhood maltreatment can be categorized as “none”, “mild”, “moderate” or “severe” on each subscale individually. Here, a dichotomous variable indicating any childhood

maltreatment was defined as “yes” if “moderate” or “severe” childhood maltreatment was reported on any of the subscales (Häuser et al., 2011). Further, a summary score was calculated to indicate the overall severity of childhood maltreatment.

The BDI-II and the PHQ-9 assess depressive symptoms according to the criteria of a major depressive disorder of the DSM-IV. To ensure the comparability between the BDI-II and PHQ-9 scores, the PHQ-9 score was transformed into a BDI-II score according to Wahl et al. (2014). The BDI-II summary score indicates the severity of depressive symptoms. Additionally, a dichotomous variable identifying “moderate” or “severe” depressive symptoms was defined by BDI-II summary scores higher than 19 (Wintjen and Petermann, 2010).

2.4. Whole blood measurements

Blood samples were taken from the cubital vein. Serum and plasma samples were stored at -80°C in the Integrated Research Biobank of the University Medicine Greifswald and used in accordance with its regulations (Winter et al., 2020). As cortisol secretion is influenced by the circadian rhythm, participants were excluded from the analyses if the time of blood sampling was before 7:00 am or after 1:00 pm (SHIP-2: n = 5). Note, that participants of SHIP-TREND-0 but not SHIP-2 were asked to fast before blood sampling. Hence, fasting time was longer in SHIP-TREND-0 (mean (M) = 10:00 h, standard deviation (SD) = 4:53 h) than SHIP-2 (M = 3:09 h, SD = 2:46 h).

Glycated hemoglobin (HbA1c) concentrations were quantified by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany). White blood cell count (WBC), red blood cell count (RBC) and platelet count (PLT) were measured on the XT2000, XE 5000 or SE9000 analyzers from Sysmex (Sysmex Deutschland GmbH, Norderstedt, Germany) or on the Advia 2120i (Siemens Healthcare Diagnostics, Eschborn, Germany).

Serum cortisol was measured using a chemiluminescence-immunoassay on the AVIDA CENTAUR XP (Siemens Healthcare Diagnostics, Eschborn, Germany). The coefficients of variation for the cortisol measurements were 5.74% and 6.94% for low and high dose control material in SHIP-2 and 9.11% and 7.47% for low and high dose control material in SHIP-TREND-0, respectively.

The measurement of testosterone, estrone and estradiol concentrations has been described in detail before (Haring et al., 2012; Seyfart et al., 2018). Sex hormone concentrations were measured from frozen aliquots using liquid chromatography–mass spectrometry. For limits of quantification and inter- and intra-assay coefficients of variation please see Seyfart et al. (2018) (Seyfart et al., 2018). Note that, the assessment of testosterone, estrone and estradiol concentrations was part of a multi-omics assessment only conducted in a non-diabetic subsample of SHIP-TREND-0. Thus, no sex hormone concentrations were available for the participants of SHIP-2. For SHIP-TREND-0, testosterone concentrations were available for 377 men and 343 women of the present study sample; estrone concentrations were available for 329 men and 335 women and estradiol concentrations were available for 328 men and 167 women.

2.5. Magnetic resonance imaging

For structural magnetic resonance imaging (MRI) data of the head, participants were scanned with a 1.5-Tesla MRI scanner (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) with a T1-weighted magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence and the following parameters: axial plane, repetition time = 1900 msec, echo time = 3.4 msec, flip angle = 15° and the original resolution of $1.0 \times 1.0 \times 1.0 \text{ mm}^3$, matrix 256×176 , bandwidth 130 Hz/Pixel. Cortical reconstruction was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>) (Winter et al., 2020). Briefly, this processing includes removal of non-brain tissue, automated Talairach transformation,

intensity normalization, tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation to optimally place the gray/white and gray/cerebrospinal fluid borders. The cerebral cortex is then being parceled with respect to gyral and sulcal structure according to the Desikan-Killiany atlas (34 regions per hemisphere) (Desikan et al., 2006). Here, we consider the average thickness of each cortical region and the whole cerebral cortex. Quality control was conducted by visual inspection in accordance with the ENIGMA protocol (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>).

2.6. Statistical analyses

All statistical analyses were carried out in the combined sample of SHIP-2 and SHIP-TREND-0 using R 4.0.4. Data of the cohorts were combined. Following previous studies, ordinary least square regression models were used adjusted for cohort, sex, age, sex*age, time of blood sampling, fasting time, smoking status, alcohol consumption, HbA1c, WBC, RBC, PLT and WHtR (Hertel et al., 2017; Swainson et al., 2017; Enzinger et al., 2005; Janowitz et al., 2015; Karama et al., 2015). Non-linear modelling of the covariates was used if analyses of variances comparing linear and non-linear covariate modulation revealed a significantly lower residual sum of squares for the non-linear model. Thus, restricted cubic splines (RCS) were used with four knots (5th, 35th, 65th and 95th percentiles) to model non-linear relationships with age, time of blood sampling and fasting time.

For a basic validation of our serum cortisol concentrations and cortical thickness data, we aimed to replicate associations with sex and age. Thus, higher cortisol concentrations and lower global cortical thickness were expected in men than in women (Genazzani et al., 1975; Stalder et al., 2017; Gordon et al., 2016; Kaji et al., 2008). However, larger age effects were expected in women for the cortisol concentrations and in men for the cortical thickness (Cowell et al., 1994; Salat et al., 2004). Here, the main effect of sex and a non-linear sex-age-interaction on serum cortisol concentrations and cortical thickness were analyzed. A significance level of p -value $< .05$ was used for all analyses. The significance of the non-linear age effects was calculated using an F-test with 3 degrees of freedom representing the splines. Afterwards, as the focus of the present analyses was on potential sex differences, all analyses were recalculated sex-stratified.

Sex hormone concentrations might partly explain observed differences between men and women, as female sex hormones were associated with increased cortisol release (Bourke et al., 2012; Weiser and Handa, 2009) whereas testosterone concentrations were inversely associated with cortisol concentrations (Bourke et al., 2012; Juster et al., 2011; Cumming et al., 1983). Thus, testosterone, estrone and estradiol concentrations were added as covariates in extended analyses.

To test the collinearity between sex and the sex hormone concentrations, testosterone, estrone and estradiol concentrations were regressed on the remaining confounders (including sex), respectively. According to Senaviratna and Cooray (2019) (Senaviratna and Cooray, 2019), the Tolerance and Variance Inflation Factor (VIF) was calculated. Results of the collinearity analyses are presented in the supplement.

For a psychopathological validation of the serum cortisol concentrations, we aimed to replicate inverse associations between cortisol concentration and childhood maltreatment as well as depressive symptoms (Bourke et al., 2012; Juster et al., 2011; Cumming et al., 1983). Further, the effects of childhood maltreatment and depressive symptoms were assumed to add up (Heim et al., 2008). In sex-stratified analyses, all associations were expected to be found in women but not in men (Meewisse et al., 2007). A significance level of p -value $< .05$ was used for all analyses.

To test our main hypotheses, global cortical thickness, as well as the cortical thickness of 34 regions were regressed on serum cortisol concentrations. For analyses including the global cortical thickness, a significance level of p -value $< .05$ was used. To adjust for multiple testing focusing on the cortical thickness of 34 regions, a False Discovery Rate (FDR) < 0.05 was used instead of a p -value based significance threshold

(Benjamini and Hochberg, 1995). All analyses were recalculated sex-stratified to investigate potential sex differences.

Finally, as childhood maltreatment and depression are known to be associated with lower cortical thickness as well as lower cortisol concentrations (Lebedeva et al., 2018; Kelly et al., 2013; Wang et al., 2016), the influence of childhood maltreatment and depressive symptoms on the associations between serum cortisol concentrations and cortical thickness were tested in extended analyses.

3. Results

Table 1 presents the descriptive statistics of the whole sample and for men and women separately. Note that women had more severe depressive symptoms (men: $M = 6.24$, women: $M = 8.08$, $p = 1.118e-13$) and higher rates of moderate/severe depressive symptoms than men (men = 2.44%, women = 4.90%, $p = .001$). Similarly, the prevalence of any childhood maltreatment was higher in women than in men (men = 11.84%, women = 16.60%, $p = 9.467e-04$). In contrast, no differences were observed in the severity of childhood maltreatment (men: $M = 33.11$, women: $M = 33.73$, $p = .122$).

3.1. Validation of serum cortisol concentrations and cortical thickness data

Validating our single-occasion serum cortisol concentrations, we replicated higher serum cortisol concentrations in men than in women ($\beta = -0.158$, $t_{(2575)} = -6.852$, $p = 9.056e-12$). Additionally, higher global cortical thickness in women compared to men was replicated ($\beta = 0.178$, $t_{(2562)} = 8.957$, $p = 6.267e-19$). The associations remained stable even after including testosterone, estrone and estradiol concentrations as covariates. A detailed overview of the results of the validation analyses is provided in the supplementary material part A and Table S2 and illustrated in Fig. S2 and Fig. S3.

Besides, to validate the serum cortisol concentrations in a psychopathological background, lower serum cortisol concentrations were associated with more severe childhood maltreatment ($\beta = -0.081$, $t_{(2403)} = -4.350$, $p = 1.419e-05$) and more severe depressive symptoms ($\beta = -0.042$, $t_{(2413)} = -2.172$, $p = .030$). Adding the predictors simultaneously to the regression analyses validated the association between serum cortisol concentrations and childhood maltreatment ($\beta = -0.075$, $t_{(2401)} = -3.845$, $p = 1.238e-04$). However, the association between serum cortisol concentrations and depressive symptoms was no longer significant ($\beta = -0.018$, $t_{(2401)} = -0.894$, $p = .371$). As expected, both associations were stronger in women than in men. A detailed overview of the results of the psychopathological validation is provided in the supplementary material part B and illustrated in Fig. S4.

3.2. Associations of serum cortisol concentrations with cortical thickness

In the whole sample, higher serum cortisol concentrations were associated with a lower global cortical thickness ($\beta = -0.046$, $t_{(2558)} = -2.699$, $p = .007$; Table 2). Further, associations with serum cortisol concentrations were found in four cortical regions. Another twelve cortical regions demonstrated marginal significant results ($p < .1$). An overview of the associations between serum cortisol concentrations and cortical thickness for the whole sample is presented in Table 2. The β -values of the associations between serum cortisol concentrations and the thickness of the cortical regions for men and women separately are presented in Fig. S1.

Sex-specific analyses revealed no association between serum cortisol concentrations and global cortical thickness or any single cortical region in women (Table 2). In men, lower global cortical thickness was associated with higher serum cortisol concentrations ($\beta = -0.064$, $t_{(1412)} = -3.010$, $p = .003$). Further associations with serum cortisol concentrations were found in eleven cortical regions. A marginal significance level was reached in seven additional cortical regions. An overview of the sex-

Table 1
Descriptive statistics.

	Whole Sample		Men		Women		p-value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Age (Years)	2594	53.55 (13.17)	1441	52.25 (13.89)	1153	55.17 (12.02)	1.035e-08
Serum Cortisol (nmol/l)	2594	313.14 (114.98)	1441	336.07 (113.86)	1153	284.49 (109.87)	8.745e-31
Global Cortical Thickness (mm)	2581	2.32 (0.13)	1431	2.30 (0.13)	1150	2.33 (0.11)	2.092e-08
Childhood Maltreatment Severity ^a	2426	33.39 (9.44)	1349	33.11 (8.19)	1077	33.73 (10.80)	.122
Any Childhood Maltreatment (Yes)	2429	13.96%	1351	11.84%	1078	16.60%	9.467e-04
Depressive Symptoms Severity ^b	2436	7.06 (5.97)	1355	6.24 (5.31)	1081	8.08 (6.56)	1.118e-13
Moderate/Severe Depressive Symptoms (Yes)	2436	3.53%	1355	2.44%	1081	4.90%	.001
Fasting Time (h:min)	2594	7:40 (5:23)	1441	7:16 (5:15)	1153	8:10 (5:29)	2.730e-05
Time of Blood Sampling (h:min)	2594	9:17 (0:59)	1441	9:14 (0:59)	1153	9:20 (0:59)	.003
Waist-Height-Ratio	2594	0.53 (0.07)	1441	0.54 (0.06)	1153	0.52 (0.08)	2.162e-11
Current Smoking (Yes)	2594	22.71%	1441	24.64%	1153	20.29%	.009
Alcohol Consumption (g/day)	2594	9.70 (13.25)	1441	13.76 (15.71)	1153	4.62 (6.32)	2.735e-82
HbA1c (%)	2594	5.35 (0.68)	1441	5.37 (0.69)	1153	5.32 (0.68)	.064
WBC (Gpt/l)	2594	5.85 (1.67)	1441	5.89 (1.76)	1153	5.79 (1.55)	.116
RBC (Tpt/l)	2594	4.67 (0.40)	1441	4.85 (0.37)	1153	4.44 (0.32)	5.724e-166
PLT(Gpt/l)	2594	223.07 (52.02)	1441	210.86 (48.11)	1153	238.32 (52.71)	3.449e-41

HbA1c = glycated hemoglobin; WBC = white blood cell count; RBC = red blood cell count; PLT = platelet count.

p-values determined by 2-sided t-Test for continuous and 2-sided Fisher's Exact Test for dichotomous variables.

^a Childhood Trauma Questionnaire Summary Score (Range: 25–125).

^b Beck's Depression Inventory-II Summary Score (Range 0–63).

Table 2
Associations between serum cortisol concentrations and cortical thickness.

	Whole Sample				Men				Women			
	N	β		FDR	N	β		FDR	N	β		FDR
Global Cortical Thickness	2581	-.046	**	.007	1431	-.064	**	.003	1150	-.016		.544
Banks Superior Temporal Sulcus	2585	-.043	+	.068	1433	-.054	+	.058	1152	-.031		.944
Caudal Anterior-Cingulate Cortex	2571	.047	+	.068	1429	.013		.687	1142	.096		.102
Caudal Middle Frontal Gyrus	2564	-.065	**	.006	1423	-.080	**	.007	1141	-.036		.944
Cuneus Cortex	2586	-.028		.255	1438	-.034		.291	1148	-.016		.944
Entorhinal Cortex	2576	.004		.843	1430	-.003		.909	1146	.007		.944
Frontal Pole	2583	-.011		.634	1435	-.017		.582	1148	-.006		.944
Fusiform Gyrus	2579	-.029		.223	1435	-.054	+	.058	1144	.008		.944
Inferior Parietal Cortex	2560	-.054	*	.034	1414	-.073	*	.014	1146	-.030		.944
Inferior Temporal Gyrus	2582	-.047	+	.053	1437	-.065	*	.030	1145	-.022		.944
Insula	2590	-.025		.312	1438	-.051	+	.089	1152	.014		.944
Isthmus-Cingulate Cortex	2583	-.069	**	.006	1434	-.082	**	.007	1149	-.047		.944
Lateral Occipital Cortex	2573	-.049	+	.053	1426	-.072	*	.028	1147	-.016		.944
Lateral Orbitofrontal Cortex	2546	-.021		.367	1411	-.023		.441	1135	-.019		.944
Lingual Gyrus	2540	-.033		.153	1408	-.043		.110	1132	-.012		.944
Medial Orbito Frontal Cortex	2513	-.025		.312	1399	-.046		.110	1114	.006		.944
Middle Temporal Gyrus	2561	-.047	+	.051	1424	-.055	*	.046	1137	-.039		.944
Paracentral Lobule	2576	-.006		.783	1428	-.011		.687	1148	.004		.944
Parahippocampal Gyrus	2586	-.020		.438	1436	-.031		.356	1150	-.003		.944
Pars Opercularis	2579	-.045	+	.053	1433	-.058	*	.042	1146	-.022		.944
Pars Orbitalis	2585	-.052	*	.034	1435	-.083	**	.007	1150	-.007		.944
Pars Triangularis	2567	-.038	+	.068	1425	-.038		.136	1142	-.038		.944
Pericalcarine Cortex	2536	-.008		.723	1405	-.021		.520	1131	.010		.944
Postcentral Gyrus	2534	-.027		.233	1400	-.040		.136	1134	-.010		.944
Posterior-Cingulate Cortex	2587	-.010		.655	1439	-.020		.520	1148	.003		.944
Precuneus Cortex	2562	-.037	+	.089	1425	-.053	+	.058	1137	-.006		.944
Precuneus Cortex	2551	-.031		.170	1409	-.046	+	.089	1142	-.011		.944
Rostral Anterior Cingulate Cortex	2574	.016		.552	1432	-.012		.687	1142	.051		.944
Rostral Middle Frontal Gyrus	2574	-.045	+	.051	1428	-.068	*	.014	1146	-.012		.944
Superior Frontal Gyrus	2549	-.040	+	.068	1407	-.046	+	.077	1142	-.032		.944
Superior Parietal Cortex	2558	-.042	+	.068	1412	-.066	*	.030	1146	-.008		.944
Superior Temporal Gyrus	2515	-.033		.140	1395	-.046	+	.089	1120	-.018		.944
Supramarginal Gyrus	2565	-.041	+	.068	1423	-.056	*	.046	1142	-.019		.944
Temporal Pole	2523	-.015		.552	1406	-.017		.585	1117	-.017		.944
Transverse Temporal Cortex	2513	-.012		.634	1394	-.026		.441	1119	-.002		.944

*** FDR<0.001. ** FDR<0.01. * FDR<0.05. + FDR<0.1; NOTE: For global cortical thickness, the FDR equals the p-value.

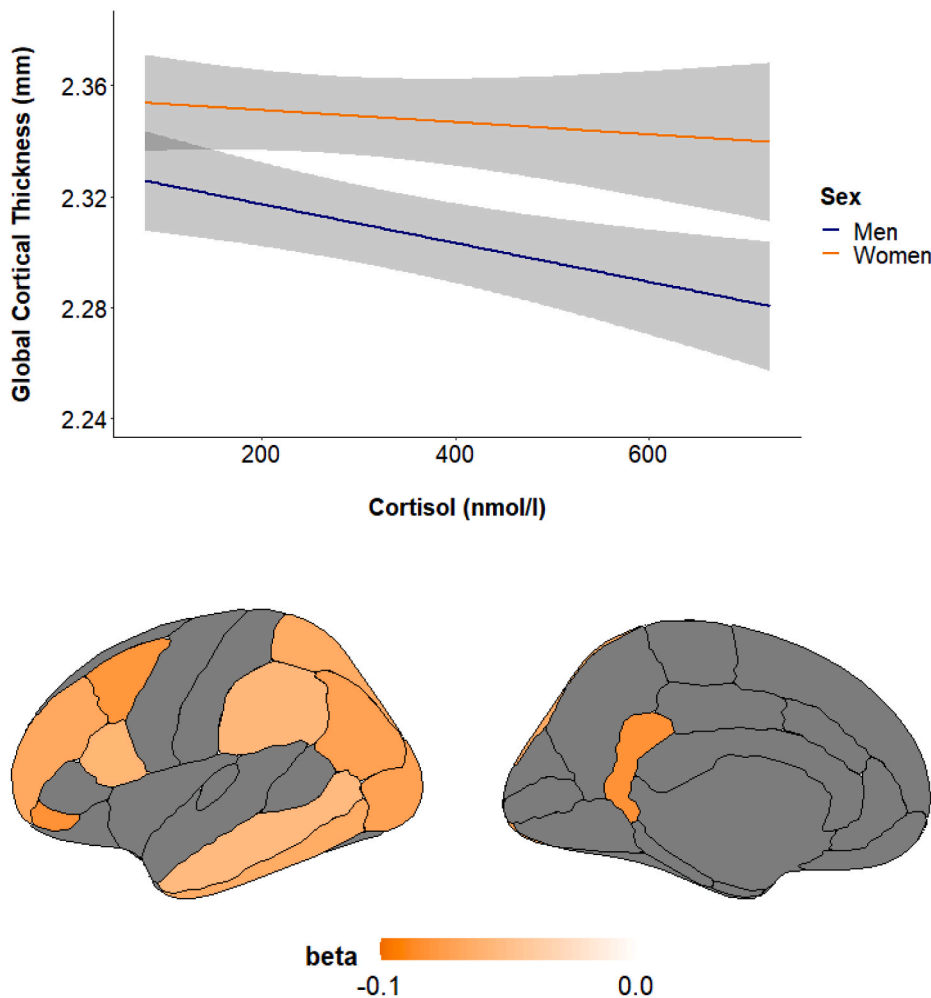


Fig. 1. Association between serum cortisol concentrations and global cortical thickness in 1431 men (blue) and 1150 women (orange).

Higher serum cortisol concentrations were associated with lower global cortical thickness in men ($\beta = 0.064$, $t_{(1412)} = -3.010$, $p = .003$) but not in women ($\beta = -0.016$, $t_{(1131)} = -0.607$, $p = .544$). Note, however, that there was no statistically significant sex*depressive symptoms effect ($\beta = 0.044$, $t_{(2557)} = 1.359$, $p = .174$). Analyses and curves were adjusted for cohort, sex, age (non-linear), sex*age (non-linear), time of blood sampling (non-linear), fasting time (non-linear), smoking status, alcohol consumption, glycated hemoglobin, white blood cell count, red blood cell count, platelet count and waist-height-ratio. The gray shaded area reflects the 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 2. Associations between serum cortisol concentrations and cortical thickness in 1431 men.

For cortical regions with an $FDR \leq .05$, β -values reflecting the strength of the association between serum cortisol concentrations and cortical thickness are presented, namely rostral middle frontal gyrus, caudal middle frontal gyrus, pars orbitalis, pars, supramarginal gyrus, superior parietal cortex, inferior parietal cortex, middle temporal gyrus, inferior temporal gyrus and isthmus-cingulate cortex, lateral occipital cortex. Numeric β -values and corresponding p-values are presented in Table 2. Analyses were adjusted for cohort, age (non-linear), time of blood sampling (non-linear), fasting time (non-linear), smoking status, alcohol consumption, glycated hemoglobin, white blood cell count, red blood cell count, platelet count and waist-height-ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

version of this article.)

specific associations between serum cortisol concentrations and cortical thickness is presented in Table 2 and Fig. 1. The results for men are additionally visualized in Fig. 2.

Extended Analyses. Including the severity of childhood maltreatment and the severity of depressive symptoms as covariates replicated most of the associations for the whole sample and men (Table S1).

4. Discussion

The present study investigated the association between serum cortisol concentrations and cortical thickness in a large epidemiological sample, particularly focusing on potential sex differences. We observed inverse associations between serum cortisol concentrations and regional cortical thickness in men but not in women. These results integrate higher cortisol concentrations in men (Stalder et al., 2017) with previous findings on adverse effects of high cortisol concentrations on the brain [e.g. Rajkowska et al., 2000; Gnjidic et al., 2008; Liu et al., 2015]. This way, the present study added results on sex-dependent associations between cortisol concentrations and cortical thickness in the general population to previous knowledge on associations between cortisol concentrations and subcortical volumes in animals and patients (Gray et al., 2017). The focus on potential sex differences in these associations using such a large and age-heterogenic sample is unique.

In detail, our data revealed higher serum cortisol concentrations to be associated with lower global cortical thickness and lower thickness in

16 cortical regions. The cortical regions mainly clustered in the frontal, temporal and parietal cortex. Although previous research mainly focused on associations between cortisol concentrations and subcortical structures, some studies also reported associations between higher cortisol concentrations and lower GR activity as well as reduced cell proliferation in the prefrontal cortex (Pittenger and Duman, 2008; Rajkowska, 2000; Alonso, 2000; Gray et al., 2017). The prefrontal cortex was reported to inhibit the corticotrophin-releasing hormone and thus the cortisol release (Deppermann et al., 2014) which would fit the inverse association between cortisol concentrations and cortical thickness in our data. In line, early maternal deprivation induced lower GR mRNA concentrations in the frontal cortex of mice (Avishai-Eliner et al., 1999). Interestingly, this effect was stronger in males than in females. Early stress was also associated with lower concentrations of BDNF (Jeanne-teau and Chao, 2013). Schulte-Herbrüggen et al. (2007) demonstrated lower concentrations of BDNF in the parietal cortex in mice with genetically reduced GR expression. Early and chronic stress is assumed to dramatically increase glucocorticoid concentrations which might lead to long-term potentiation of the GR system (Deppermann et al., 2014; Pariante, 2006). Assuming this potentiation to be associated with brain alterations, an overproduction of corticosterone was associated with lower anterior cingulate volumes in rats (Cerqueira et al., 2005). Analogous, Andela et al. (2015) reported lower cortical volume and larger ventricles in patients with Cushing's syndrome. Cushing's syndrome is often comorbid with depressive disorders (Gray et al., 2017).

Postmortem, a reduced number and size of glia cells in the anterior cingulate cortex as well as reduced GR mRNA expression in the frontal and temporal cortex were reported in depressed patients (Cotter et al., 2001; Webster et al., 2002). In rats, antidepressant treatment increased the GR mRNA expression in the hippocampus but not the parietal cortex (Seckl and Fink, 1992). However, another study associated a higher corticosterone exposure in rats due to social defeat with a late decrease in GR binding affinity in the parietal cortex (Buwalda et al., 2001). Hence, the latency and the size of the effect of high cortisol concentrations might differ in various brain regions. Although increased cortisol concentrations impact the GR activity and morphology in cortical structure, the exact mechanisms and effects particularly on cortical thickness are still elusive.

In sex-stratified analyses, we observed associations between serum cortisol concentrations and cortical thickness in men but not in women. As demonstrated before and replicated here, serum cortisol concentrations were higher in men than in women (Stalder et al., 2017). As the entry of circulating cortisol to the brain is hampered by the blood-brain barrier, one might assume that high cortisol concentrations are needed to induce cortical thinning. Thus, lower serum cortisol concentrations in women might explain the missing associations between cortisol and cortical thickness in females in the present work. In line, Kaji et al. (2008) reported cortisol concentrations to be associated with thinner cortex in premenopausal women with Cushing's syndrome but not in healthy premenopausal or postmenopausal women. Further, Juster et al. (2016) reported greater diurnal variation in saliva cortisol concentrations in women which have also been associated with more cortical thickness and thus, would counteract the inverse effects of higher basal cortisol concentrations on cortical thickness.

Higher cortisol concentrations have been related to lower cortical thickness before (Liu et al., 2015; Kaji et al., 2008; Kremen et al., 2010) but sex differences, so far, have not been clearly identified. On the one hand, our results fit previous findings of Kremen et al. (2010) who reported inverse associations between saliva cortisol concentrations and cortical thickness of the prefrontal cortex in a male sample. On the other hand, Stomby et al. (2016) reported only small sex differences in the associations between regional cortical thickness and saliva cortisol concentrations, too small to reach significance in 100 elderly women and 100 elderly men. In contrast to Stomby et al. (2016), our data were based on more than 2500 participants including a wider age range (21–90 years vs. 55–80 years). Additionally, the present analyses were based on an epidemiological sample. In contrast, Liu et al. (2015) investigated the association between cortical thickness and serum cortisol concentrations in depressed patients but observed inverse associations independent of sex. The severity and range of depressive symptoms were low in our sample. Nevertheless, adjusting for depressive symptoms and childhood maltreatment did not affect our results.

Our data supported higher cortical thickness in women and stronger age-related cortical thinning in men (Cowell et al., 1994; Savic and Arver, 2014; Sowell et al., 2007). Regionally, sex differences in cortical thickness were reported in the frontal, parietal and temporal cortex before (Sowell et al., 2007). These regions match the cortical regions associated with cortisol concentrations in our data. Further, Savic and Arver (2014) reported an inverse association between cortical thickness and testosterone concentrations as well as a positive association between cortical thickness and estradiol concentrations both in the parietal cortex. Hence, sex differences in the associations between cortisol concentrations and cortical thickness observed in our study match sex differences reported before and might be influenced by an interaction of the HPA and HPG axis.

Juster et al. (2016) reported sex differences in saliva cortisol concentrations only after adjusting for testosterone concentrations. In contrast, including testosterone, estrone or estradiol concentrations in our data reduced the sex differences in serum cortisol concentrations. Using basal serum cortisol concentrations in our study instead of diurnal slope and stress-reactive saliva cortisol concentrations (Juster et al.,

2016) might partly explain the discrepancy. In the interpretation of our results, however, a possible collinearity issue between sex and testosterone concentrations need to be concerned. Nevertheless, collinearity was of no concern for estrone and estradiol concentrations and results including testosterone, estrone and estradiol concentrations were similar to each other. Analogous to the sex differences in serum cortisol concentrations, the interaction between the HPA and HPG axis might partly explain the associations between serum cortisol concentrations and cortical thickness. Nevertheless, testosterone, estrone and estradiol concentrations were only available for a subset of the present sample. The statistical power of the reduced sample, however, was too small to replicate the associations between serum cortisol concentrations and cortical thickness (data not presented). Thus, we could not evaluate the statistical meaning of adding the sex hormone concentrations to these association analyses. No doubt, the analyses would be of prime importance to understand the relationship between cortisol concentrations and cortical thickness in more detail and to deepen the insight into neurobiological effects of the interaction between the HPA and HPG axis.

Besides the biological sex, the experience of severe and chronic stress (Fogelman and Canli, 2018; Yehuda et al., 2009) and mental symptoms (Heim et al., 2001, 2008; Meewisse et al., 2007) have been repeatedly reported to influence basal cortisol concentrations. According to Heim et al. (2008), blunted basal cortisol concentrations after lasting external (e.g. childhood maltreatment) or internal stress (e.g. depressive symptoms) depict an increased sensitization of the HPA axis. This biological adjustment could also lead to the protection of other biological systems. Thus, lower serum cortisol concentrations were demonstrated to be associated with higher cortical thickness in our data. Interestingly, some of the cortical regions associated with serum cortisol concentrations in men in our analyses have been associated with stress or trauma before: Wrocklage et al. (2017) reported lower cortical thickness in the isthmus-cingulate cortex and the superior parietal cortex to be associated with higher PTSD symptomatology. Michalski et al. (2017) observed the thickness of the rostral middle frontal gyrus to be inversely associated with perceived stress. Corbo et al. (2016) reported cortical thinning within the rostral middle frontal cortex, the pars orbitalis, the pars triangularis, the superior temporal gyrus and the superior parietal cortex after combat exposure.

High cortisol concentrations due to childhood maltreatment lead to a sensitization of the HPA axis during childhood and adolescents, probably including neuronal changes (Heim et al., 2008; Groeneweg et al., 2011). Hence, lower cortical thickness after childhood maltreatment might be a long-term result of early adaptation (Kelly et al., 2013; Wang et al., 2016). Simultaneously, childhood maltreatment is strongly associated with major depression (Kessler, 1997; Paykel, 2001). In our data, the effect of childhood maltreatment on serum cortisol concentrations was independent of depressive symptoms. In contrast to previous reports (Yehuda et al., 2009; Heim et al., 2001, 2008), however, the association between depressive symptoms and serum cortisol concentrations was not independent of childhood maltreatment. Whereas childhood maltreatment precedes cortical thickness in adulthood, causality between cortical thickness and depressive symptoms cannot be evaluated in cross-sectional analyses as done in the present study. In patients with depression, higher cortisol concentrations were associated with more severe courses and treatment resistance (Fischer et al., 2017; Stetler and Miller, 2011). Higher cortisol concentrations in saliva and blood had been associated with lower cortical thickness in depressed patients (Liu et al., 2015; Lebedeva et al., 2018) mirroring the present results in the general population. Although the present study replicated the inverse associations between serum cortisol concentrations and childhood maltreatment (Fogelman and Canli, 2018) and depressive symptoms (Heim et al., 2001, 2008), these relations did not explain the association between serum cortisol concentrations and cortical thickness. Nevertheless, the severity and range of childhood maltreatment and depressive symptoms were low in our sample.

Integrating the interaction of the HPA and HPG axis (Gray et al., 2017; Juster et al., 2016; Woods et al., 2006) with the theory of sensitization of the HPA axis (Heim et al., 2008), greater variation in female sex hormone concentrations was related to more depressive symptoms (Vivian-Taylor and Hickey, 2014; Ryan et al., 2009). Further, childhood maltreatment has been associated with several negative female-specific health outcomes such as higher rates of amenorrhea, lower fertility and delayed menopause (Allsworth et al., 2004; Jacobs et al., 2015). Thus, due to more pronounced variation in the hormonal concentrations, women might have a higher vulnerability to basal cortisol alterations influencing the relation of basal cortisol concentrations and cortical thickness (Juster et al., 2016).

Sex differences in the associations between basal cortisol concentrations and cortical thickness have been hardly researched so far (Stomby et al., 2016) and thus, our study adds important information to the literature, particularly as it is based on a large epidemiological sample. Thorough adjustment for multiple potential confounders is another unique characteristic of the present work. Earlier studies investigating sex-specific associations with cortisol concentrations were based on rather small sample sizes (Stomby et al., 2016; Stalder et al., 2017) or included patients with selected diseases as functional somatic disorders or PTSD (Meewisse et al., 2007; Tak et al., 2011). In contrast, our analyses were based on more than 2500 individuals from the general population. At least part of our analyses included serum concentrations of testosterone, estrone and estradiol which is novel, particularly based on a sample size of more than 500 participants. Although the interaction between the HPA and HPG axis was discussed before (Gray et al., 2017), sex hormone concentrations were rarely included in analyses focusing on cortisol concentrations so far (Juster et al., 2016).

4.1. Limitations

The present results were based on cross-sectional analyses using a large sample size. Thus, no causal conclusions can be drawn from a statistical point of view. All analyses were based on basal serum cortisol concentrations. Neither cortisol reactivity to stress tests nor longitudinal cortisol concentrations were available.

Serum cortisol and sex hormone concentrations were determined in single blood samples obtained in the mornings. As SHIP is focusing on a comprehensive assessment of the individual's general health status rather than hormonal variations, no additional blood sampling was available. The exact time of blood sampling was included in the regression analyses and modelled non-linearly to adjust for effects of the circadian rhythm. The serum cortisol concentrations were validated in a multi-omics study including cortisol-related transcriptome before (Hertel et al., 2017). Unfortunately, there was no information on the wake-up time of the participants and thus, we were unable to adjust for this confounding effect. Additionally, information about physical activity directly before the blood sampling was not available.

An interaction between sex hormones and the HPA axis was discussed before, partly by activating the same receptors or paralleled receptor density (Gray et al., 2017; Bourke et al., 2012; Juster et al., 2011). Further, sex differences in cortisol concentrations were reported after the adjustment for sex hormone concentrations hinting at potential suppressor effects (Juster et al., 2016). Thus, the effects of sex hormones and cortisol might add up or inhibit each other. Therefore, we decided to add sex hormones as potential confounders in the present analyses instead of testing potential interaction effects. Nevertheless, potential interaction effects should also be tested in future studies. Additionally, a possible collinearity problem between testosterone concentrations and sex was observed in our data. This should be kept in mind in future studies by focusing on various sex hormone concentrations and heading to sex-separated analyses as partly provided in our study.

Although we excluded OC users from the analyses, pre- and postmenopausal women were included without researching potential differences between them. Moreover, no detailed information about the

stages of the menstrual cycle was included for premenopausal women. According to a review of Baker and Driver (2007), results on varying cortisol concentrations during the menstrual cycle are inconsistent including, on the one hand, studies reporting no variation in basal cortisol concentrations (Liening et al., 2010) and, on the other hand, studies observing lower basal cortisol concentrations in the follicular than in the luteal phase (Genazzani et al., 1975; Shibui et al., 2000). As the present study aimed to focus on sex differences rather than altering cortisol concentrations due to the menstrual and reproductive cycle in women, our analyses were not forced in this direction. Nevertheless, future studies investigating these associations are highly important.

Finally, sex-differences were observed for smoking status and alcohol consumption which are not tied to the biological sex but are associated with altered HPA axis activity. Although we adjusted all analyses for these confounders, we cannot rule out that the observed sex differences in the serum cortisol concentrations might partly rely on sex differences in these two variables. Further, we had neither information on the age of onset or duration of the childhood maltreatment nor about lifetime depression history or duration of depressive symptoms.

4.2. Conclusions

The present study demonstrated sex-specific associations between serum cortisol concentrations and cortical thickness. In advantage to previous studies primarily investigating associations between cortisol concentrations and subcortical regions (Gray et al., 2017; Kremen et al., 2011), our analyses focused on cortical thickness. Associations clustered in the frontal, temporal and parietal cortex. All of these regions were associated with stress-induced alterations in GR activity and GR mRNA expression before (Avishai-Eliner et al., 1999; Schulte-Herbrüggen et al., 2007; Cerqueira et al., 2005; Cotter et al., 2001; Webster et al., 2002; Buwalda et al., 2001). However, future studies including cortical surface or comparing effects in cortical and subcortical regions, as well as studies focusing on regions with a high GR density are important to validate our results.

Childhood maltreatment and depressive symptoms, often discussed in relation to cortisol concentrations and cortical thickness (Fogelman and Canli, 2018; Heim et al., 2008; Liu et al., 2015; Wang et al., 2016), did not diminish the inverse association between serum cortisol concentrations and cortical thickness in our male sample. Although the interaction of the HPA and HPG axis was demonstrated to be very important for the sex differences in basal serum cortisol concentrations, the present data were not applicable to test similar influences on the association between serum cortisol concentrations and cortical thickness. Future studies are needed to close this gap.

5. Ethics

The data collection and all analyses conducted in the present manuscript were performed according to the Declaration of Helsinki, including the written informed consent of all participants. All examinations and methods of the SHIP studies were approved by the institutional review board of the University Greifswald.

Funding sources

SHIP is part of the Community Medicine Research net of the University of Greifswald which is funded by the Federal Ministry of Education and Research (01ZZ9603, 01ZZ0103 and 01ZZ0403), the Ministry of Cultural Affairs and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Whole-body MRI was supported by a joint grant from Siemens Healthineers, Erlangen, Germany and the Federal State of Mecklenburg West Pomerania. This study was supported by the EU-JPND Funding for BRIDGET (FKZ:01ED1615) and the National Institute of Health (NIH) grant AG059421.

Author contributions

JKK and HJG designed the present project. JKK conceived and performed the statistical analyses. SF supported the statistical analyses. JKK wrote the manuscript and was responsible for the visualization of the results. HJG supervised the project. SF, KW and RB processed the MRI data. AH, NF and MN managed the laboratory assessments. MN, HV and HJG were part of the data curation and funding acquisition. All authors have read and agreed to the submitted version of the manuscript.

CRedit authorship contribution statement

Johanna Klinger-König: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Stefan Frenzel:** Methodology, Data curation, Writing – review & editing. **Anke Hannemann:** Resources, Data curation, Writing – review & editing. **Katharina Wittfeld:** Data curation, Writing – review & editing. **Robin Bülow:** Resources, Writing – review & editing. **Nele Friedrich:** Resources, Writing – review & editing. **Matthias Nauck:** Resources, Writing – review & editing, Project administration. **Henry Völzke:** Writing – review & editing, Project administration, Funding acquisition. **Hans J. Grabe:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

HJG has received travel grants and speakers honoraria from Fresenius Medical Care, Neuraxpharm, Servier and Janssen Cilag.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jynstr.2021.100416>.

References

- Adam, E.K., Quinn, M.E., Tavernier, R., McQuillan, M.T., Dahlke, K.A., Gilbert, K.E., 2017. Diurnal cortisol slopes and mental and physical health outcomes: a systematic review and meta-analysis. *Psychoneuroendocrinology* 83, 25–41.
- Allsworth, J.E., Zierler, S., Lapane, K.L., Krieger, N., Hogan, J.W., Harlow, B.L., 2004. Longitudinal study of the inception of perimenopause in relation to lifetime history of sexual or physical violence. *J. Epidemiol. Community Health* 58, 938–943.
- Alonso, G., 2000. Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia* 31, 219–231.
- Andela, C.D., van Haalen, F.M., Ragnarsson, O., Papakokkinou, E., Johannsson, G., Santos, A., Webb, S.M., Biermasz, N.R., van der Wee, N.J.A., Pereira, A.M., 2015. Mechanisms in endocrinology: cushing's syndrome causes irreversible effects on the human brain: a systematic review of structural and functional magnetic resonance imaging studies. *Eur. J. Endocrinol.* 173, R1–R14.
- ATC-Index, 2007. Anatomisch-therapeutisch-chemische Klassifikation mit Tagesdosen: Amtliche Fassung des ATC-Index mit DD-Angaben für Deutschland.
- Avishai-Eliner, S., Hatalski, C.G., Tabachnik, E., Eghbal-Ahmadi, M., Baram, T.Z., 1999. Differential regulation of glucocorticoid receptor messenger RNA (GR-mRNA) by maternal deprivation in immature rat hypothalamus and limbic regions. *Dev. Brain Res.* 114, 265–268.
- Baker, F.C., Driver, H.S., 2007. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Med.* 8, 613–622.
- Baumeister, S.E., Alte, D., Meyer, C., John, U., 2005. Riskanter Alkoholkonsum und alkoholbezogene Störungen in Vorpommern: die Studie "Leben und Gesundheit in Vorpommern" (SHIP) und der Bundesgesundheitsurvey 1998 im Vergleich. *Gesundheitswesen* 67, 39–47.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery rate: a practical and powerful approach to multiple testing. *J. Roy. Stat. Soc. B* 57, 289–300.
- Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl.* 27, 169–190.
- Bourke, C.H., Harrell, C.S., Neigh, G.N., 2012. Stress-induced sex differences: adaptations mediated by the glucocorticoid receptor. *Horm. Behav.* 62, 210–218.
- Buwalda, B., Felszeghy, K., Horváth, K.M., Nyakas, C., Boer, S.F. de, Bohus, B., Koolhaas, J.M., 2001. Temporal and spatial dynamics of corticosteroid receptor down-regulation in rat brain following social defeat. *Physiol. Behav.* 72, 349–354.
- Cerqueira, J.J., Catania, C., Sotiropoulos, I., Schubert, M., Kalisch, R., Almeida, O.F.X., Auer, D.P., Sousa, N., 2005. Corticosteroid status influences the volume of the rat cingulate cortex - a magnetic resonance imaging study. *J. Psychiatr. Res.* 39, 451–460.
- Corbo, V., Salat, D.H., Powell, M.A., Milberg, W.P., McGlinchey, R.E., 2016. Combat exposure is associated with cortical thickness in Veterans with a history of chronic pain. *Psychiatry Res. Neuroimaging* 249, 38–44.
- Cotter, D., Mackay, D., Landau, S., Kerwin, R., Everall, I., 2001. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch. Gen. Psychiatr.* 58, 545–553.
- Cowell, P.E., Turetsky, B.I., Gur, R.C., Grossman, R.I., Shtasel, D.L., Gur, R.E., 1994. Sex differences in aging of the human frontal and temporal lobes. *J. Neurosci.* 14, 4748–4755.
- Cumming, D.C., Quigley, M.E., Yen, S.S., 1983. Acute suppression of circulating testosterone levels by cortisol in men. *J. Clin. Endocrinol. Metab.* 57, 671–673.
- Deppermann, S., Storchak, H., Fallgatter, A.J., Ehls, A.-C., 2014. Stress-induced neuroplasticity: (mal)adaptation to adverse life events in patients with PTSD—a critical overview. *Neuroscience* 283, 166–177.
- Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31, 968–980.
- Drevets, W.C., 2004. Neuroplasticity in mood disorders. *Dialogues Clin. Neurosci.* 6, 199–216.
- Eick, C., Klinger-König, J., Zylla, S., Hannemann, A., Budde, K., Henning, A.K., Pietzner, M., Nauck, M., Völzke, H., Grabe, H.J., Hertel, J., 2021. Broad metabolome alterations associated with the intake of oral contraceptives are mediated by cortisol in premenopausal women. *Metabolites* 11, 193.
- Enzinger, C., Fazekas, F., Matthews, P.M., Ropele, S., Schmidt, H., Smith, S., Schmidt, R., 2005. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology* 64, 1704–1711.
- Fischer, S., Strawbridge, R., Vives, A.H., Cleare, A.J., 2017. Cortisol as a predictor of psychological therapy response in depressive disorders: systematic review and meta-analysis. *BJP* 210, 105–109.
- Fogelman, N., Canli, T., 2018. Early life stress and cortisol: a meta-analysis. *Horm. Behav.* 98, 63–76.
- Genazzani, A.R., Lemarchand-Béraud, T., Aubert, M.L., Felber, J.P., 1975. Pattern of plasma ACTH, hGH, and cortisol during menstrual cycle. *J. Clin. Endocrinol. Metab.* 41, 431–437.
- Gnjidić, Z., Sajko, T., Kudelić, N., Malenica, M., Vizner, B., Vrkljan, M., Hat, J., Rumboldt, Z., 2008. Reversible "brain atrophy" in patients with Cushing's disease. *Coll. Antropol.* 32, 1165–1170.
- Gordon, J.L., Eisenlohr-Moul, T.A., Rubinow, D.R., Schrubbe, L., Girdler, S.S., 2016. Naturally occurring changes in estradiol concentrations in the menopause transition predict morning cortisol and negative mood in perimenopausal depression. *Clin. Psychol Sci* 4, 919–935.
- Gray, J.D., Kogan, J.F., Marrocco, J., McEwen, B.S., 2017. Genomic and epigenomic mechanisms of glucocorticoids in the brain. *Nat. Rev. Endocrinol.* 13, 661–673.
- Groeneweg, F.L., Karst, H., de Kloet, E.R., Joëls, M., 2011. Rapid non-genomic effects of corticosteroids and their role in the central stress response. *J. Endocrinol.* 2, 153–167.
- Haring, R., Hannemann, A., John, U., Radke, D., Nauck, M., Wallaschofski, H., Owen, L., Adaway, J., Keevil, B.G., Brabant, G., 2012. Age-specific reference ranges for serum testosterone and androstenedione concentrations in women measured by liquid chromatography-tandem mass spectrometry. *J. Clin. Endocrinol. Metab.* 97, 408–415.
- Häuser, W., Schmutz, G., Brähler, E., Glaesmer, H., 2011. Maltreatment in childhood and adolescence: results from a survey of a representative sample of the German population. *Dtsch Arztebl Int* 108, 287–294.
- Hegenscheid, K., Seipel, R., Schmidt, C.O., Völzke, H., Kühn, J.-P., Biffar, R., Kroemer, H. K., Hosten, N., Puls, R., 2013. Potentially relevant incidental findings on research whole-body MRI in the general adult population: frequencies and management. *Eur. Radiol.* 23, 816–826.
- Heim, C., Newport, D.J., Bonsall, R., Miller, A.H., Nemeroff, C.B., 2001. Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *Am. J. Psychiatr.* 158, 575–581.
- Heim, C.M., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* 33, 693–710.
- Hertel, J., König, J., Homuth, G., Van der Auwera, S., Wittfeld, K., Pietzner, M., Kacprowski, T., Pfeiffer, L., Kretschmer, A., Waldenberger, M., Kastenmüller, G., Artati, A., Suhre, K., Adamski, J., Langner, S., Völker, U., Völzke, H., Nauck, M., Friedrich, N., Grabe, H.J., 2017. Evidence for stress-like alterations in the HPA-Axis in women taking oral contraceptives. *Sci. Rep.* 7, 14111.
- Jacobs, M.B., Boynton-Jarrett, R.D., Harville, E.W., 2015. Adverse childhood event experiences, fertility difficulties and menstrual cycle characteristics. *J. Psychosom. Obstet. Gynaecol.* 36, 46–57.
- Janowitz, D., Wittfeld, K., Terock, J., Freyberger, H.J., Hegenscheid, K., Völzke, H., Habes, M., Hosten, N., Friedrich, N., Nauck, M., Domanska, G., Grabe, H.J., 2015. Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples. *Neuroimage* 122, 149–157.

- Jeanneteau, F., Chao, M.V., 2013. Are BDNF and glucocorticoid activities calibrated? *Neuroscience* 239, 173–195.
- Joëls, M., de Kloet, E.R., 2017. 30 Years of the Mineralocorticoid Receptor: the brain mineralocorticoid receptor: a saga in three episodes. *J. Endocrinol.* 234, T49–T66.
- John, U., Hensel, E., Ldemann, J., Piek, M., Sauer, S., Adam, C., Born, G., Alte, D., Greiser, E., Haertel, U., Hense, H.-W., Haerting, J., Willich, S., Kessler, C., 2001. Study of Health in Pomerania (SHIP): a health examination survey in an east German region: objectives and design. *Soz.-Präventivmed.* 46, 186–194.
- Juster, R.-P., Bizik, G., Picard, M., Arsénault-Lapierre, G., Sindi, S., Trepanier, L., Marin, M.-F., Wan, N., Sekerovic, Z., Lord, C., Fiocco, A.J., Plusquellec, P., McEwen, B.S., Lupien, S.J., 2011. A transdisciplinary perspective of chronic stress in relation to psychopathology throughout life span development. *Dev. Psychopathol.* 23, 725–776.
- Juster, R.-P., Raymond, C., Desrochers, A.B., Bourdon, O., Durand, N., Wan, N., Pruessner, J.C., Lupien, S.J., 2016. Sex hormones adjust “sex-specific” reactive and diurnal cortisol profiles. *Psychoneuroendocrinology* 63, 282–290.
- Kaji, H., Yamauchi, M., Chihara, K., Sugimoto, T., 2008. Glucocorticoid excess affects cortical bone geometry in premenopausal, but not postmenopausal, women. *Calcif. Tissue Int.* 82, 182–190.
- Karama, S., Ducharme, S., Corley, J., Chouinard-Decorte, F., Starr, J.M., Wardlaw, J.M., Bastin, M.E., Deary, I.J., 2015. Cigarette smoking and thinning of the brain’s cortex. *Mol. Psychiatry* 20, 778–785.
- Kelly, P.A., Viding, E., Wallace, G.L., Schaer, M., Brito, S.A., Robustelli, B., McCrory, E. J., 2013. Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: neural markers of vulnerability? *Biol. Psychiatry* 74, 845–852.
- Kessler, R.C., 1997. The effects of stressful life events on depression. *Annu. Rev. Psychol.* 48, 191–214.
- Kremen, W.S., O’Brien, R.C., Panizzon, M.S., Prom-Wormley, E., Eaves, L.J., Eisen, S.A., Eyler, L.T., Hauger, R.L., Fennema-Notestine, C., Fischl, B., Grant, M.D., Hellhammer, D.H., Jak, A.J., Jacobson, K.C., Jernigan, T.L., Lupien, S.J., Lyons, M.J., Mendoza, S.P., Neale, M.C., Seidman, L.J., Thermenos, H.W., Tsuang, M.T., Dale, A. M., Franz, C.E., 2010. Salivary cortisol and prefrontal cortical thickness in middle-aged men: a twin study. *Neuroimage* 53, 1093–1102.
- Kremen, W.S., Panizzon, M.S., Lyons, M.J., Franz, C.E., 2011. Cortisol and brain: beyond the hippocampus. *Biol. Psychiatry* 69, e9. ; author reply e11.
- Kroenke, K., Spitzer, R.L., 2002. The PHQ-9: a new depression diagnostic and severity measure. *Psychiatr. Ann.* 32, 509–515.
- Lebedeva, A., Sundström, A., Lindgren, L., Stomby, A., Aarsland, D., Westman, E., Winblad, B., Olsson, T., Nyberg, L., 2018. Longitudinal relationships among depressive symptoms, cortisol, and brain atrophy in the neocortex and the hippocampus. *Acta Psychiatr. Scand.* 137, 491–502.
- Liening, S.H., Stanton, S.J., Saini, E.K., Schultheiss, O.C., 2010. Salivary testosterone, cortisol, and progesterone: two-week stability, interhormone correlations, and effects of time of day, menstrual cycle, and oral contraceptive use on steroid hormone levels. *Physiol. Behav.* 99, 8–16.
- Liu, X., Kakeda, S., Watanabe, K., Yoshimura, R., Abe, O., Ide, S., Hayashi, K., Katsuki, A., Umeno-Nakano, W., Watanabe, R., Ueda, I., Moriya, J., Nakamura, J., Korogi, Y., 2015. Relationship between the cortical thickness and serum cortisol levels in drug naïve, first-episode patients with major depressive disorder: a surface-based morphometric study. *Depress. Anxiety* 32, 702–708.
- Liu, J.J.W., Ein, N., Peck, K., Huang, V., Pruessner, J.C., Vickers, K., 2017. Sex differences in salivary cortisol reactivity to the Trier Social Stress Test (TSST): a meta-analysis. *Psychoneuroendocrinology* 82, 26–37.
- McEwen, B.S., 2004. Structural plasticity of the adult brain: how animal models help us understand brain changes in depression and systemic disorders related to depression. *Dialogues Clin. Neurosci.* 6, 119–133.
- Meewisse, M.-L., Reitsma, J.B., Vries, G.-J de, Gersons, B.P.R., Olff, M., 2007. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *BJP* 191, 387–392.
- Michalski, L.J., Demers, C.H., Baranger, D.A.A., Barch, D.M., Harms, M.P., Burgess, G.C., Bogdan, R., 2017. Perceived stress is associated with increased rostral middle frontal gyrus cortical thickness: a family-based and discordant-sibling investigation. *Gene Brain Behav.* 16, 781–789.
- Mifsud, K.R., Reul, J.M.H.M., 2018. Mineralocorticoid and glucocorticoid receptor-mediated control of genomic responses to stress in the brain. *Stress* 21, 389–402.
- Oinonen, K.A., Mazmanian, D., 2002. To what extent do oral contraceptives influence mood and affect? *J. Affect. Disord.* 70, 229–240.
- Pariante, C.M., 2006. The glucocorticoid receptor: part of the solution or part of the problem? *J. Psychopharmacol.* 20, 79–84.
- Patil, C.G., Lad, S.P., Katznelson, L., Laws, E.R., 2007. Brain atrophy and cognitive deficits in Cushing’s disease. *Neurosurg. Focus* 23, E11.
- Paykel, E.S., 2001. The evolution of life events research in psychiatry. *J. Affect. Disord.* 62, 141–149.
- Pittenger, C., Duman, R.S., 2008. Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology* 33, 88–109.
- Rajkowska, G., 2000. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol. Psychiatry* 48, 766–777.
- Ryan, J., Burger, H.G., Szoek, C., Leher, P., Ancelin, M.-L., Henderson, V.W., Dennerstein, L., 2009. A prospective study of the association between endogenous hormones and depressive symptoms in postmenopausal women. *Menopause* 16, 509–517.
- Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S.R., Busa, E., Morris, J. C., Dale, A.M., Fischl, B., 2004. Thinning of the cerebral cortex in aging. *Cerebr. Cortex* 14, 721–730.
- Savic, I., Arver, S., 2014. Sex differences in cortical thickness and their possible genetic and sex hormonal underpinnings. *Cerebr. Cortex* 24, 3246–3257.
- Schulte-Herbrüggen, O., Hellweg, R., Chourbaji, S., Ridder, S., Brandwein, C., Gass, P., Hörtnagl, H., 2007. Differential regulation of neurotrophins and serotonergic function in mice with genetically reduced glucocorticoid receptor expression. *Exp. Neurol.* 204, 307–316.
- Seckl, J.R., Fink, G., 1992. Antidepressants increase glucocorticoid and mineralocorticoid receptor mRNA expression in rat hippocampus in vivo. *Neuroendocrinology* 55, 621–626.
- Senaviratna, N.A.M.R., Cooray, T.M.J.A., 2019. Diagnosing Multicollinearity of Logistic Regression Model, vol. 1, pp. 1–9. <http://www.journalajpas.com/index.php/ajpas/article/view/30132>.
- Seyfart, T., Friedrich, N., Kische, H., Bülow, R., Wallaschowski, H., Völzke, H., Nauck, M., Keevil, B.G., Haring, R., 2018. Association of sex hormones with physical, laboratory, and imaging markers of anthropometry in men and women from the general population. *PLoS One* 13, e0189042.
- Shibui, K., Uchiyama, M., Okawa, M., Kudo, Y., Kim, K., Liu, X., Kamei, Y., Hayakawa, T., Akamatsu, T., Ohta, K., Ishibashi, K., 2000. Diurnal fluctuation of sleep propensity and hormonal secretion across the menstrual cycle. *Biol. Psychiatry* 48, 1062–1068.
- Simmons, N.E., Do, H.M., Lipper, M.H., Laws, E.R., 2000. Cerebral atrophy in Cushing’s disease. *Surg. Neurol.* 53, 72–76.
- Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., Xu, D., Zhu, H., Thompson, P.M., Toga, A.W., 2007. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebr. Cortex* 17, 1550–1560.
- Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., Kirschbaum, C., Miller, R., 2017. Stress-related and basic determinants of hair cortisol in humans: a meta-analysis. *Psychoneuroendocrinology* 77, 261–274.
- Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosom. Med.* 73, 114–126.
- Stomby, A., Boraxbekk, C.-J., Lundquist, A., Nordin, A., Nilsson, L.-G., Adolfsson, R., Nyberg, L., Olsson, T., 2016. Higher diurnal salivary cortisol levels are related to smaller prefrontal cortex surface area in elderly men and women. *Eur. J. Endocrinol.* 175, 117–126.
- Swainson, M.G., Batterham, A.M., Tsakirides, C., Rutherford, Z.H., Hind, K., 2017. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLoS One* 12, e0177175.
- Tak, L.M., Cleare, A.J., Ormel, J., Manoharan, A., Kok, I.C., Wessely, S., Rosmalen, J.G. M., 2011. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. *Biol. Psychiatry* 87, 183–194.
- Vivian-Taylor, J., Hickey, M., 2014. Menopause and depression: is there a link? *Maturitas* 79, 142–146.
- Völzke, H., Alte, D., Schmidt, C.O., Radke, D., Lorbeer, R., Friedrich, N., Aumann, N., Lau, K., Piontek, M., Born, G., Havemann, C., Ittermann, T., Schipf, S., Haring, R., Baumeister, S.E., Wallaschowski, H., Nauck, M., Frick, S., Arnold, A., Junger, M., Mayerle, J., Kraft, M., Lerch, M.M., Dorr, M., Refellmann, T., Empen, K., Felix, S.B., Obst, A., Koch, B., Glaser, S., Ewert, R., Fietze, I., Penzel, T., Doren, M., Rothmann, W., Haerting, J., Hannemann, M., Ropcke, J., Schminke, U., Jurgens, C., Tost, F., Rettig, R., Kors, J.A., Ungerer, S., Hegenscheid, K., Kuhn, J.-P., Kuhn, J., Hosten, N., Puls, R., Henke, J., Gloger, O., Teumer, A., Homuth, G., Volker, U., Schwahn, C., Holtfreter, B., Polzer, I., Kohlmann, T., Grabe, H.J., Rosskopf, D., Kroemer, H.K., Kocher, T., Biffar, R., John, U., Hoffmann, W., 2011. Cohort profile: the study of health in Pomerania. *Int. J. Epidemiol.* 40, 294–307.
- Wahl, I., Lowe, B., Bjorner, J.B., Fischer, F., Langs, G., Voderholzer, U., Aita, S.A., Bergemann, N., Brähler, E., Rose, M., 2014. Standardization of depression measurement: a common metric was developed for 11 self-report depression measures. *J. Clin. Epidemiol.* 67, 73–86.
- Wang, L., Yang, L., Yu, L., Song, M., Zhao, X., Gao, Y., Han, K., An, C., Xu, S., Wang, X., 2016. Childhood physical neglect promotes development of mild cognitive impairment in old age - a case-control study. *Psychiatr. Res.* 242, 13–18.
- Webster, M.J., Knable, M.B., O’Grady, J., Orthmann, J., Weickert, C.S., 2002. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol. Psychiatry* 7, 985–994, 924.
- Weiser, M.J., Handa, R.J., 2009. Estrogen impairs glucocorticoid dependent negative feedback on the hypothalamic-pituitary-adrenal axis via estrogen receptor alpha within the hypothalamus. *Neuroscience* 159, 883–895.
- Wierenga, L.M., Langen, M., Oranje, B., Durston, S., 2014. Unique developmental trajectories of cortical thickness and surface area. *Neuroimage* 87, 120–126.
- Winter, T., Friedrich, N., Lamp, S., Schäfer, C., Schattschneider, M., Bollmann, S., Brümmer, D., Riemann, K., Petersmann, A., Nauck, M., 2020. The integrated research Biobank of the university medicine Greifswald. *Open J. Bioresour.* 7.
- Wintjen, L., Petermann, F., 2010. Beck-depressions-inventar revision (BDI-II). *Z. Psychiatr. Psychol. Psychother.* 58, 243–245.
- Woods, N.F., Carr, M.C., Tao, E.Y., Taylor, H.J., Mitchell, E.S., 2006. Increased urinary cortisol levels during the menopausal transition. *Menopause* 13, 212–221.
- Wrocklage, K.M., Averill, L.A., Cobb Scott, J., Averill, C.L., Schweinsburg, B., Trejo, M., Roy, A., Weissner, R., Kelly, C., Martini, B., Harpaz-Rotem, I., Southwick, S.M., Krystal, J.H., Abdallah, C.G., 2017. Cortical thickness reduction in combat exposed U.S. veterans with and without PTSD. *Eur. Neuropsychopharmacol.* 27, 515–525.
- Yehuda, R., Bierer, L.M., Andrew, R., Schmeidler, J., Seckl, J.R., 2009. Enduring effects of severe developmental adversity, including nutritional deprivation, on cortisol metabolism in aging Holocaust survivors. *J. Psychiatr. Res.* 43, 877–883.