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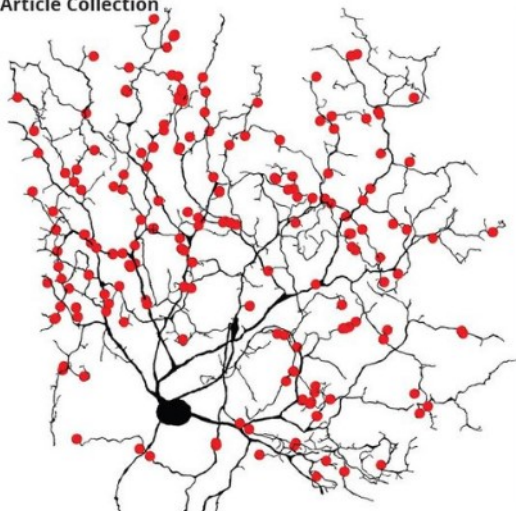
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Through this article collection, we hope to provide researchers with more information on the application of volume electron microscopy techniques, allowing them to further their research in this field.

RESEARCH REPORT

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Associations between cortisol stress responses and limbic volume and thickness in young adults: An exploratory study

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Abstract

The investigation of the relationship between neural measures of limbic structures and hypothalamic pituitary adrenal axis responses to acute stress exposure in healthy young adults has so far focused in particular on task-based and resting state functional connectivity studies. Thus, the present study examined the association between limbic volume and thickness measures and acute cortisol responses to the psychosocial stress paradigm Scan*STRESS*. Using Permutation Analysis of Linear Models controlling for sex, age and total brain volume, the associations between (sex-specific) cortisol increases and human connectome project style anatomical variables of limbic structures (i.e. volume and thickness) were investigated in 66 healthy and young (18–33 years) subjects (35 men, 31 women taking oral contraceptives). In addition, exploratory (sex-specific) bivariate correlations between cortisol increases and structural measures were conducted. The present data provide interesting new insights into the involvement of striato-limbic structures in psychosocial stress processing, suggesting that acute cortisol stress responses are also associated with mere structural measures of the human brain. Thus, our preliminary findings suggest that not only situation- and context-dependent reactions of the limbic

Abbreviations: AUC, area under the curve; BOLD, blood oxygenation level dependent; cACC, caudal anterior cingulate cortex; DELFIA, dissociation-enhanced lanthanide fluorescence immunoassay; FWER, family-wise error rate; fMRI, functional magnetic resonance imaging; Glc-Tea, glucose tea; HCP, Human Connectome Project; HPA axis, hypothalamic pituitary adrenal axis; lOFC, lateral orbitofrontal cortex; mOFC, medial orbitofrontal cortex; OCs, oral contraceptives; OFC, orbitofrontal cortex; PALM, Permutation Analysis of Linear Models; PCC, posterior cingulate cortex; PFC, prefrontal cortex; rACC, rostral anterior cingulate cortex; ROI, region of interest; RS, resting state; T_1w, T_1-weighted; T_2w, T_2-weighted; TBV, total brain volume; TSST, Trier Social Stress Test.

system (i.e. blood oxygenation level-dependent reactions) are related to acute (sex-specific) cortisol stress responses but also basal and somewhat more constant structural measures. Our study hereby paves the way for further analyses in this context and highlights the relevance of the topic.

1 | INTRODUCTION

In recent decades, research on the relationship between neural measures and psychoneuroendocrine responses to acute (psychosocial) stress has focused in particular on functional magnetic resonance (fMRI) studies implementing task-based and/or resting state (RS) designs. In this context, studies on the association between structural measures of the brain, for example, volume and thickness, and stress-induced hypothalamic pituitary adrenal (HPA) axis responses have been neglected. To the best of our knowledge, only a handful of studies subsists contributing to a better understanding of this association in healthy subjects. For instance, in a small ($n = 13$) sample, Pruessner et al. (2007) detected a positive correlation between bilateral hippocampal volume and area under the curve (AUC) cortisol in response to the Trier Social Stress Test (TSST) in young men (Kirschbaum et al., 1993). Three further TSST studies reported no significant associations between cortisol responses and hippocampal, amygdalar, as well as prefrontal cortex (PFC) volume (Barry et al., 2017; Liu et al., 2012), and a negative correlation with amygdalar volume in a subsample of healthy subjects (Klimes-Dougan et al., 2014), with Liu et al. (2012) and Klimes-Dougan et al. (2014) examining adolescents. Moreover, Sindi et al. (2014) revealed negative associations between hippocampal volume and cortisol levels in unfavorable stressful testing conditions specific for young (ages 18–35, word-list recall task) versus old (ages 60–75, face-association memory task) age groups. Considering AUC cortisol as a grouping factor, Admon et al. (2017) found high and low levels of cortisol to be associated with less hippocampal volume compared to moderate cortisol release in response to a prolonged version of the Maastricht Acute Stress Test (Smeets et al., 2012) in women. Taken together, these studies present an inconsistent pattern of findings, and only two studies examined the relationship in response to a psychosocial stressor (TSST) in healthy young adults (Barry et al., 2017; Pruessner et al., 2007).

Apart from a few studies in newborns and (young) children (Blankenship et al., 2019; Buss et al., 2012;

Fowler et al., 2021; Keresztes et al., 2020; Merz et al., 2019; Moog et al., 2021; Wiedenmayer et al., 2006), there mainly exist studies elaborating the interplay between basal HPA axis responses and structural brain measures. HPA axis markers thereby range from simple one-time collected salivary cortisol samples (Cho, 2001), 24-h urinary cortisol and basal adrenocorticotropic hormone levels (Wolf et al., 2002), to diurnal cortisol assessments and/or cortisol awakening responses (Dedovic et al., 2010; Ennis et al., 2019; Kremen et al., 2010; Lu et al., 2013; Lupien et al., 1998; MacLullich et al., 2005; Stomby et al., 2016; Sudheimer et al., 2014; Treadway et al., 2009), morning salivary cortisol after dexamethasone administration (Cacciaglia et al., 2017), as well as hair cortisol (R. Chen et al., 2016). In addition, two studies focused on perceived stress measures instead of cortisol responses (Blix et al., 2013; Piccolo & Noble, 2018). Apart from studies that did not detect any association (Chen et al., 2016; Kremen et al., 2010; MacLullich et al., 2005; Treadway et al., 2009), predominantly negative associations between HPA axis and structural measures have been reported, particularly for the hippocampus.

Assuming that these markers of HPA axis regulation are more stable than situation- and context-dependent responses to a specific experimental setting, it may seem more reasonable to link precisely these measures to structural brain variables (i.e. volume and thickness). Similarly, such structural measures seem to be more constant compared to task- and RS-based responses—at least in certain age groups. However, there is evidence that structural features of the brain are indeed related to acute stress responses (Herman et al., 2005; McEwen et al., 2016; Sapolsky, 2003). In this respect, the limbic system with its inherent and associated structures is of particular interest, including areas beyond the (para)hippocampus, amygdala and PFC, namely, striatal and cingulate subfields as well as the thalamus (Berretz et al., 2021; Henze et al., 2021, 2020; Noack et al., 2019; Reinelt et al., 2019; Ulrich-Lai & Herman, 2009; Van Oort et al., 2017). These same structures also exhibit sex-specific neural response patterns to stress as well as

associations with cortisol, especially in Blood Oxygenation Level Dependent (BOLD)–based fMRI studies (Chung et al., 2016; Dahm et al., 2017; Goldfarb et al., 2019; Henckens et al., 2010; Henze et al., 2021; Kogler et al., 2015, 2016; Seo et al., 2017, 2011; Veer et al., 2012; Vogel et al., 2015; Wang et al., 2007). Hence, sex-specific associations between acute cortisol responses and limbic structural measures may also be relevant and need further investigation.

Based on this, the present study scrutinised the relationship between (sex-specific) cortisol responses to the psychosocial stressor ScanSTRESS (Streit et al., 2014) and volumetric as well as thickness measures of the limbic system in young adults. Cortisol (as well as affect, heart rate and task-based neural) responses of the studied sample have already been published (Henze et al., 2020). However, the present Human Connectome Project (HCP) style anatomical data (Van Essen et al., 2013, 2012) offered the potential to further investigate the interplay of neural substrates and acute HPA axis markers in more detail. Given the limited number of studies on this topic to date, we designated our study as exploratory.

2 | MATERIALS AND METHODS

The present study comprised the sample of Henze et al. (2020) excluding one male subject as a 3D-structural T_2-weighted (T_2w) image could not be obtained. Initially, 67 young, healthy, scanner-naive participants were recruited via flyers and social media Internet platforms. The final sample for the present study consisted of 66 subjects (mean age 23.08 ± 3.16 years), with 31 women (mean age 22.10 ± 2.12 years) and 35 men (mean 23.94 ± 3.68 age years). Owing to HPA axis activity differences depending on menstrual cycle phase and oral contraceptives (OCs) usage (Kudielka & Kirschbaum, 2005; Zänkert et al., 2019), only women taking OCs were tested. We included all types of OCs (single and combination agents) and performed the fMRI measurements during active phases of OC use, that is, not during intake breaks between cycles. Exclusion criteria for this study

further included self-reported history of or current psychiatric, neurological or endocrine disorders; treatment with psychotropic medications or other medication affecting central nervous system or endocrine functions; daily tobacco or alcohol use; incompatibility with fMRI scanning (e.g. metal parts and pregnancy); regular night-shift work; and undergoing a current stressful episode (e.g. major exams or emotional stress due to separation from partner or serious illness/death of a family member).

All subjects provided written informed consent and the study was approved by the local ethics committee of the University of Regensburg. Test sessions took place between 1 and 6 PM to minimise influences of the circadian rhythm of cortisol secretion (Kudielka et al., 2004). The sequence of the test protocol can be seen in Figure 1.

For the present analysis, only cortisol stress responses and structural measures of our subjects were relevant. Therefore, the following is limited to the description of these parameters.

To assess cortisol responses to ScanSTRESS, saliva samples were collected at 10 time points referring to −1 as stress onset (−75, −15, −1, +15, +30, +50, +65, +80, +95 and +110 min) using 'Cortisol Salivettes' (Sarstedt, Nuembrecht, Germany). Saliva samples were analysed using a time-resolved fluorescence immunoassay with fluorometric end-point detection [DELFIA (dissociation-enhanced lanthanide fluorescence immunoassay); Dressendörfer et al., 1992] with an intra-assay coefficient of variation between 4.0% and 6.7% and an inter-assay coefficient of variation between 7.1% and 9.0%.

ScanSTRESS was conceived as a block design with alternating stress and control blocks presented in two runs. In control blocks, subjects solved simple figure and number matching tasks. In stress blocks, subjects were challenged with rotation and arithmetic tasks while being monitored by an investigator panel, exposed to time pressure, and receiving disapproving feedback. The original protocol (Streit et al., 2014) was slightly modified to enhance stress-induced responses, as described in Henze et al. (2020), without changing the paradigm itself. First, a prolonged (45 min) relaxing phase prior to stress was implemented to create appropriate baseline conditions
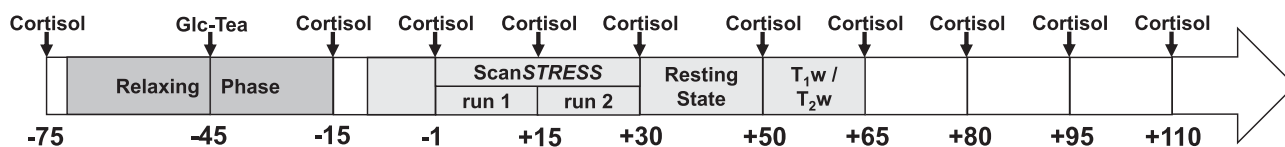

FIGURE 1 Experimental procedure including collection of saliva samples (cortisol) and administration of a sugary drink (glucose tea, Glc-Tea). The relaxing phase is shaded in dark grey, and the scanner procedure, in light grey. Displayed are the time points in minutes relative to the start of ScanSTRESS.

(i.e. low cortisol levels). Moreover, a detailed description and comprehensive clarification about the general scanning procedure was provided to minimise subjects' concerns prior to scanning that may confound with the response to the paradigm itself (McGlynn et al., 2007; Thorpe et al., 2008). Second, a sugary drink (75 g glucose in 200 mL herbal tea) was administered to facilitate cortisol reactivity (Zänkert et al., 2020). Third, a more abrupt passage (<10 min) from relaxation to stress exposure was achieved.

Subjects were scanned in a Siemens MAGNETOM Prisma 3 T MRI (Siemens Healthcare, Erlangen, Germany) equipped with a 64-channel head coil. Two series of BOLD echo planar imaging sequences (ScanSTRESS, results reported in Henze et al., 2021, 2020), multiband RS (results are yet to be published) and anatomical sequences were performed. The anatomical measurements included a 3D-structural T_1-weighted (T_1w) image (T1/TR/TE = 1200/2400/2.18 ms, flip-angle = 8°, distance factor = 50%) and a 3D-structural T_2w image (TR/TE = 3200/564, flip angle: variable) with 0.8 mm isotropic resolution and 256 mm field of view.

Pulse sequence parameters matched those used in the HCP so that the structural steps of the HCP minimal pre-processing pipelines (v.4.3.0) could be applied to our HCP-style data (Glasser et al., 2013). The initial processing of this pipeline includes an alignment between the T_1w and T_2w images, bias field and gradient distortion corrections, and registrations of the data to the Montreal Neurological Institute space. FreeSurfer (v7.1.1) was used for cortical parcellation and subcortical segmentation of the T_1w volume, including the estimation of total brain volume (TBV). FreeSurfer processing included removal of non-brain tissue, automated Talairach transformation, segmentation, intensity normalisation, tessellation of grey/white matter boundary, topology correction and surface deformation. The T_2w image was included in the processing stream to better refine the pial surface by removing dura and vasculature. Furthermore, every subject's structural output was visually inspected before applying asegstats2table and aparcstats2table to extract volume (subcortical) and thickness (cortical) measures of limbic structures for each hemisphere.

In addition to IBM SPSS Statistics Version 25 (IBM Corp., Armonk, NY) and the packages haven, tidyverse, psych, ggplot2, ggside and labelled in R 4.2.1 (Landis, 2022; Larmarange et al., 2023; R Core Team, 2023; Revelle, 2023; Wickham, 2016; Wickham et al., 2019, 2023), Permutation Analysis of Linear Models (PALM, Winkler et al., 2014), implemented in MATLAB R 2021a was used to examine associations between individual cortisol stress responses and structural measures of the limbic system. According to the current literature

on the interplay of neural substrates and acute HPA axis responses (e.g. Berretz et al., 2021; Noack et al., 2019; Van Oort et al., 2017), the following regions of interest (ROIs) were selected: Volume was extracted for the thalamus, striatum (ncl. caudatus, ncl. accumbens and putamen), hippocampus and amygdala. Thickness was determined for the cingulate cortex (rostral anterior cingulate cortex, rACC; caudal anterior cingulate cortex, cACC; and posterior cingulate cortex, PCC), parahippocampus and the orbitofrontal cortex (OFC: lateral and medial OFC, lOFC and mOFC). A total of four models were tested, in which lateralised structural measures (volume and thickness) of the left and right hemispheres served separately as dependent variables, considering that regulation of the HPA axis was assumed to be lateralised (Cerqueira et al., 2008). Since the variables sex, age and TBV have an impact on structural brain measures (Giedd et al., 1999; Moog et al., 2021), they were included as control variables, with TBV only taken into account when volumetric measures were considered as dependent variables. Hence, each model ($n = 4$) with lateralised structural measures as dependent variables included the independent variables *sex*, *age* and *total brain volume* (where appropriate) as control variables as well as individual (sex-specific) cortisol increases as variables of interest.

To adequately examine the association between acute cortisol increases and structural measures of the brain, we chose to consider the respective lateralised structural measure as a dependent variable as this is the most suitable way to (a) account for potential influences of the variables *sex*, *age* and *TBV* (where appropriate) on structural measures and (b) account for the inherent sex difference in the variable *cortisol increase* (by including individual sex-specific cortisol increases). Table 1 depicts our tested model(s) and also lists the contrasts considered. It should be noted that for the variables sex-specific cortisol (*cortisol increase men* and *cortisol increase women*), *age* and *TBV* the exact continuous values were included in the linear model(s) and that only the variable *sex* was coded as a grouping variable with 0 (=men) and 1 (=women). The grouping variable *cortisol increase men*, for instance, was coded to include the actual value for male subjects and 0 for female subjects; the same procedure was used for the variable *cortisol increase women*, but in the opposite manner. All variables were mean-centred. Ultimately, this approach allowed us to correct for and/or explore in more detail the potential influence of sex-specific cortisol responses. Family-wise error rate (FWER) corrections were performed in PALM within modality and contrast (p_{FWER}) and using -corrmod and -corrcon to FWER correct p-values across modalities and contrasts (p_{FWERmc}) (Alberton et al., 2020).

TABLE 1 Statistical model tested with PALM separately for both hemispheres and volume and thickness measures.

Contrast	Cortisol increase men	Cortisol increase women	Sex	Age	TBV
Cortisol	1	1	0	0	0
Men > women	1	−1	0	0	0
Women > men	−1	1	0	0	0
Men	1	0	0	0	0
Women	0	1	0	0	0

Note: Shaded in grey is the regressor *total brain volume* (TBV), which was not included in the models for thickness measures.

TABLE 2 Sample characteristics of cortisol increase, total brain volume, as well as hemisphere-specific volume and thickness measures for the thalamus, ncl. caudatus, ncl. accumbens, putamen, hippocampus, amygdala, rostral anterior cingulate cortex (rACC), caudal ACC (cACC), posterior cingulate cortex (PCC), parahippocampus, lateral orbitofrontal cortex (lOFC), and medial OFC (mOFC).

	Mean	SD	Range Min	Max	Kurtosis (±SE)	Skewness (±SE)
Cortisol increase (nmol/L)	3.351	4.601	−2.300	22.360	4.212 (±.582)	1.851 (±.295)
Women	1.612	2.889	−1.820	11.510	5.525 (±.821)	2.221 (±.421)
Men	4.892	5.283	−2.300	22.360	2.581 (±.778)	1.443 (±.398)
AUCg	605.913	300.301	222.540	1747.680	4.296 (±.582)	1.866 (±.295)
Women	516.430	205.482	222.540	930.300	−.531 (±.821)	.550 (±.421)
Men	685.170	348.398	327.300	1747.680	2.734 (±.778)	1.781 (±.398)
AUCi	334.592	318.483	−24.840	1448.480	3.395 (±.582)	1.813 (±.295)
Women	225.501	182.408	−.260	763.610	2.899 (±.821)	1.586 (±.421)
Men	431.216	379.596	−24.840	1448.480	1.244 (±.778)	1.333 (±.398)
Total brain volume (mm^3)	1220662.300	113435.057	990274.000	1534427.000	.162 (±.582)	.463 (±.295)
Women	1141886.030	73065.700	990274.000	1286201.000	−.474 (±.821)	.077 (±.421)
Men	1290435.570	96018.205	1102269.000	1534427.000	.335 (±.778)	.607 (±.398)
Volumetric measures (mm^3)						
Left thalamus	8494.856	865.398	6899.100	10651.000	−.417 (±.582)	.406 (±.295)
Right thalamus	7872.770	819.070	6009.200	9718.000	−.221 (±.582)	.435 (±.295)
Left ncl. caudatus	3880.138	427.435	2894.000	5211.900	.238 (±.582)	.162 (±.295)
Right ncl. caudatus	3958.630	415.668	3027.600	5042.800	−.188 (±.582)	.135 (±.295)
Left ncl. accumbens	535.147	87.320	350.700	749.500	−.196 (±.582)	.243 (±.295)
Right ncl. accumbens	586.097	87.830	411.800	799.400	.018 (±.582)	.287 (±.295)
Left putamen	4982.076	603.378	3870.700	6669.800	.206 (±.582)	.567 (±.295)
Right putamen	5193.839	506.718	4204.100	6531.700	.148 (±.582)	.409 (±.295)
Left hippocampus	4434.492	416.719	3578.200	5261.900	−.623 (±.582)	.145 (±.295)
Right hippocampus	4468.656	442.015	3717.900	5578.900	−.474 (±. 582)	.506 (±.295)
Left amygdala	1633.774	223.715	1228.400	2207.000	−.497 (±.582)	.504 (±.295)
Right amygdala	1830.209	223.743	1458.900	2485.600	.779 (±.582)	.720 (±.295)
Thickness measures (mm)						
Left rACC	3.347	.245	2.760	3.860	.024 (±.582)	−.228 (±.295)
Right rACC	3.359	.224	2.890	3.830	−.640 (±.582)	.165 (±.295)
Left cACC	2.819	.321	1.830	3.460	.363 (±.582)	−.445 (±.295)
Right cACC	2.712	.259	2.240	3.390	.640 (±.582)	.744 (±.295)

(Continues)

T A B L E 2 (Continued)

	Mean	SD	Range Min	Max	Kurtosis (±SE)	Skewness (±SE)
Left PCC	2.745	.140	2.430	3.140	.557 (±.582)	.161 (±.295)
Right PCC	2.744	.127	2.490	3.240	2.490 (±.582)	.729 (±.295)
Left parahippocampus	3.026	.339	2.190	3.850	.046 (±.582)	−.179 (±.295)
Right parahippocampus	2.875	.262	2.290	3.470	−.383 (±.582)	−.032 (±.295)
Left lOFC	3.148	.167	2.670	3.490	.052 (±.582)	−.416 (±.295)
Right lOFC	3.140	.136	2.770	3.450	−.106 (±.582)	−.226 (±.295)
Left mOFC	2.905	.196	2.270	3.570	2.329 (±.582)	−.013 (±.295)
Right mOFC	2.983	.196	2.350	3.380	.495 (±.582)	−.487 (±.295)

Abbreviations: AUCg, area under the curve with respect to the ground; AUCi, area under the curve with respect to the increase; SD, standard deviation; min, minimal value, max, maximum value; SE, standard error.
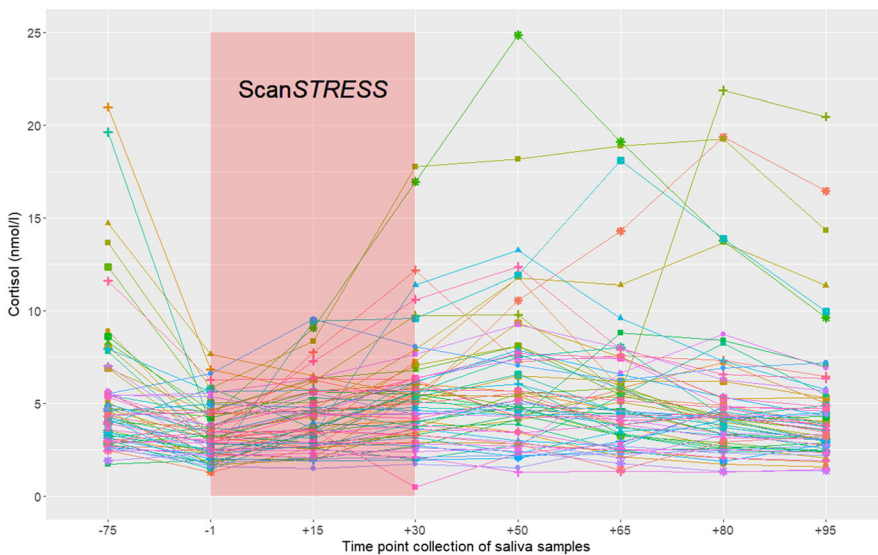

F I G U R E 2 Individual salivary cortisol profiles (nmol/L) covering all 10 measurement time points of the cortisol assessment.

Cortisol increase was defined as the difference between the individual cortisol peak (sample +30, +50, +65) and the pre-stress cortisol level (sample −1). As we were interested in the association between structural brain measures and acute cortisol stress responses, we focused on the individual cortisol increase rather than AUC measures, which takes into account both pre-stress and recovery phase values and represent an index of total cortisol release. In contrast, the cortisol increase only considers the period of acute stress exposure and the latency phase of HPA axis reactivity (Dickerson & Kemeny, 2004).

3 | RESULTS

Table 2 provides descriptive information of the present sample regarding volumetric (mm³) and thickness (mm) measures as well as sex-specific cortisol increases (in nmol/L) and TBV (mm³). Figure 2 depicts individual cortisol response profiles of all subjects included in our study. The relevant analysis codes and data included in our tested models are available at https://epub.uni-regensburg.de/53549/.

Statistics of PALM analyses are shown in Table 3 for volume and thickness measures of the left hemisphere and in Table 4 for the same measures of the right hemisphere. Figure 3 depicts scatterplots between (sex-specific) cortisol increases and left and right hemisphere volumetric measures. Figure 4 shows the associations with thickness measures; both figures integrate density plots.

In general, Figure 3 illustrates that the association between cortisol increase and volume tends to be positive. The only association displaying some statistical evidence for the total sample (contrast *cortisol*) after using

TABLE 3 Results of the PALM calculations for volume and thickness measures of the left hemisphere.

Contrast	Thalamus	Ncl. caudatus	Ncl. accumbens	Putamen	Hippocampus	Amygdala
Cortisol						
t	.3909	−.7003	.7038	.2096	.1563	**1.6206**
p_{uncorr}	.3430	.7641	.2487	.4244	.4394	**.0566**
p_{FWER}	.8567	.9970	.7344	.9098	.9212	**.2586**
p_{FWERmc}	.9999	1.0000	.9947	.9999	.9999	**.6548**
Men > women						
t	.3556	**1.9248**	1.0724	.6216	.3868	.7264
p_{uncorr}	.3678	**.0301**	.1428	.2634	.3448	.2351
p_{FWER}	.8756	**.1423**	.5353	.7793	.8651	.7321
p_{FWERmc}	.9999	**.4394**	.9434	.9974	.9999	.9939
Women > men						
t	−.3556	−1.9248	−1.0724	−.6216	−.3868	−.7264
p_{uncorr}	.6323	.9700	.8573	.7367	.6553	.7650
p_{FWER}	.9850	1.0000	.9997	.9951	.9872	.9965
p_{FWERmc}	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Men						
t	.9113	**1.7250**	**2.2073**	1.0536	.6850	**2.7981**
p_{uncorr}	.1840	**.0464**	**.0203**	.1459	.2505	**.0052**
p_{FWER}	.6086	**.2147**	**.0838**	.5368	.7229	**.0213**
p_{FWERmc}	.9763	**.5741**	**.2673**	.9466	.9951	**.0747**
Women						
t	−.0093	−1.4804	−.2692	−.2568	−.1466	.3986
p_{uncorr}	.4990	.9271	.5841	.6153	.5633	.3401
p_{FWER}	.9493	.9999	.9799	.9792	.9671	.8513
p_{FWERmc}	1.0000	1.0000	1.0000	1.0000	1.0000	.9999
Contrast	**rACC**	**cACC**	**PCC**	**Parahippocampus**	**lOFC**	**mOFC**
Cortisol						
t	−.7523	−.7689	−.0944	.8072	.3628	.1514
p_{uncorr}	.7781	.7772	.5530	.2038	.3685	.4439
p_{FWER}	.9213	.9237	.7790	.4193	.6051	.6921
p_{FWERmc}	1.0000	1.0000	1.0000	.8981	.9966	1.0000
Men > women						
t	−.1109	−.5410	−.5761	−.8470	−.7915	−.5740
p_{uncorr}	.5290	.6936	.7020	.8044	.7728	.7024
p_{FWER}	.7748	.8948	.9029	.9452	.9396	.9028
p_{FWERmc}	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Women > men						
t	.1109	.5410	.5761	.8470	.7915	.5740
p_{uncorr}	.4711	.3065	.2981	.1957	.2273	.2977
p_{FWER}	.7087	.5349	.5207	.4072	.4311	.5215
p_{FWERmc}	1.0000	.9769	.9695	.8814	.9052	.9699

(Continues)

TABLE 3 (Continued)

Contrast	rACC	cACC	PCC	Parahippocampus	lOFC	mOFC
Men						
t	−1.0038	−1.5861	−.8624	−.1885	−.6231	−.5793
p_{uncorr}	.8354	.9387	.8020	.5753	.7331	.7139
p_{FWER}	.9502	.9875	.9353	.7951	.9005	.8922
p_{FWERmc}	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Women						
t	−.3178	−.0751	.2883	.9048	.6465	.4120
p_{uncorr}	.6334	.5515	.4070	.1791	.2780	.3563
p_{FWER}	.8418	.7755	.6376	.3847	.4903	.5903
p_{FWERmc}	1.0000	1.0000	.9991	.8521	.9513	.9936

Note: Effects explained in more detail in the main text are printed in bold. p_{FWER} stands for p-values FWER-corrected within modality and contrast, and p_{FWERmc} stands for p-values FWER-corrected across modalities and contrasts.

TABLE 4 Results of the PALM calculations for volume and thickness measures of the right hemisphere.

Contrast	Thalamus	Ncl. caudatus	Ncl. accumbens	Putamen	Hippocampus	Amygdala
Cortisol						
t	−.6007	−.5844	.7021	.2487	−.0010	.8247
p_{uncorr}	.7208	.7184	.2311	.4192	.5000	.2006
p_{FWE}	.9877	.9869	.6805	.8595	.9186	.6190
p_{FWERmc}	1.0000	1.0000	.9943	.9999	1.0000	.9830
Men > women						
t	.7602	**2.1817**	−.9068	1.2305	.8009	−.0539
p_{uncorr}	.2217	**.0157**	.8137	.1169	.2126	.5398
p_{FWE}	.6615	**.0769**	.9979	.4122	.6401	.9436
p_{FWERmc}	.9904	**.2838**	1.0000	.8662	.9854	1.0000
Women > men						
t	−.7602	−2.1817	.9068	−1.2305	−.8009	.0539
p_{uncorr}	.7784	.9844	.1864	.8832	.7875	.4603
p_{FWE}	.9921	1.000	.5763	.9992	.9938	.9101
p_{FWERmc}	1.0000	1.0000	.9712	1.0000	1.0000	1.0000
Men						
t	.3120	**2.1936**	−.3887	**1.8960**	1.0486	.8689
p_{uncorr}	.3606	**.0170**	.6443	**.0257**	.1495	.1884
p_{FWE}	.8346	**.0888**	.9728	**.1551**	.5067	.5908
p_{FWERmc}	.9998	**.2783**	1.0000	**.4424**	.9372	.9776
Women						
t	−.7493	−1.5716	.8865	−.5927	−.4685	.4503
p_{uncorr}	.7720	.9409	.1877	.7307	.6864	.3047
p_{FWE}	.9930	1.000	.5862	.9875	.9794	.7869
p_{FWERmc}	1.0000	1.0000	.9755	1.0000	1.0000	.9994

T A B L E 4 (Continued)

Contrast	rACC	cACC	PCC	Parahippocampus	lOFC	mOFC
Cortisol						
t	−.0679	1.1257	−.2752	.1855	.2204	.1396
p_{uncorr}	.5318	.1289	.6171	.4311	.4223	.4505
p_{FWE}	.7505	.2774	.8134	.6567	.6439	.6740
p_{FWERmc}	1.0000	.6907	1.0000	.9999	.9994	1.0000
Men > women						
t	−.6313	−1.6182	−.1903	−.8294	−.9752	−.6031
p_{uncorr}	.7261	.9494	.5584	.7923	.8302	.7173
p_{FWE}	.8983	.9926	.7690	.9340	.9515	.8921
p_{FWERmc}	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Women > men						
t	.6313	**1.6182**	.1903	.8294	.9752	.6031
p_{uncorr}	.2740	**.0507**	.4417	.2078	.1699	.2828
p_{FWE}	.4866	**.1341**	.6659	.4063	.3463	.5002
p_{FWERmc}	.9417	**.3917**	.9998	.8576	.7791	.9511
Men						
t	−.9046	−.8356	−.5633	−.8750	−1.0262	−.6309
p_{uncorr}	.8095	.7937	.7121	.8032	.8393	.7345
p_{FWE}	.9276	.9183	.8714	.9238	.9413	.8846
p_{FWERmc}	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Women						
t	.3340	**1.5169**	−.0289	.5784	.6813	.4230
p_{uncorr}	.3872	**.0613**	.5214	.2827	.2562	.3511
p_{FWE}	.6123	**.1588**	.7423	.5059	.4651	.5734
p_{FWERmc}	.9962	**.4481**	1.0000	.9589	.9218	.9897

Note: Effects explained in more detail in the main text are printed in bold. p_{FWER} stands for p-values FWER-corrected within modality and contrast, and p_{FWERmc} stands for p-values FWER-corrected across modalities and contrasts.

PALM (see Table 3) concerns the left amygdala. However, this association presents itself only at the level of uncorrected p-values. In the male subsample (contrast *men*), this association is particularly evident and this effect is the only one also exhibiting significance at the level of uncorrected and FWER-corrected p-values (pFWER). However, this effect disappears when the FWER correction is applied across modalities and contrasts (pFWERmc). Similarly, there is a tendency for positive associations between cortisol increases and striatal volume in men. For the left hemisphere, this concerns the ncl. caudatus and ncl. accumbens, whereas for the right hemisphere, ncl. caudatus and putamen are involved. Moreover, there appears to be an interaction between sex-specific cortisol increases and bilateral ncl. caudatus volume, in that the association is more positive in men than in women. This tendency for a sex-specific dissociation is also visible in Figure 3c,d. Interestingly,

the reverse picture seems to emerge for the association between sex-specific cortisol increases and the thickness of the right cACC (see Table 4) describing a more positive association in women than men but with even lower statistical significance.

A closer look at Figure 3c,d indicates that one subject had both the largest ncl. caudatus volume and, at the same time, achieved the highest—but endocrinologically plausible—increase in cortisol. Excluding this outlier did not result in any substantial change regarding the effects shown.

To enhance the exploratory nature of our study, Figure 5 provides correlation matrices for the total sample (Figure 5a) and sex-specific matrices (Figure 5b) including correlations in men below the diagonal and those in women above the diagonal. Depicted are bivariate correlations between lateralised structural measures (volume and thickness), which were not corrected for the
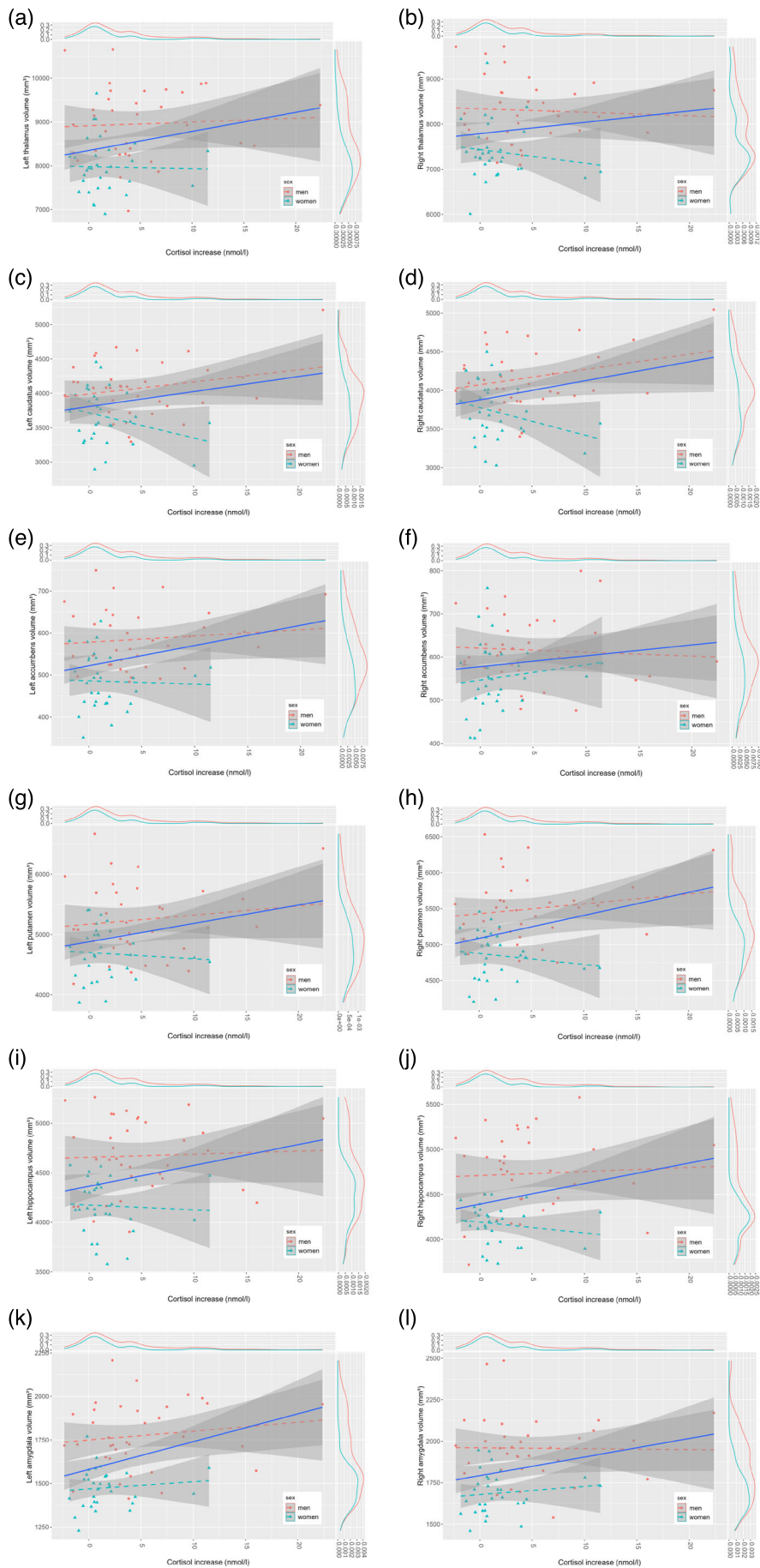
FIGURE 3 Scatterplots of (sex-specific) associations between individual cortisol increases (nmol/L) and volumetric measures of the (a) left thalamus, (b) right thalamus, (c) left ncl. caudatus, (d) right ncl. caudatus, (e) left ncl. accumbens, (f) right ncl. accumbens, (g) left putamen, (h) right putamen, (i) left hippocampus, (j) right hippocampus, (k) left amygdala and (l) right amygdala. Shown are the linear slopes of the individual models for the total sample (solid lines) and the sex-specific models (dotted lines). Moreover, density plots are presented.

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FIGURE 4 Scatterplots of (sex-specific) associations between individual cortisol increases (nmol/L) and thickness measures of the (a) left rostral anterior cingulate cortex (rACC), (b) right rACC, (c) left caudal anterior cingulate cortex (cACC), (d) right cACC, (e) left posterior cingulate cortex (PCC), (f) right PCC, (g) left parahippocampus, (h) right parahippocampus, (i) left lateral orbitofrontal cortex (lOFC), (j) right lOFC, (k) left medial orbitofrontal cortex (mOFC) and (l) right mOFC. Shown are the linear slopes of the individual models for the total sample (solid lines) and the sex-specific models (dotted lines). Moreover, density plots are presented.
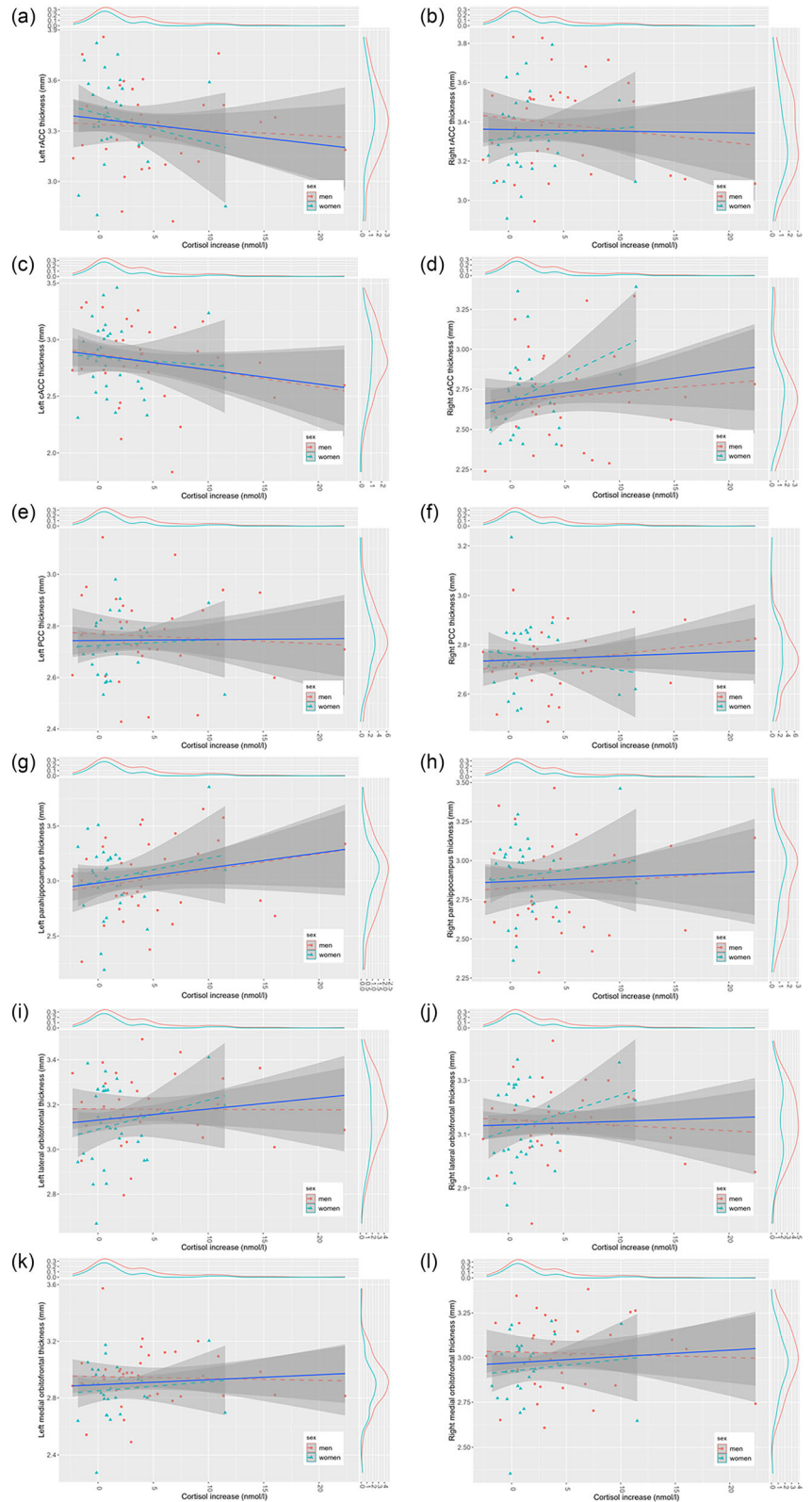
influence of *sex*, *age* and *TBV*, and aggregate cortisol measures. The latter also includes, in addition to *cortisol increase*, the two AUC measures (AUCg and AUCi) representing the total volume of cortisol secreted, which were calculated according to Pruessner et al.

(2003) as follows: AUC with respect to the ground (AUCg) was calculated by adding eight individual trapezoidal areas, defined by the respective measurement times in the protocols (see Figure 1 from sample −15 to sample +110). AUC with respect to the increase (AUCi)

was determined by subtracting the area between the ground and the pre-stress measurement (sample -1) from AUCg values. Descriptively, these correlation structures support the PALM results to some extent indicating rather positive associations between all three aggregate cortisol measures and striato-limbic volume for the total sample, but rather mixed results regarding thickness. Likewise, there might be some evidence for a dissociation in sex-specific associations between cortisol and striatal volume, tending to be more positive in men but more negative in women (see Figure 5b). However, the results for thickness remain inconclusive in the context of potential sex effects.

4 | DISCUSSION

This is the first study investigating the association between structural measures of a larger number of limbic regions and acute cortisol responses to psychosocial stress in a healthy sample of young adults with a balanced number of female and male subjects. Furthermore, this is the first study applying a psychosocial stress paradigm for imaging environments in this context. In the following, given the exploratory nature of our study, we refrain from making any qualitative statements (i.e. an association is definitely positive or negative) about the relationship between cortisol stress responses and structural measures of the brain and therefore make no claim to adequately substantiated significance of our results. Comments on effect directions are descriptive only and are primarily intended to illustrate the involvement of individual structures in the HPA axis response to acute stress processing. The statistical results presented are also intended to illustrate that more basal and somewhat stable brain measures are also related to acute stress responses and do not allow conclusions to be drawn because of the low precision of the multivariate coefficients. In view of the above, some evidence of associations between acute
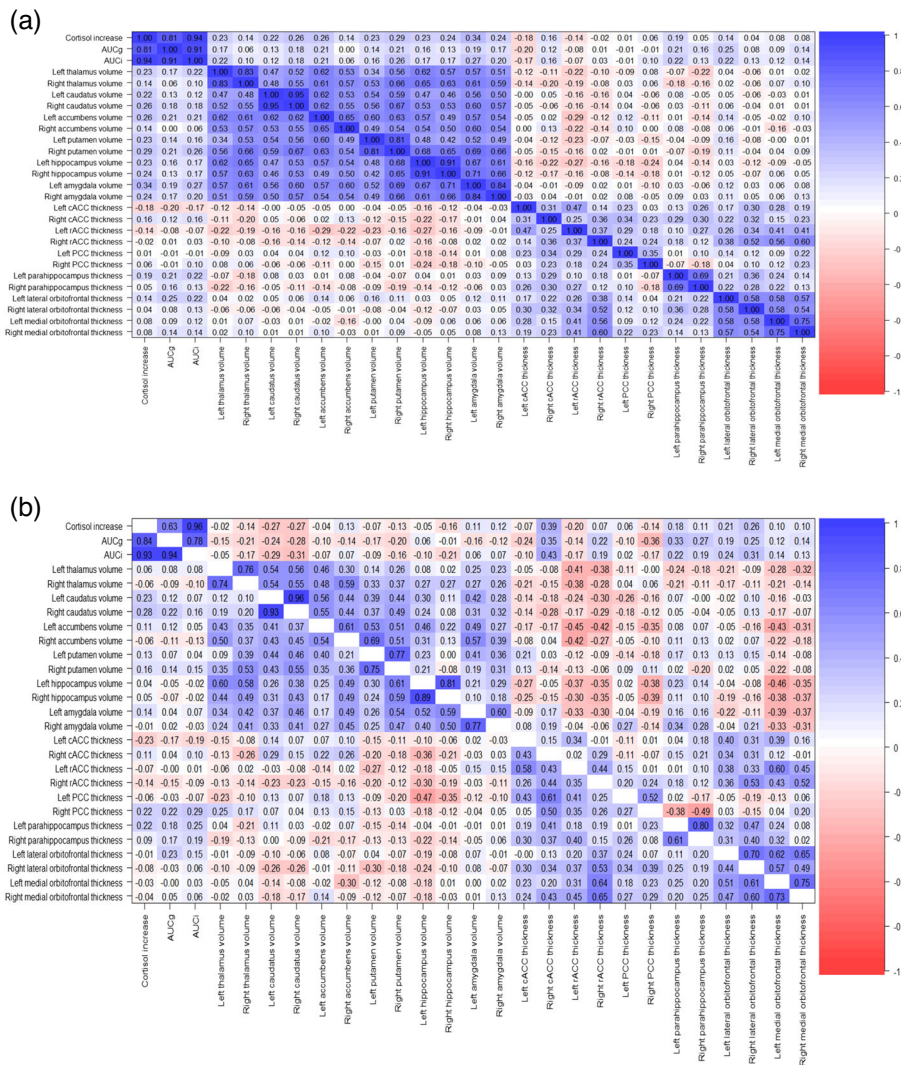

FIGURE 5 Exploratory correlation matrices between cortisol measures (nmol/L) (cortisol increase; area under the curve with respect to the ground, AUCg; area under the curve with respect to the increase, AUCi) and volume and thickness measures of the brain for (a) the whole sample and (b) men and women separately (sex-specific). In (b), the correlations for OC-taking women are shown above the diagonal and for men below.

(sex-specific) cortisol increases and striato-limbic volume emerged.

For striatal volume, our data may suggest a sex-specific dissociation regarding the association with cortisol increases in women compared to men (see Figure 3c–h). On a descriptive level, this dissociation is also evident from the correlation structures depicted in Figure 5b. Considering the results of PALM, this dissociation was most evident for the ncl. caudatus in that we see a more positive association in men but a more negative association in women. Interestingly, this dissociation tends to be reversed for the right ncl. accumbens (see Figure 3f), at least on a descriptive level. Moreover, this observation appears to be relevant in that it once again suggests striatal structures to be crucial when examining sex differences in the association between HPA axis markers and limbic measures (Henze et al., 2021; Hidalgo-Lopez et al., 2020; Yoest et al., 2018). This might also confirm that in the context of stress-related sex differences in the brain, it might be the quality of the responses (e.g. activation vs. deactivation and positive vs. negative association) for the same structures rather than different brain regions that are decisive (Henze et al., 2021; Shalev et al., 2020).

As noted above, the issue of laterality also seems relevant in terms of studying the association between cortisol responses and brain variables (structure, BOLD responses etc.). Our data do not allow to draw a definitive conclusion as to whether the regulation of the HPA axis might be lateralised. Moreover, a sufficient explanation for why one hemisphere may be more dominant in the context of stress processing has not yet been provided. However, one explanatory approach could be to divide a stress response into more physiological (left hemisphere) and emotional (right hemisphere) components (Cerqueira et al., 2008). Interestingly, neither the present structural data nor the task-based results from our sample refute this hypothesis (Henze et al., 2021, 2020). For certain structures, there seems to be some dominance of one or the other hemisphere regarding the association with cortisol increases, which should be further investigated in the future, and is confirmed by the following.

Our results may suggest that acute cortisol increases are to some extent associated with left hemispheric amygdalar volume. Even though the findings regarding the association of brain structures and cortisol responses in healthy adults are very limited so far, it still seems interesting that the majority of effects have concerned the amygdala (Barry et al., 2017; Klimes-Dougan et al., 2014; Liu et al., 2012). The same picture emerges when task-based and resting state-based connectivity studies are considered. This not only shows that the focus of interest is a priori on the amygdala as ROI in respective studies but also represents the limbic structure most frequently responsive during and after psychosocial stress processing (e.g. Berretz et al., 2021; Henze et al., 2021, 2020; Noack et al., 2019; Van Oort et al., 2017; Veer et al., 2011, 2012). It therefore stands to reason that the amygdala should continue to be studied as intensively and profoundly as has been done so far. Accordingly, as the present structural data can be very clearly distinguished from situation- and task-specific contexts as in the typical elicitation of BOLD responses, this possibly highlights the relevance of this preliminary finding. To date, the sole responsiveness of a structure during or after a particular task cannot be interpreted with certainty as a reaction to the intended or induced state (e.g. stress, fear and pain). In this regard, it is essential to demonstrate statistically proven relatedness to other responses to this experimental manipulation that are not measured in the brain. In the case of acute stress induction, for example, the value of the possible statement that the mere morphology of a structure is related to the HPA axis response to stress (e.g. in the form of cortisol) and vice versa seems obvious. Beyond that, our data suggest to also consider other striato-limbic structures and to generate multimethod data mapping different qualitative and quantitative measures of the human brain (i.e. structure, task-based and connectivity data).

For instance, another structure that has been shown to be relevant in the presented context by its representation in the literature is the thalamus. The results seem particularly ambiguous here, but the structure should continue to be considered in the future, and not only because of its centrality in the limbic system. Based on its attributed role as a gateway, dynamic brain responses originating from the thalamus deserve further evaluation especially with regard to sex effects. Regarding the above-mentioned involvement of the striatum in sex-specific cortisol reactions, the thalamus as an adjacent structure could act as an additional coordinator (Henze et al., 2021; Reinelt et al., 2019; Seo et al., 2017, 2011; Wang et al., 2007).

Other published effects mainly concerned the hippocampus, which was less reflected in our data. Given the function of this structure in the context of memory processing, this is remarkable, as one could possibly assume that brain morphological changes should occur in this region due to, for example, chronic stress experience (Botdorf et al., 2022; Hardcastle et al., 2020; Kim et al., 2015). Examining samples at risk in terms of associations between structural measures and acute stress responses could be a potential prospect at this point (Misaki et al., 2021).

With respect to thickness measures the presented results are highly inconclusive. We found little evidence

for associations involving the right cACC in this case. Given the focus of previous studies mentioned in the introduction on (a) the relationship between hippocampal structure and basal, that is, non-stress-induced, cortisol responses and (b) amygdalar morphology and (stress-induced) cortisol responses, this preliminary finding concerning the cingulate cortex may be of particular interest. It possibly shows that it is not appropriate to limit the investigation of the interplay between limbic structures and (acute) responses of the HPA axis to the hippocampus, amygdala and also the subfields of the PFC. Indeed, the majority of BOLD-dependent studies in the context of acute stress exposure continue to focus on these structures (Berretz et al., 2021; Chen et al., 2020; Henze et al., 2020; Noack et al., 2019; Sakamoto et al., 2005; Van Oort et al., 2017). In particular, with regard to the PFC, it should be noted that it is not appropriate to study it as a whole, but rather in sub-regional resolution. This is also supported in the literature, particularly with regard to the OFC, which undergoes morphological changes in response to, for example, early life adversity and plays a crucial role in encoding stressful experiences (Jacobs & Moghaddam, 2021; Monninger et al., 2020; Sequeira & Gourley, 2021).

As we have repeatedly pointed out, the presented findings are of preliminary character and therefore have to be treated as such. This is also confirmed by the work of Harrewijn et al. (2020), who have demonstrated that large samples are needed to have a chance to detect true qualitative and quantitative effects on the one hand or to identify true null effects when studying the relationship between cortisol responses and those of the brain on the other. However, the non-parametric approach via PALM and the correlation structures displayed in Figure 5 show that structural measures of the brain are indeed associated with acute cortisol stress responses. Accordingly, the presented data with exploratory findings may be indicative and thus expand the research field of 'stress imaging'.

Moreover, Figure 5 shows that the relationship between structural measures and cortisol increase as a measure of acute stress reactivity is highly consistent with those of AUC measures representing the volume of cortisol secreted. Furthermore, we can see that volume and thickness measures are also interrelated, although volumetric measures seem to render a more consistent picture than thickness measures. Although only the association between individual cortisol increases and left ncl. caudatus volume in men survived all but one correction for multiple testing, the data presented suggest interesting new insights into the associations between striato-limbic structures and acute HPA axis responses

to stress by reconfirming the involvement of typical brain areas. In addition, it should be noted that the presented model(s) take into account variables with empirically proven influence on volume and thickness (i.e. sex, age and TBV) (Giedd et al., 1999; Moog et al., 2021). Compared to previous studies not considering (all) these variables and containing less high-resolution structural data (Admon et al., 2017; Klimes-Dougan et al., 2014; M. Pruessner et al., 2007; Sindi et al., 2014), the informative value of the present HCP-style data may be obvious.

However, the present analysis had some limitations that have to be acknowledged. First, the composition of the sample—especially regarding the variable cortisol—has to be taken into account, as it only included men and women taking OCs. Secondly, a larger sample size would be desirable, allowing for the inclusion of women in different menstrual cycle phases. This should, as far as possible, not only distinguish between OC-taking and free-cycling women (in comparison to each other and to men) but also consider different OC methods (single vs. different combination agents) as well as different hormonal contraceptives and menstrual cycle phases (Brønnick et al., 2020; Pletzer et al., 2023; Song et al., 2023). This undoubtedly requires the generation of large-scale samples in the context of stress induction in the MRI, which do not yet exist.

5 | CONCLUSION

Although previous studies were able to link acute cortisol responses to mainly BOLD-based responses of limbic structures, the present results confirm that structural and thus somewhat more stable measures of the brain may also be associated with neuroendocrine stress processing. In addition, the present study extends the knowledge of the relationship between striato-limbic structural features and HPA axis markers, which until now mainly included basal responses. As an exploratory study, our research hopefully paves the way for future investigations in the field.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

PEER REVIEW
The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16161.

DATA AVAILABILITY STATEMENT
The analysis code and data are freely available at the following link: https://epub.uni-regensburg.de/53549/.

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