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Mapping pathways to neuronal atrophy in healthy, mid-aged adults: From chronic stress to systemic inflammation to neurodegeneration?

Julia K. Schaefer [a], Veronika Engert [b,c], Sofie L. Valk [d,e,f], Tania Singer [g,1], Lara M. C. Puhlmann [b,h,1,*]

[a] Cognitive Neuropsychology, Department of Psychology, Ludwig-Maximilians-Universität München, Germany
[b] Research Group "Social Stress and Family Health", Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[c] Institute of Psychosocial Medicine, Psychotherapy and Psychooncology, Jena University Clinic, Friedrich-Schiller University, Jena, Germany
[d] Otto Hahn Group Cognitive Neurogenetics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[e] Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), Research Centre Jülich, FZ Jülich, Jülich, Germany
[f] Institute of Systems Neuroscience, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[g] Social Neuroscience Lab, Max Planck Society, Berlin, Germany
[h] Leibniz Institute for Resilience Research, Mainz, Germany

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ABSTRACT

Growing evidence implicates systemic inflammation in the loss of structural brain integrity in natural ageing and disorder development. Chronic stress and glucocorticoid exposure can potentiate inflammatory processes and may also be linked to neuronal atrophy, particularly in the hippocampus and the human neocortex. To improve understanding of emerging maladaptive interactions between stress and inflammation, this study examined evidence for glucocorticoid- and inflammation-mediated neurodegeneration in healthy mid-aged adults.

N = 169 healthy adults (mean age = 39.4, 64.5% female) were sampled from the general population in the context of the ReSource Project. Stress, inflammation and neuronal atrophy were quantified using physiological indices of chronic stress (hair cortisol (HCC) and cortisone (HEC) concentration), systemic inflammation (interleukin-6 (IL-6), high-sensitive C-reactive protein (hs-CRP)), the systemic inflammation index (SII), hippocampal volume (HCV) and cortical thickness (CT) in regions of interest. Structural equation models were used to examine evidence for pathways from stress and inflammation to neuronal atrophy. Model fit indices indicated good representation of stress, inflammation, and neurological data through the constructed models (CT model: robust RMSEA = 0.041, robust χ^2 = 910.90; HCV model: robust RMSEA <0.001, robust χ^2 = 40.95). Among inflammatory indices, only the SII was positively associated with hair cortisol as one indicator of chronic stress (β = 0.18, p < 0.05). Direct and indirect pathways from chronic stress and systemic inflammation to cortical thickness or hippocampal volume were non-significant. In exploratory analysis, the SII was inversely related to mean cortical thickness.

Our results emphasize the importance of considering the multidimensionality of systemic inflammation and chronic stress, with various indicators that may represent different aspects of the systemic reaction. We conclude that inflammation and glucocorticoid-mediated neurodegeneration indicated by IL-6 and hs-CRP and HCC and HEC may only emerge during advanced ageing and disorder processes, still the SII could be a promising candidate for detecting associations between inflammation and neurodegeneration in younger and healthy samples. Future work should examine these pathways in prospective longitudinal designs, for which the present investigation serves as a baseline.

* Corresponding author. Leibniz Institute for Resilience Research, Mainz, Germany.
 E-mail addresses: puhlmann@cbs.mpg.de, lara.puhlmann@lir-mainz.de (L.M.C. Puhlmann).
[1] these authors share senior authorship.

1. Introduction

1.1. Short overview

Mental health conditions and other disorders of the brain are highly prevalent and rank among the leading causes for global burden of disease (James et al., 2018; Wittchen et al., 2011). Chronic stress and pro-inflammatory activity are both linked to neuronal atrophy in cortical and subcortical structures, forming pathways that are implicated in accelerated ageing, cognitive impairment and the development of psychiatric brain disorders, such as Major Depressive Disorder (MDD) (Chrousos, 2009; Chung et al., 2002; Kremen et al., 2010; Lebedeva et al., 2018; Marsland et al., 2015; McEwen, 2008; Sapolsky, 2004). To date, there has been limited research comprehensively exploring the intricate relationship between chronic stress, systemic inflammation, and brain morphology. Specifically, there is a lack of understanding regarding the development of their maladaptive interactions and potential pathways to disorders. A thorough understanding of these interactions, including chronic and subclinical levels of systemic indicators, could not only provide insight into early intervention opportunities but also offer valuable information on effective intervention strategies.

The present study addresses this gap by comprehensively investigating the interplay between glucocorticoid (GC) exposure, systemic inflammation, and cortical and subcortical brain morphology in a healthy mid-aged sample. Data was collected at baseline of a large-scale, multi-disciplinary longitudinal mental training intervention study, the ReSource Project (Singer et al., 2016). Using structural equation models (SEMs), we evaluate evidence for different neurobiological pathways that may indicate emerging maladaptive processes, which is crucial to identify neurobiological risk factors and targets for future preventive interventions.

1.2. Chronic stress

Among the most important endocrine mediators of the stress response and its long-term health effects are GCs like cortisol, the end-product of the human hypothalamus-pituitary-adrenal (HPA) axis. Released as part of a cascade of stress-mediators, cortisol is an essential signalling agent in mainly down-regulatory feedback loops that centrally involve the brain (McEwen, 2007). Prolonged exposure to stress and GC signalling appears to impair these regulatory mechanisms, potentially via reduced sensitivity to GC signalling (glucocorticoid receptor resistance (GCR) hypothesis, Cohen et al., 2012) leading to a failure to properly terminate HPA axis activity (Chrousos et al., 1993; Chrousos, 1995). While glucocorticoid resistance is typically expected after long-term stress exposure (Cohen et al., 2012), changes in HPA axis functioning in terms of inability to suppress post-dexamethasone cortisol levels have been found in otherwise healthy populations (MacLullich et al., 2006; Jeckel et al., 2010).

Chronic stress and the resulting sustained GC exposure have been linked to neuronal atrophy in a range of studies. Particularly well-documented is the neurotoxic effect of sustained GC exposure in the hippocampus (Geerlings and Gerritsen, 2017; Lupien et al., 1998; McEwen and Gould, 1990; McEwen, 1999; Sapolsky and Pulsinelli, 1985; Sapolsky, 1990), the brain region expressing the highest density of GC receptors (McEwen, 1982). Inverse associations with basal cortisol levels have, however, also been found for regional and total brain volumes (Sigurdsson et al., 2012), and HPA axis dysregulation seems to be linked to smaller left anterior cingulate cortex (ACC) volumes (MacLullich et al., 2006) and frontal lobe atrophy (Gold et al., 2005). Similarly, total diurnal cortisol output is inversely associated with cortical thickness (CT) (Lebedeva et al., 2018). Furthermore, sustained GC exposure has been linked to the development of prevalent disorders such as MDD and the corresponding neuronal atrophy (Duman & Monteggia). In patients with early-stage MDD, serum cortisol levels were inversely correlated with CT in several brain areas (Liu et al., 2015). Overall, neurotoxic effects of stress and GC exposure thus appear to extend beyond the hippocampus to cortical brain regions (Lupien and Lepage, 2001).

Given these adverse and neurotoxic impacts of chronic stress, there is a pressing need for a deeper comprehension of the health relevance of subclinical cortisol levels, particularly in mid-aged and healthy individuals. The association between reported experienced stress and elevated GC levels in healthy adults is not straightforward and detected in some (Almadi et al., 2013) but not other studies (Jeckel et al., 2010; Engert et al., 2018; Prado-Gascó, et al., 2019). Researchers are thus looking for biomarkers of physiological stress and disorder, which may facilitate early detection of stress load and disease risk. This necessity served as the impetus for the current study.

1.3. Systemic inflammation

Similar to the stress response, the acutely adaptive innate immune response can become damaging if not appropriately terminated. Failure to downregulate pro-inflammatory activity can result in systemic inflammation, a maladaptive state that manifests itself with prolonged, low-level elevations of pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and high-sensitive C-reactive Protein (hs-CRP), the most commonly assessed markers of systemic inflammation (Slavich, 2020; Rohleder, 2019).

Like chronic stress, systemic inflammation is associated with a range of psychological disorders such as MDD (Rosenblat et al., 2014) and Schizophrenia (Stojanovic et al., 2014).

Neuroinflammation and the co-occurrence of systemic inflammation and neuronal have been implicated in the development of these disorders. Early studies in rats show that neuropathological changes and loss of synapses and granule neurons are associated with chronic neuroinflammation and IL-6 concentrations (Campbell et al., 1993; Heyser et al., 1997; Qiu et al., 1998). IL-6 also appears to modulate neurogenesis in the dentate gyrus of the mouse hippocampus (Vallieres et al., 2002).

In humans, associations between inflammation and brain morphology are commonly studied in clinical samples. Systemic inflammation in terms of elevated CRP, IL-6 and TNF-α levels is inversely correlated to lower CT and cortical grey matter volume in patients with schizophrenia (Jacomb et al., 2018; Massuda et al., 2014), and it has been associated with the promotion of neurodegeneration in chronic neurodegenerative diseases, such as Alzheimer's disease (Holmes et al., 2007). Similar associations have also been found in subclinical samples, albeit less prominently, providing evidence for an inflammatory pathway towards progressive neuronal atrophy and disorder development. Studies involving healthy subjects report inverse associations between IL-6 or CRP levels and hippocampal grey matter and total brain volume (Jefferson et al., 2007; Marsland et al., 2008), as well as cortical thinning in middle aged (van Velzen et al., 2017) and elderly individuals without dementia (Fleischman et al., 2010; McCarrey et al., 2014; Gu et al., 2017). Biological ageing processes are accompanied by enhanced levels of inflammatory markers (Godbout and Johnson, 2004; Wei et al., 1992; Ye and Johnson, 1999) and also appear to play an important role in the interplay of chronic stress and systemic inflammation (Gouin et al., 2008). Thus, early onset of inflammation-mediated neuronal atrophy may serve as a risk marker for accelerated ageing and neurodegenerative disorders.

1.4. Stress, inflammation, and brain structure

Chronic stress and cortisol exposure closely interact with systemic (or chronic low-grade) inflammation. While GCs generally have a regulatory effect on the acute immune response (Waage et al., 1990), prolonged psychosocial stress is associated with elevated low-grade inflammation (Rohleder, 2014, 2019). It is thus presumed that chronic

stress may alter GC signalling and lead to a pro-inflammatory effect (Ader et al., 1995; Arimura et al., 1994; Black, 2002; Chrousos, 2000; Hänsel et al., 2010; McEwen et al., 1997). The GC receptor hypothesis for example assumes that due to permanent exposure to GCs, not only receptors in hypothalamus and pituitary but also in immune cells such as macrophages become insensitive to GCs, which can lead to the disruption of GC-induced suppression of inflammation (Cohen et al., 2012; Miller et al., 2008; Stark et al., 2001). Multiple human studies suggest a link between increased stress experience and inflammation, including in healthy adults (Maes et al., 1998; Miller et al., 2002). Chronic stress and systemic inflammation are highly synergistic in their interactive effect on many pathologies such as Metabolic Syndrome (MtS) (Almadi et al., 2013), MDD (Robles et al., 2016) or coronary artery disease (Nijm and Jonasson, 2009).

Although the interplay between chronic stress and systemic inflammation and their joint contribution to alterations in brain morphology has been subject to several high-profile reviews, studies examining these associations in a joint statistical model and in a healthy sample are rare. Summarizing the animal literature, Sorrells and Sapolsky (2007) and Kubera et al. (2011) conclude that in animal models, stress-induced inflammation enhances neurodegeneration, which in turn may provoke depression-like behaviours (see also inflammatory and neurodegenerative hypothesis, Maes et al., 2009). Fewer studies have been able to investigate this maladaptive triangulation in humans, although one review on MDD patients identifies similar relations on chronic stress, neuroinflammation and alterations in brain structure and function (Kim and Won, 2017). Regarding endocrine stress markers, reduced GC responsiveness and enhanced IL-6 levels were also related to thinner cortices in patients with mood disorders (van Velzen et al., 2017) and to smaller hippocampi for patients with MDD specifically (Frodl et al., 2012).

1.5. Present study

In addition to the clinical studies mentioned, there is limited understanding of how chronic stress, systemic inflammation, and brain structure are connected in healthy adults and the general population. This may hinder the use of subclinical levels of glucocorticoids and inflammatory markers as early indicators of diseases related to neurodegeneration. The extent to which chronic stress and systemic inflammation are linked to neuronal atrophy in the absence of disorder or advanced aging, as well as the potential combined effects of stress and inflammation as risk factors for neurodegenerative processes, remains understudied. This study aims to address these questions to enhance our understanding of disorder development and to identify chronic stress and inflammation as risk factors for early neurodegenerative processes. To map the interrelation of physiological indices related to chronic stress, systemic low-grade inflammation, and cortical and subcortical brain morphology, we used multimodal cross-sectional data from N = 169 healthy adults (N = 150 for subcortical morphology). Data collected at baseline of a large-scale, multi-disciplinary longitudinal mental training intervention study, the ReSource Project (Singer et al., 2016). In the context of this study, chronic stress refers to the prolonged stress physiological load over several weeks and months, measured via hair cortisol (HCC) and hair cortisone (HEC) concentrations (Short et al., 2016; Stalder and Kirschbaum, 2012; Stalder et al., 2012). Systemic inflammation was indicated by blood serum levels of IL-6, hs-CRP and the systemic inflammation index (SII). Finally, we examined brain morphology via hippocampal volume (HCV), since hippocampal structure and function are closely tied to stress and neuroinflammation, as well as via thickness of the neocortex (cortical thickness, CT). CT provides an anatomically specific (Lemaitre et al., 2012; Winkler et al., 2010) and particularly sensitive measures of grey matter variation, especially in ageing (Hutton et al., 2009), for example compared to volume-based methods.

In previous work of the ReSource Project, we demonstrated the

multidimensionality of the psychophysiological construct stress and its relation to various health and sleep measures using network analysis (Engert et al., 2018). Here, we now examine inflammation and stress as latent constructs and in their relation to brain morphology. Using SEMs, we test secondary hypotheses on specific physiological pathways to neurostructural atrophy involving mediation and moderation pathways through stress and inflammation: We expected a positive association between the latent constructs chronic stress and systemic inflammation, representing stress-related inflammation, potentially mediated via the body mass index (BMI), which we previously found associated with single inflammatory and stress-related biomarkers in the same sample (Engert et al., 2018). We also expected a negative relation of elevated chronic stress and systemic inflammation on both CT and HCV, in form of either an indirect association of stress via inflammation, or a moderation effect in terms of a statistical interaction of the latent variables systemic inflammation and chronic stress. Finally, next to IL-6 and hs-CRP as our primary indicators of systemic inflammation, we further tested an indirect association from chronic stress to brain structure via the systemic inflammation index (SII) which is assumed to have prognostic value for overall survival in certain cancers (Hong et al., 2015; Zhong et al., 2017) but has not yet been examined in humans with regard to psychosocial factors such as stress-related inflammation.

2. Methods

2.1. Sample and recruitment

Data for the present investigation was collected in the context of a large-scale 9-month longitudinal mental training study, the ReSource Project (Singer et al., 2016). Healthy participants with an age range of 20–55 years (mean age = 39.4, SD = 9.8) were recruited (see Tables 2a and 2b). All participants underwent mental and physical health screenings as well as two clinical diagnostic interviews [Structured Clinical Interview for DSM-IV Axis-I (SCID-I) (Wittchen and Pfister, 1997); SCID-II for Axis-II disorders (First et al., 1997)]. Participants were excluded if they fulfilled the criteria for an Axis I disorder in the past two years or an Axis-II disorder at any time in their life. Additional exclusion criteria were several chronic physical pathologies and intake of medication affecting the HPA axis or central nervous system. A detailed description of the recruitment procedure and information about the final sample of the ReSource Project can be found in Singer et al. (2016), chapter 7. The ReSource Project was registered via the Protocol Registration System of ClinicalTrial.gov (Identifier NCT01833104) and the study was approved by the research ethics boards of Leipzig University (ethic number: 376/12-ff) and Humboldt University Berlin (ethic numbers: 2013–20, 2013–29, 2014–10). Participants gave written informed consent, received financial compensation, and could withdraw from the study at any time.

For the present investigation, only data collected at the pre-training baseline (T0) of the ReSource Project was evaluated. Although the data reported here were previously published in the context of other research questions mostly pertaining to the effect of ReSource training (Degering et al., 2023; Engert et al., 2018; Puhlmann et al., 2019a; Puhlmann et al., 2019b; Puhlmann et al., 2021a; Puhlmann et al., 2021b; Valk et al., 2017, 2023), none of these studies investigated the complex relation between measures of chronic stress physiology, inflammatory activity and brain morphology, and potentially associated pathways of moderation and mediation. The present study is an a-posteriori exploratory study not planned during the designing of the ReSource Project and all formulated hypotheses and models should be considered secondary.

2.2. Measures

2.2.1. Indices of chronic stress

Hair cortisol (HCC) and Hair Cortisone Concentration (HEC). A popular biomarker of chronic stress is the extraction of HCC, and HEC as a

complementary measure, which both serve as indices of systemic cortisol exposure (Short et al., 2016; Stalder and Kirschbaum, 2012; Stalder et al., 2012). HCC appears to be quite robust to confounders and is associated with well-known correlates of stress-related cardiometabolic parameters such as systolic blood pressure and BMI (Stalder et al., 2017). Both HCC and HEC are generally more stable compared to serum or salvia cortisol levels that are part of a dynamic system with day-to-day changes in activity (Ross et al., 2014). For their assessment, hair strands were collected close to the scalp and a 3 cm segment, corresponding to approximately 3 months of cortisol exposure, was analysed. Concentrations of HCC and cortisone were measured with liquid chromatography-tandem mass spectrometry (LC–MS/MS) (Gao et al., 2016).

2.2.2. Indices of systemic inflammation

Interleukin-6 (IL-6) and high-sensitive C-Reactive Protein (hs-CRP). IL-6 and hs-CRP were used as primary indices of systemic inflammation. For the assessment of IL-6 and hs-CRP levels, 5.5 ml blood was collected and stored at −80 °C. Hs-CRP was measured with a latex-enhanced immunoturbidimetric assay using the Siemens Advia 1800 Clinical Chemistry System (Siemens Healthineers, Tarrytown, NY, USA). IL-6 levels were detected with a solid phase enzyme-labelled chemiluminescence immunometric assay using the random access chemiluminescence-immunoassay system (IMMULITE, 2000; Siemens Healthineers, Tarrytown, NY, USA) (for more details see Engert et al. (2018)). Levels of IL-6 follow a circadian cycle, with lower levels during daytime and higher levels during the night (Vgontzas et al., 2005). To account for these fluctuations, time of sampling was documented and included as a control variable in all analysis.

2.2.3. Systemic inflammation index (SII)

Systemic inflammation is a complex and extensive process, during which not only levels of IL-6 and hs-CRP but also the count of circulating leukocytes such as neutrophile granulocytes and monocytes is increased while the lymphocyte count is decreased (Rink et al., 2015). Some studies use ratios of neutrophils, thrombocytes (platelets) and lymphocytes as indicators for systemic inflammation (Systemic inflammation Index, SII; Hong et al., 2015; Wu et al., 2016). The SII can thus be derived from a complete blood count and is calculated as the product of thrombocytes and neutrophils divided by lymphocytes (Hong et al., 2015; Hu et al., 2014; Wu et al., 2016).

The SII is assumed to have prognostic value for overall survival in certain cancers (Hong et al., 2015; Zhong et al., 2017). Even though the SII is an index of systemic inflammation, it has not yet been examined with regard to psychosocial factors in humans. In the current study, IL-6 and hs-CRP were considered as the main marker of systemic inflammation, and the SII was related to chronic stress and brain structure in an additional analysis.

2.2.4. MRI acquisition

High resolution T1-weighted structural MRI images were acquired on a 3T Trio TIM scanner (Siemens Verio; Siemens, Erlangen, Germany) with a 32 -channel head coil, using magnetization-prepared rapid gradient echo (MPRAGE; 176 sagittal slices; repetition time, 2300 ms; echo time, 2.98 ms; inversion time, 900 ms; flip angle, 7; field of view, 240256 mm2; and matrix, 240256; 111 mm3 voxels) sequence.

2.2.5. Cortical thickness (CT) calculation and selection of regions of interest (ROIs)

We used Freesurfer version 5.1.0 (consistent with previous publications from the ReSource Project, e.g. Valk et al., 2017) to generate cortical surface models for the calculation of CT following previously reported steps (Dale et al., 1999; Fischl et al., 1999; see also Valk et al., 2017). Briefly, T1-weighted images were intensity normalized and skull stripped, and the grey/white matter cortical boundary tessellated. After automatic correction of topology, the surface deformations converged the cortical interfaces of the inner boundary (grey/white matter) and outer boundary (grey matter/cerebrospinal fluid), following intensity gradients. Surface reconstruction was visually inspected by two independent raters and inaccuracies manually corrected. CT was then calculated as the shortest distance from the grey/white matter boundary to the grey matter/CSF boundary at each vertex on the tessellated surface. For more details of the processing steps see Dale et al. (1999); Fischl et al. (1999) and Han et al. (2006). Regions of interest (ROIs) for CT analyses were parcellated following the Desikan-Killiany Atlas as implemented in FreeSurfer 5.1.0.

To not overload our models, and since it is advised to build SEMs on a strong conceptual foundation (Bentler and Chou, 1987; Hoyle, 1995), we focused on CT of 14 regions of interest identified from the literature. We compared ROIs of studies with healthy samples (Kaur et al., 2015; Kremen et al., 2010; Marsland et al., 2015; Piras et al., 2012; Savic, 2015; van Velzen et al., 2017), pathological samples (Chiappelli et al., 2017; Jacomb et al., 2018; Lebedeva et al., 2018; Liu et al., 2015; Massuda et al., 2014; Ottino-Gonzalez et al., 2017; Veit et al., 2014), aged samples (Fleischman et al., 2010), longitudinal studies (Gu et al., 2017; McCarrey et al., 2014) and two reviews (Byrne et al., 2016; Sheline, 2003), selecting ROIs in which CT had been found to relate to either HCC/HEC or IL-6/CRP. All ROIs and the final factor solution for ROIs is presented in Table 1 (for more details on ROI selection see *Supplementary Methods C*).

2.2.6. Hippocampal volume (HCV) calculation

On the base of the high resolution T1-weighted structural MRI images CA1-3, CA4/DG, and subiculum (SUB) were segmented, with a patch-based algorithm in every subject. Briefly, the algorithm employs a population-based patch normalization relative to a template library (Kulaga-Yoskovitz et al., 2015), which has shown high segmentation accuracy of hippocampal subfields in previous validations (Caldairou et al., 2016). All HCV segmentations were quality controlled by two independent raters and any segmentations with average quality rating scores lower than 5 were excluded from the analysis (details on the algorithm and quality control procedure see Puhlmann et al., 2021a). While Freesurfer also provides estimates of HCV, we use the patch-based method throughout the ReSource Project following our preregistered study. The resulting surface-based estimates show decent overlap with Freesurfer estimates (Puhlmann et al., 2021a).

2.2.7. Other measures

BMI, hormonal status and smoking behaviour are suggested as potential covariates of markers of stress, inflammation and brain structure (Kajantie and Phillips, 2006; Thayer et al., 2010; Ugur et al., 2018; Veit, R. et al., 2014; Wright et al., 2006).

The body mass index (BMI), as the relation of the individual's body weight in kilograms to the squared height, was incorporated as an indicator for adipose tissue. Hormonal status was documented through the categories male, female no cycle, female hormonal contraceptives and female natural cycle and smoking status was measured as binary variable, smokers/non-smokers.

2.3. Data analysis

Data analysis was conducted using Structural Equation Models (SEMs). SEMs allow the testing of complex interrelations by representing conceptual research models through a system of connected regression-style equations. An additional benefit of SEMs is the possibility to include latent factors, which are estimated based on multiple indicator variables via factor analysis. In our hypothesized model, we indicated chronic stress via HCC and HEC, systemic inflammation via IL-6 and hs-CRP, and CT via the selected ROIs, based on the above reviewed evidence. Using multiple indices increases the reliability of latent factors and reduces the influence of random measurement noise. Total left and right HCV were added as measurement variables without forming a

Table 1
Latent factor solution of ROIs.

Latent Variable	ACC	Frontal Lobe	Temporal Lobe	Entorhinal Cortex	Parahippocampal Cortex
Indicator Variables	left Frontal Rostral ACC	left Frontal Superior Gyrus	left Temporal Fusiform Gyrus	left Entorhinal Cortex	left Parahippocampal Cortex
	right Frontal rostral ACC	right Frontal Superior Gyrus	right Temporal Fusiform Gyrus	right Entorhinal Cortex	right Parahippocampal Cortex
	left Frontal Caudal ACC right Frontal Caudal ACC	left Frontal Caudal Middle Gyrus right Frontal Caudal Middle Gyrus	left Superior Temporal Banks right Superior Temporal Banks		
		left Paracentral Gyrus right Paracentral Gyrus left Precentral Gyrus right Precentral Gyrus	left Temporal Inferior Gyrus right Temporal Inferior Gyrus left Transverse-temporal Gyrus right Transverse-temporal Gyrus left Temporal Middle Gyrus right Temporal Middle Gyrus left Temporal Superior Gyrus right Temporal Superior Gyrus		

Final five latent factor solution, each latent factor listed with all its ROI indicator variables.

latent construct as literature did not indicate subfield specific associations.

2.3.1. Sample size calculation

Following recommendations to ensure adequately powered SEMs (MacCallum et al., 1996; Westland, 2010), we assessed whether the pre-existing sample size was sufficient for the planned model using the *A-priori Sample Size Calculator for Structural Equation Models* (Soper, 2022). Given the levels of complexity in both models, the available sample sizes of N = 169 respectively N = 150 could be considered sufficient. For more details on the sample size calculation see *Supplementary Methods E*.

2.3.2. Variable pre-processing

The biological variables IL-6, hs-CRP, HCC and HEC were ln-transformed to remedy their typical skewed distribution. Outliers defined as $\pm SD = 3$ were winsorized to the upper or lower boundary of 3 SDs, respectively. Estimating the models with non-winsorized data did not change our findings. For more details on the statistical pre-

processing of variables see *Supplementary Methods D*.

2.3.3. Fitting the SEMs

To address our conceptual model of interrelations, we fit one SEM to map the chronic stress and systemic inflammation in relation to CT, and one in relation to HCV (Figs. 1 and 2, respectively). Chronic stress and systemic low-grade inflammation were included as latent factors as described above, with one indicator variable fixed to $\lambda = 1$, as recommended for hypothesis-driven measurement models with few indicator variables (Hayduk and Littvay, 2012). The SII was included exploratorily as an additional endogenous variable. BMI was modelled as a mediator from chronic stress to systemic inflammation following previous results (Engert et al., 2018). Age, hormonal status (male, female no cycle, female hormonal contraceptives, female natural cycle) and information about smokers/non-smokers were always included as exogenous variables (i.e., variables that perform only as independent variable) to account for their well-established influence on cortisol/cortisone, inflammatory proteins and brain structure (Fleischman et al., 2010; Godbout and Johnson, 2004; Kajantie and Phillips, 2006; Thayer et al.,
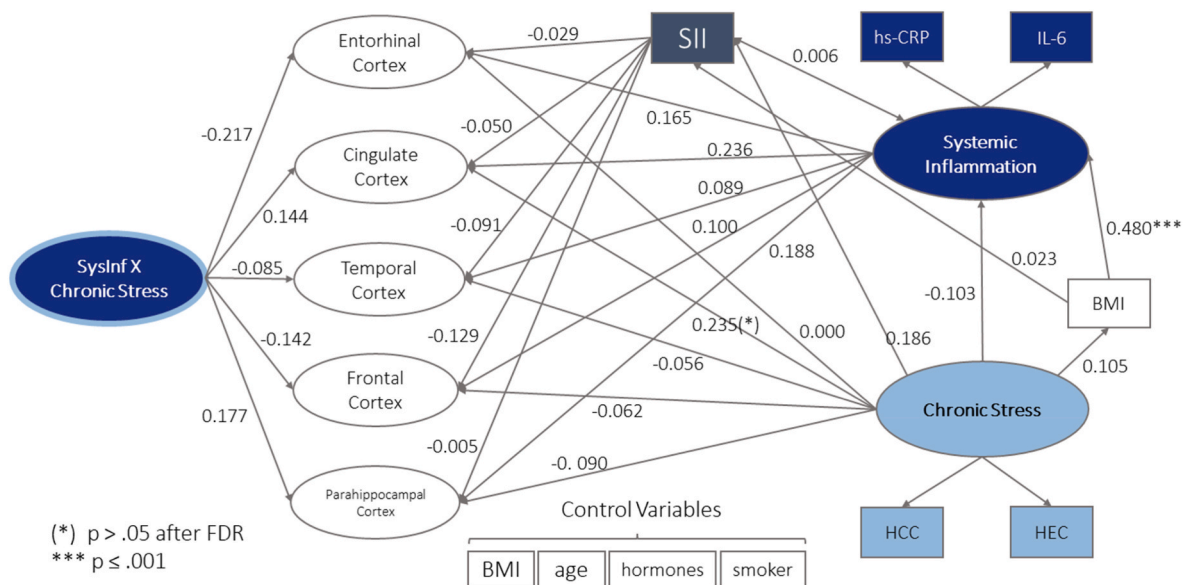

Fig. 1. Structural model with all latent factors of CT, latent factor chronic stress with indicator variables HCC and HEC, latent factor systemic inflammation with indicator variables IL-6 and hs-CRP and interaction factor of inflammation and chronic stress. Standardized (latent and observed variables) path coefficients are reported. All variances, indicator variables for the CT ROIs and covariations of error terms are hidden for visual clarity. Spheres represent latent factors, square boxes measured variables. BMI is modelled as a control variable for all variables except for chronic stress and systemic inflammation, where it was modelled as a mediator variable.
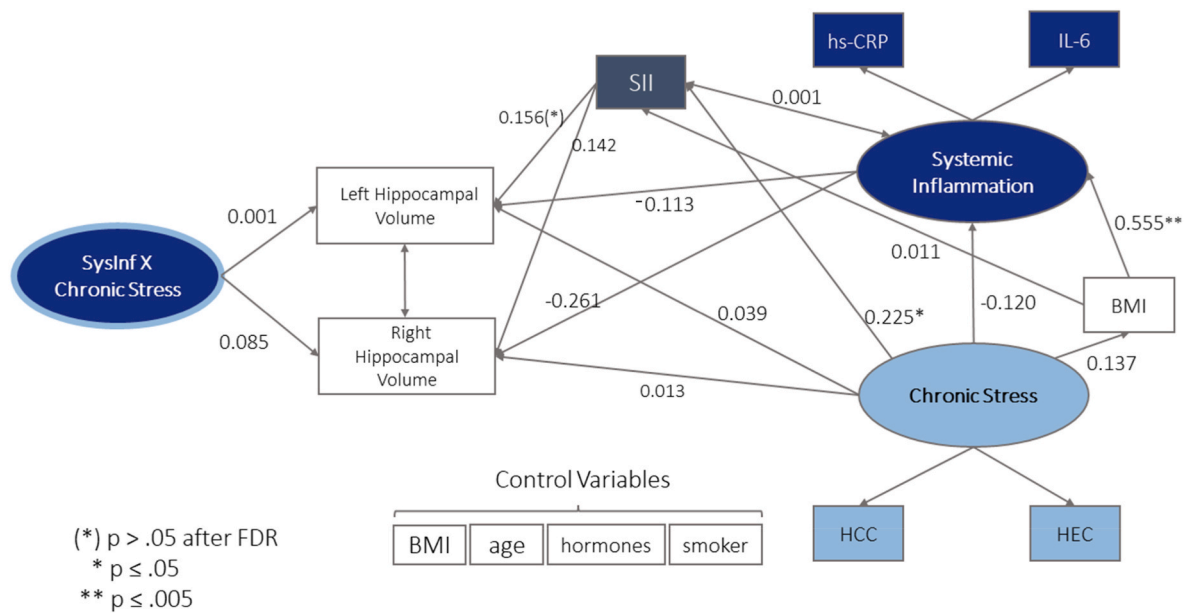
Fig. 2. Structural model with HCV in left and right hemisphere, latent factor chronic stress with indicator variables HCC and HEC, latent factor systemic inflammation with indicator variables IL-6 and hs-CRP and interaction factor of inflammation and chronic stress. Standardized (latent and observed variables) path coefficients are reported. All variances, indicator variables for the CT ROIs and covariations of error terms are hidden for visual clarity. Spheres represent latent factors, square boxes measured variables. BMI is modelled as a control variable for all variables except for chronic stress and systemic inflammation, where it was modelled as a mediator variable.

2010; Ugur et al., 2018; Veit, R. et al., 2014; Wright et al., 2006).

As the first physiological endpoint, CT was added to the SEM. To robustly represent CT without averaging across functionally and structurally heterogeneous regions, we formed five latent CT factors based on the ROI estimates (Table 1). For more details on the formation of latent factors of cortical thickness see Supplementary Methods C.

The second model relating chronic stress and systemic inflammation to HCV was identical to the model comprising CT, except that all latent factors of CT were replaced with the two exogenous variables HCV in the left and right hemisphere.

2.3.4. Path analyses and model comparisons

To test the statistical significance of direct associations, potential moderation effects and indirect associations between the latent constructs and indicator variables of interest, we conducted path-analyses within the two fitted SEMs. Indirect associations were evaluated within an implicit procedure (Rungtusanatham et al., 2014), testing for the joint significance of every constituent path of an indirect association. For moderation analysis, product indicators for latent interaction factors were calculated, following the residual centring approach (Little et al., 2006), which is also recommended by Steinmetz et al. (2011). All path coefficient estimates are reported in the all-variables-standardized-version, *Std.all*. For evaluating statistical significance an α-level of 0.05 was applied. Family-wise error correction was performed on significant parameters by applying the false discovery rate (FDR) (Benjamini and Hochberg, 1995) to correct for multiple comparisons of paths to each of the different brain areas included in the model. Once all models were set, direct model comparisons of nested models were evaluated through significance testing of chi2 differences.

3. Results

3.1. Final sample

From the $N = 332$ subjects included at study baseline (T0) (Singer et al., 2016), $n = 169$ provided data for all present variables of interest in the CT model and $n = 150$ in the HCV model and could thus be used in

the SEM analysis (see Table 2a) and b), for more details see also Supplementary Table S1).

Missing data was excluded case wise, as implemented by the lavaan (Rosseel, 2012) and sem (Fox, 2006) packages to ensure a true and unbiased correlation matrix as input for the SEM. Most cases were excluded due to missing HCC or HEC data, because sampling of hair for the assessment of HCC and HEC was presented to participants as an optional rather than a core testing procedure, leading to lower adherence rates (see Puhlmann et al., 2021a,b for further details).

3.2. Correlations of stress and inflammation biomarkers

Before building latent constructs, partial correlations between the key risk factors in our hypothesized pathways were calculated, namely the chronic stress indicator variables HEC and HCC, inflammation indicators hs-CRP and IL-6, as well as SII and BMI. We replicated previously identified associations (see Engert et al., 2018) and additionally

Table 2a
Sample Characteristics CT for model (N = 169).

	Female	male	overall
	(N = 109)	(N = 60)	(N = 169)
Mean age (SD)	41.0 (9.40)	36.6 (9.84)	39.4 (9.75)
Mean BMI (SD)	23.0 (3.29)	24.3 (2.84)	23.5 (3.19)
no cycle (%)	25 (22.9)	0 (0)	25 (14.8)
hormonal contraceptives (%)	24 (22.0)	0 (0)	24 (14.2)
natural cycle (%)	60 (55.0)	0 (0)	60 (35.5)
Smoking status (%)	16 (14.7)	5 (8.3)	21 (12.4)
Median SII (Gpt/l) [range]	471 [170, 1280]	406 [147, 1320]	445 [147, 1320]
Median IL-6 (pg/ml) [range]	1.49 [1.28, 24.6]	1.44 [1.28, 3.40]	1.47 [1.28, 24.6]
Median hs-CRP (mg/L) [range]	0.925 [0.128, 13.2]	0.500 [0.138, 5.98]	0.709[0.128, 13.2]
Median HCC (pg/mg) [range]	3.31 [0.486, 95.2]	4.81 [0.181, 52.1]	3.83 [0.181, 95.2]
Median HEC (pg/mg) [range]	8.89 [1.87, 66.1]	14.6 [2.54, 51.0]	11.0 [1.87, 66.1]

Table 2b
Sample Characteristics for HCV model (N = 150).

	Female	male	overall
	(N = 98)	(N = 52)	(N = 150)
Mean age (SD)	40.9 (9.52)	36.1 (9.34)	39.2 (9.70)
Mean BMI (SD)	23.1 (3.41)	24.4 (2.91)	23.6 (3.30)
no cycle (%)	23 (23.5)	0 (0)	23 (15.3)
hormonal contraceptives (%)	21 (21.4)	0 (0)	21 (14.0)
natural cycle (%)	54 (55.1)	0 (0)	54 (36.0)
Smoking status (%)	14 (14.3)	3 (5.8)	17 (11.3)
Median SII (Gpt/l) [range]	477 [170, 1280]	406 [178, 1320]	452 [170, 1320]
Median IL-6 (pg/mL) [range]	1.49 [1.29, 24.6]	1.44 [1.28, 2.10]	1.48 [1.28, 24.6]
Median hs-CRP (mg/L) [range]	0.943 [0.128, 13.2]	0.532 [0.138, 5.98]	0.741[0.128, 13.2]
Median HCC (pg/mg) [range]	3.59 [0.486, 95.2]	4.63 [0.181, 52.1]	3.99 [0.181, 95.2]
Median HEC (pg/mg) [range]	8.85 [1.87, 61.8]	13.7 [2.54, 45.6]	10.9 [1.87, 61.8]

found that the SII was significantly positively correlated with HCC (p < 0.05) (see Table 3).

In initial sanity checks, we also confirmed the significance of several common associations not directly related to our conceptual research model, such as negative associations of age with latent CT factors and HCV, and positive associations between BMI and inflammation (see Supplementary Tables S8 and S9).

3.3. Cortical thickness model

Setting up the full CT Model (N = 169) as described above (see Fig. 1), resulted in an overidentified model with good model fit indicated by most model fit measures (robust chi2 (910.904) < 2*df (706), robust CFI (0.929), robust TLI (0.918), robust RMSEA (0.041), robust SRMR (0.059)). Path analysis indicated that the factor chronic stress was not associated with any factor representing CT (see Supplementary Table S2). Although there was a significant association of chronic stress and CT in the anterior cingulate cortex, this relation was no longer significant after correcting for multiple comparisons with the positive false discovery rate (see Fig. 1). Similarly, there was no significant indirect association of chronic stress and CT via systemic inflammation (Fig. 1).

Path analysis further showed that systemic inflammation was not associated with any factor representing CT (see Fig. 1) and that chronic stress did not play a moderating role in the association of systemic inflammation and CT (see Supplementary Table S3) and Fig. 1).

3.4. Hippocampal Model

Setting up the HCV model, modelling the same paths as in the CT model, two Heywood cases occurred. They were handled by setting the

Table 3
Partial Correlations among stress-, and inflammation-related measures.

	SII	BMI	IL6	hs-CRP	HCC
BMI	0.04				
IL6	0.11	0.15*			
hs-CRP	−0.01	0.30****	0.33****		
HCC	0.18*	0.12	−0.01	0.03	
HEC	0.07	0.06	0.02	−0.04	0.69****

Partial correlations among stress-, and inflammation-related measures, controlling for age, hormonal status (male, female no cycle, female hormonal contraceptives, female natural cycle) and smoking status (smoker, non-smoker). *p < .05; **p < .01; ***p < .001; ****p < .0001.

product indicator variables to be equal (for more details on the handling of Heywood cases see Supplementary Methods B). All model fit indices and parameter estimates in the HCV model are reported in the Heywood case corrected version. Thus, the full HCV model (see Fig. 2), too, resulted in an overidentified model with good model fit (robust chi2 (40.945) < 2*df (60), robust CFI (1.000), robust TLI (1.117 truncated to 1.000) robust RMSEA (0.000), robust SRMR (0.060)) (see Hu and Bentler, 1999; MacCallum et al., 1996).

For the Hippocampal Model, similar to CT, path analysis showed no associations of either chronic stress or systemic inflammation with the left or right HCV (see Fig. 2; Supplementary Tables S4 and S5)). There was also no significant specific indirect association with chronic stress via systemic inflammation and chronic stress did not play a moderating role in the relation between systemic inflammation and HCV.

All results of the path analyses were confirmed when addressing the same hypothesized paths via model comparison of constrained models with the paths of interest individually fixed to zero, compared to unconstrained models.

3.5. Exploratory analysis

Introducing the SII as a potentially interesting supplement when it comes to measuring the relation of inflammation and brain structure, we evaluated the association of SII with factors of CT and HCV, as well as an indirect association of chronic stress via the SII, in exploratory path analysis (see Figs. 1 and 2).

None of these associations was significant in the CT model (see Supplementary Table S6). In the HCV model the SII was significantly positively associated with the left HCV (see Supplementary Table S7), which was no longer significant after correcting for multiple comparisons with the positive false discovery rate. The SII was furthermore significantly related to the latent factor chronic stress (*p < .05*) in the HCV model (see Fig. 2), in line with its positive correlation with the measurement variable HCC (see Table 3).

To account for potential associations masked by the grouping of IL-6 and hs-CRP, we included hs-CRP and IL-6 as separate variables in both the CT and the HCV model, which did not reveal any unknown significant associations or changed our results in any significant manner (see Supplementary Tables S11 and S12).

Most of the specific brain regions included in the prespecified SEMs were identified in studies with at-risk populations. It is possible that other brain regions are sensitive to chronic stress and inflammation in the present healthy, mid-aged sample. To address this possibility, we conducted an exploratory SEM with whole brain mean CT as the target endpoint. We set up this post-hoc model, to explore associations between the observed variables hs-CRP, IL-6 and SII, the latent variable chronic stress, indicated by HCC and HEC and the latent factor mean cortical thickness as whole brain measure, indicated by mean CT of the left and right hemisphere. Setting up the whole brain model (N = 169) as described below (see Fig. 3), resulted in an overidentified model with good model fit, indicated by most model fit measures (robust chi2 (23.737), robust CFI (0.987), robust TLI (0.958), robust RMSEA (0.060), robust SRMR (0.023)). No associations with hs-CRP, IL-6 or chronic stress were found, but interestingly, the SII was significantly inversely related with mean cortical thickness (see Fig. 3 & Supplementary Table S10).

4. Discussion

Chronic stress and related glucocorticoid (GC) exposure are linked to systemic inflammation (Chrousos, 2000; Cohen et al., 2012; Hänsel et al., 2010), and both processes have been implicated in advanced neurodegeneration (Gu et al., 2017; Jefferson et al., 2007; Kim and Won, 2017; Lebedeva et al., 2018; Lupien et al., 1998; Marsland et al., 2008; McEwen and Gould, 1990; McEwen, 1999). Less is known, however, about the relation of biomarkers of low-grade inflammation, chronic
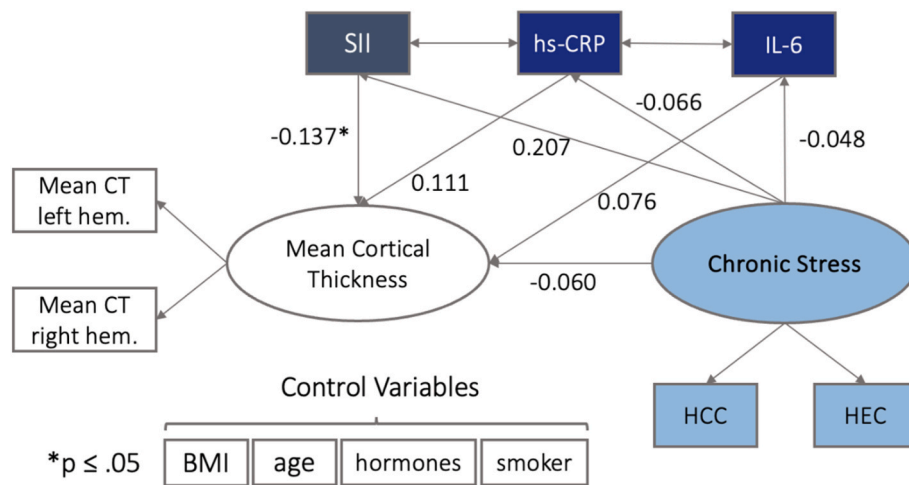
Fig. 3. Structural model with latent factor Mean Cortical Thickness (indicator variables mean cortical thickness left and right hemisphere), latent factor Chronic Stress with indicator variables HCC and HEC and further observed variables: IL-6, hs-CRP and SII. Standardized (latent and observed variables) path coefficients are reported. All variances and covariations of error terms are hidden for visual clarity. Spheres represent latent factors, square boxes measured variables. All variables are controlled for BMI, age, hormonal -and smoking status.

stress and brain morphology in healthy subclinical populations. The present study adopted a structural equation modelling (SEM) approach to map these relations in a population-based sample of healthy adults, recruited in the context of the ReSource Project (Singer et al., 2016), including the influence of age and BMI, with the aim of informing the use of these indices in future preventive healthcare approaches.

Models replicated patterns of associations between age and cortical thickness (Salat et al., 2004), age and BMI, and sex and BMI (Heymsfield et al., 1993; Mazariegos et al., 1994). In line with other studies (Wright et al., 2006) we also find a positive association of the latent systemic inflammation factor with the body mass index (BMI). This result replicates our earlier work in the same participants, showing a link between BMI and specifically IL-6 levels in a network analysis investigating the multidimensional interrelations of a large set of stress- and health-related measures (Engert et al., 2018). Subcutaneous adipose tissue is a contributor to increased levels of cytokines and especially IL-6 (Kern et al., 2001; Mohamed-Ali et al., 1997), properties that seem to be represented well in our latent inflammation factor. However, none of the formulated expectations could be supported in this sample. Chronic stress was not associated with HCV or any CT in the identified ROIs, directly or indirectly via systemic inflammation. Similarly, systemic inflammation, was neither directly associated with HCV or CT, nor was this association moderated by chronic stress. The systemic inflammation index (SII) based on neutrophil, thrombocyte and lymphocyte cell counts emerged as a potentially interesting additional inflammatory marker that was associated with HCC, although this link was rendered nonsignificant when HCC and HEC were grouped into a latent chronic stress factor in the CT model. Furthermore, in the exploratory whole brain model, the SII exhibited significant inverse associations with mean cortical thickness. This might hint towards the SII as an useful supplement when it comes to measuring the relation of inflammation and brain structure.

Especially in patients and at-risk groups such as older adults, evidence for a link between neuronal atrophy and chronic enhanced cortisol levels (Lebedeva et al., 2018) as well as systemic inflammation (Fleischman et al., 2010; Jefferson et al., 2007; Kaur et al., 2015; van Velzen et al., 2017) is substantial. Chronic stress and systemic inflammation have also been quite reliably associated (Arimura et al., 1994; Black, 2002; Chrousos, 2000; Cohen et al., 2012; Hänsel et al., 2010; McEwen et al., 1997; Munck & Náray-Fejes-Tóth, 1994; Stark et al., 2001). Thus, it is likely that the absence of associations between chronic stress, systemic inflammation and brain structure in the present study are related to the sample demographics. Participants were thoroughly

screened for health at the beginning of the ReSource project as it was a 9-month intense longitudinal training study (Singer et al., 2016). Participants were excluded if they were taking medication affecting the HPA axis or the central nervous system but were not specifically screened for anti-inflammatory medication.

Even for a healthy sample our participants displayed relatively low inflammatory levels of CRP (comparing the current sample medians to serum levels considered normal, CRP (mg/L) current median = 0.709; ref median = 2.8; see Table 2 and Ridker et al., 2000). Accordingly, the results suggest that it is likely that maladaptive interactions only become pronounced as degenerative processes begin to take hold. This may prompt the conclusion that preventive interventions should best be focused on these sensitive periods and at-risk samples. In our own previous work in this sample, we also found that a meditation-based mental training with potential health benefits only reduced CRP and IL-6 values of participants with elevated levels at baseline (Puhlmann et al., 2019b).

To map transitions from health to disorder, future studies at this intersection should attempt to identify critical levels of GCs and cytokines for risk and degenerative processes, already in sub-clinical samples. As mentioned above, many of the associations between chronic stress, systemic inflammation and atrophy of brain structure are strongly influenced by age and more pronounced in elderly subjects (Buford and Willoughby, 2008; Chung et al., 2002; Godbout and Johnson, 2004; Gouin et al., 2008; Kiecolt-Glaser et al., 2003; Licastro et al., 2005; Marsland et al., 2015; Weaver et al., 2002; Wei et al., 1992; Ye and Johnson, 1999), where they emerge even in the absence of disorder (e. g., Gu et al., 2017). With an age range of 20–55 years and a mean age of 40.7 years, the current mid-aged sample was younger than the samples of older to old adults commonly examined in studies that find associations between stress, inflammation and CT (e.g., mean ages of 55, 59, 69 and 81; Fleischman et al., 2010; Kremen et al., 2010; Lebedeva et al., 2018; McCarrey et al., 2014). It can be extrapolated that effects emerge only as ageing proceeds, but our sample was not suited properly to test this hypothesis. Future work should address this research question, using samples with even broader age ranges that include old and very old individuals and, ideally, in prospective longitudinal studies. Since these studies do require a lot of commitment from the participants side and might reflect some cohort specific attitudes such as in the case of our cohort, openness to a mental training intervention, potential selection biases should always be kept in mind when findings are interpreted and generalized.

Although stress and inflammation have been found to affect brain structure in many studies (DePablos et al., 2006; Kubera et al., 2011;

Ottino-Gonzalez et al., 2017; Sorrells and Sapolsky, 2007), there is still no consensus on the scope, characteristics and direction of this effect. Possibly, other pathways than hypothesized here may converge better in healthy samples, especially when combined with more nuanced measurement approaches. For example, chronically enhanced levels of GCs can potentially have different, even opposing effects in the central nervous system and the periphery, and the precise neurotoxic effect of GC-related inflammation also depends on the specific brain area of inflammation (Sorrells and Sapolsky, 2007). SEMs can be employed to test a combination of pro- and anti-inflammatory GC pathways in future investigations.

Rather than adopting a more nuanced approach, as we did in this study, other studies have opted to analyse the combined burden of chronic stress and inflammation via the allostatic load (AL) index. This integrative measure of prolonged stress exposure and associated physiological sequelae, including inflammation and metabolic changes, has been identified as a correlate of cortical structure (Juster et al., 2010; McEwen, 1993; Ottino-Gonzalez et al., 2017). While this might be a promising approach in terms of identifying at-risk groups and monitoring overall health trajectories, we argue that more nuanced systemic models are necessary to understand the emergence of disorder and potential therapeutic pathways, such as stress-reduction, more fully.

Relatedly, correlations of individual biomarkers showed that the SII, but not IL-6 or hs-CRP, was significantly positively correlated with HCC. This is one indication that the SII may be a valuable contribution to the construct of systemic inflammation when it comes to associations with physiological chronic stress. The lack of correlation with IL-6 and hs-CRP confirms that it captures divergent aspects of inflammation and underscores that some associations are only revealed in granular approaches that differentiate distinct markers of the same construct.

4.1. Strength and weaknesses

Previous studies of chronic stress, systemic inflammation and neuronal atrophy have mostly examined only two out of the three variables at a time. Here, we took a more comprehensive approach and jointly modelled all three variables, allowing us to examine multiple pathways of association simultaneously, while also considering the risk factors age, BMI, hormonal status and smoking status. By conducting a sample size calculation, we ensured our sample size to be sufficient for the estimation of both our models. Although this approach is a significant strength of our study, issues with variable convergence to latent factors may also have hindered pathway detection. Hs-CRP and IL-6 did not show high shared variance in their formative latent factor in our models. This raised the question of whether IL-6 and hs-CRP, after controlling for age, BMI, hormonal and smoking status, share sufficient variance to be grouped. We did not find any associations of IL-6 and hs-CRP with brain morphology that was masked by their grouping, still future studies should consider implementing IL-6 and hs-CRP as separate measures of systemic inflammation. Furthermore, although two indicator variables for a latent construct are sufficient in some cases (Hayduk and Littvay, 2012), three or more indicator variables are often recommended (Bentler and Chou, 1987; Hayduk and Littvay, 2012). Especially complex constructs such as systemic inflammation might benefit from a wider selection of measurement variables including more inflammatory cytokines that have been implicated in neurodegeneration such as TNF-alpha or IL-8. This might overcome the limitations of only including IL-6 and CRP, since their reflection of systemic inflammation might not be as straight forward as previously thought (Del Giudice and Gangestad, 2018). In general, SEMs and the hypothesized pathways might converge better in samples with naturally higher variation in stress and inflammation markers, such as ageing and patient populations.

Another strength of the present study is the selection of literature-based regions of interest (ROIs) for CT as well as the literature-based assumptions about the modelled paths. This approach is, however, also relatively conservative, working only with CT averages in previously identified regions. As shown in our exploratory whole brain model, analyses with whole-brain measures such as mean cortical thickness may have more power and be therefore more sensitive to subtle associations, but do not allow the mapping of complex pathways.

While the present investigation is informative for preventive healthcare approaches, future studies may focus on more diverse samples or sensitive periods. Next to ageing, consequences of a permanent exposure to stress are also particularly severe in children, especially if chronic stress is experienced during the developmental period (Björntorp, 2001; Pervanidou and Chrousos, 2012).

Finally, the cross-sectional design of our analysis needs to be acknowledged as a limitation when it comes to causal or at least longitudinal conclusions. Pathway analyses in the context of longitudinal studies will be crucial to establish a quasi-causal chain between chronic stress, systemic inflammation and neurodegeneration in humans.

4.2. Conclusion

A better understanding of the interplay between chronic stress and systemic inflammation in their common contribution to neurodegeneration is crucial to combat stress-related disorders that emerge from cumulative burden in this interdependent system (McEwen, 2000, 2007). The present study used SEMs for nuanced modelling of the relation between chronic stress, systemic inflammation and brain morphology as latent constructs. Models identified no evidence for meaningful associations between these three latent constructs in a sample of healthy middle-aged adults from the general population. We conclude that inflammation and glucocorticoid-mediated neurodegeneration indicated by IL-6 and hs-CRP and HCC and HEC may not be reliably detectable in healthy, mid-aged populations. It is possible that these maladaptive processes and interactions only emerge in advanced ageing, risk- or disorder processes. Nonetheless, the SII could be a promising candidate for detecting associations between inflammation and neurodegeneration in younger and healthy samples.

Although latent constructs did not covary in our analyses as expected, multivariate models were successfully fit and replicated established associations for example between age and neuronal atrophy. These findings can serve as a baseline for studies investigating similar research questions in pathological or ageing populations. We further identified the SII as a potential informative marker of systemic inflammation in human psychobiological studies, which was associated with hair cortisol levels and whole brain mean cortical thickness. Overall, we advocate the use of both the SII and path modelling in future studies to do justice to the complexity and interconnectivity of psychophysiological constructs.

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CRediT authorship contribution statement

Julia K. Schaefer: Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Veronika Engert:** Conceptualization, Data curation, Supervision, Writing – review & editing, Project administration. **Sofie L. Valk:** Data curation, Supervision, Writing – review & editing. **Tania Singer:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing. **Lara M.C. Puhlmann:** Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100781.

References

Ader, R., Cohen, N., Felten, D., 1995. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet 345 (8942), 99–103. https://doi.org/10.1016/S0140-6736(95)90066-7.

Almadi, T., Cathers, I., Chow, C.M., 2013. Associations among work-related stress, cortisol, inflammation, and metabolic syndrome. Psychophysiology 50 (9), 821–830. https://doi.org/10.1111/psyp.12069.

Arimura, A., Takaki, A., Komaki, G., 1994. Interactions between cytokines and the hypothalamic-pituitary-adrenal axis during stress. Ann. N. Y. Acad. Sci. 739, 270–281. https://doi.org/10.1111/j.1749-6632.1994.tb19829.x.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. B 57 (1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x.

Bentler, P.M., Chou, C.-P., 1987. Practical issues in structural modeling. Socio. Methods Res. 16 (1), 78–117. https://doi.org/10.1177/0049124187016001004.

Björntorp, P., 2001. Do stress reactions cause abdominal obesity and comorbidities? Obes. Rev. : an official journal of the International Association for the Study of Obesity 2 (2), 73–86. https://doi.org/10.1046/j.1467-789x.2001.00027.x.

Black, P.H., 2002. Stress and the inflammatory response: a review of neurogenic inflammation. Brain Behav. Immun. 16 (6), 622–653. https://doi.org/10.1016/S0889-1591(02)00021-1.

Buford, T.W., Willoughby, D.S., 2008. Impact of dhea(s) and cortisol on immune function in aging: a brief review. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 33 (3), 429–433. https://doi.org/10.1139/H08-013.

Byrne, M.L., Whittle, S., Allen, N.B., 2016. The role of brain structure and function in the association between inflammation and depressive symptoms: a systematic review. Psychosom. Med. 78 (4), 389–400. https://doi.org/10.1097/PSY.0000000000000311.

Caldairou, B., Bernhardt, B.C., Kulaga-Yoskovitz, J., Kim, H., Bernasconi, N., Bernasconi, A., 2016. A surface patch-based segmentation method for hippocampal subfields. In: International Conference on Medical Image Computing and Computer-Assisted Intervention. Springer, Cham, pp. 379–387.

Campbell, I.L., Abraham, C.R., Masliah, E., Kemper, P., Inglis, J.D., Oldstone, M.B., Mucke, L., 1993. Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. Proc. Natl. Acad. Sci. U.S.A. 90 (21), 10061–10065. https://doi.org/10.1073/pnas.90.21.10061.

Chiappelli, J., Kochunov, P., Savransky, A., Fisseha, F., Wisner, K., Du, X., Hong, L.E., 2017. Allostatic load and reduced cortical thickness in schizophrenia. Psychoneuroendocrinology 77, 105–111. https://doi.org/10.1016/j.psyneuen.2016.11.021.

Chrousos, G.P., Detera-Wadleigh, S.D., Karl, M., 1993. Syndromes of glucocorticoid resistance. Ann. Intern. Med. 119 (11), 1113–1124.

Chrousos, G.P., 1995. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N. Engl. J. Med. 332 (20), 1351–1363. https://doi.org/10.1056/NEJM199505183322008.

Chrousos, G.P., 2000. Stress, chronic inflammation, and emotional and physical well-being: concurrent effects and chronic sequelae. J. Allergy Clin. Immunol. 106 (5), S275–S291. https://doi.org/10.1067/mai.2000.110163.

Chrousos, G.P., 2009. Stress and disorders of the stress system. Nat. Rev. Endocrinol. 5 (7), 374–381. https://doi.org/10.1038/nrendo.2009.106.

Chung, H.Y., Kim, H.J., Kim, K.W., Choi, J.S., Yu, B.P., 2002. Molecular inflammation hypothesis of aging based on the anti-aging mechanism of calorie restriction. Microscopy Inflammation, Stress and Cortical Thickness 41 research and technique 59 (4), 264–272.

Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., Turner, R.B., 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc. Natl. Acad. Sci. U.S.A. 109 (16), 5995–5999. https://doi.org/10.1073/pnas.1118355109.

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis: I. segmentation and surface reconstruction. Neuroimage 9 (2), 179–194. https://doi.org/10.1006/nimg.1998.0395.

Degering, M., Linz, R., Puhlmann, L.M., Singer, T., Engert, V., 2023. Revisiting the stress recovery hypothesis: differential associations of cortisol stress reactivity and recovery after acute psychosocial stress with markers of long-term stress and health. Brain, Behavior, & Immunity-Health 28, 100598.

Del Giudice, M., Gangestad, S.W., 2018. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. Brain Behav. Immun. 70, 61–75.

DePablos, R.M., Villaran, R.F., Arguelles, S., Herrera, A.J., Venero, J.L., Ayala, A., Machado, A., 2006. Stress increases vulnerability to inflammation in the rat prefrontal cortex. J. Neurosci. 26 (21), 5709–5719. https://doi.org/10.1523/JNEUROSCI.0802-06.2006.

Engert, V., Kok, B.E., Puhlmann, L.M., Stalder, T., Kirschbaum, C., Apostolakou, F., Singer, T., 2018. Exploring the multidimensional complex systems structure of the stress response and its relation to health and sleep outcomes. Brain Behav. Immun. 73, 390–402. https://doi.org/10.1016/j.bbi.2018.05.023.

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W., Benjamin, L.S., 1997. Structured Clinical Interview for DSM-IV® Axis II Personality Disorders (SCID-II). American Psychiatric Press Inc, Washington, D.C.

Fischl, B., Sereno, M.I., Tootell, R.B., Dale, A.M., 1999. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum. Brain Mapp. 8 (4), 272–284.

Fleischman, D.A., Arfanakis, K., Kelly, J.F., Rajendran, N., Buchman, A.S., Morris, M.C., Bennett, D.A., 2010. Regional brain cortical thinning and systemic inflammation in older persons without dementia. J. Am. Geriatr. Soc. 58 (9), 1823–1825. https://doi.org/10.1111/j.1532-5415.2010.03049.x.

Fox, J., 2006. Teacher's corner: structural equation modeling with the sem package in r. Struct. Equ. Model. : A Multidiscip. J. 13 (3), 465–486. https://doi.org/10.1207/s15328007sem1303{\textunderscore}7.

Frodl, T., Carballedo, A., Hughes, M.M., Saleh, K., Fagan, A., Skokauskas, N., Connor, T.J., 2012. Reduced expression of glucocorticoid-inducible genes gilz and sgk-1: high IL-6 levels are associated with reduced hippocampal volumes in major depressive disorder. Transl. Psychiatry 2 (3). https://doi.org/10.1038/tp.2012.14 e88-e88.

Gao, W., Kirschbaum, C., Grass, J., Stalder, T., 2016. Lc–ms based analysis of endogenous steroid hormones in human hair. J. Steroid Biochem. Mol. Biol. 162, 92–99.

Geerlings, M.I., Gerritsen, L., 2017. Late-life depression, hippocampal volumes, and hypothalamic-pituitary-adrenal axis regulation: a systematic review and meta-analysis. Biol. Psychiatr. 82 (5), 339–350. https://doi.org/10.1016/j.biopsych.2016.12.032.

Godbout, J.P., Johnson, R.W., 2004. Interleukin-6 in the aging brain. J. Neuroimmunol. 147 (1), 141–144. https://doi.org/10.1016/j.jneuroim.2003.10.031.

Gold, S.M., Dziobek, I., Rogers, K., Bayoumy, A., McHugh, P.F., Convit, A., 2005. Hypertension and hypothalamo-pituitary-adrenal axis hyperactivity affect frontal lobe integrity. J. Clin. Endocrinol. Metabol. 90 (6), 3262–3267. https://doi.org/10.1210/jc.2004-2181.

Gouin, J.-P., Hantsoo, L., Kiecolt-Glaser, J.K., 2008. Immune dysregulation and chronic stress among older adults: a review. Neuroimmunomodulation 15 (4–6), 251–259. https://doi.org/10.1159/000156468.

Gu, Y., Vorburger, R., Scarmeas, N., Luchsinger, J.A., Manly, J.J., Schupf, N., Brickman, A.M., 2017. Circulating inflammatory biomarkers in relation to brain structural measurements in a non-demented elderly population. Brain Behav. Immun. 65, 150–160. https://doi.org/10.1016/j.bbi.2017.04.022.

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S., 2006. Reliability of mri-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. others Neuroimage 32 (1), 180–194.

Hänsel, A., Hong, S., Cámara, R.J.A., von Känel, R., 2010. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci. Biobehav. Rev. 35 (1), 115–121. https://doi.org/10.1016/j.neubiorev.2009.12.012.

Hayduk, L.A., Littvay, L., 2012. Should researchers use single indicators, best indicators, or multiple indicators in structural equation models? BMC Med. Res. Methodol. 12, 159. https://doi.org/10.1186/1471-2288-12-159.

Heymsfield, S.B., Wang, Z., Baumgartner, R.N., Dilmanian, F.A., Ma, R., Yasumura, S., 1993. Body composition and aging: a study by in vivo neutron activation analysis. J. Nutr. 123 (Suppl. l_2), 432–437.

Heyser, C.J., Masliah, E., Samimi, A., Campbell, I.L., Gold, L.H., 1997. Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain. Proc. Natl. Acad. Sci. U.S.A. 94 (4), 1500–1505. https://doi.org/10.1073/pnas.94.4.1500.

Holmes, C., Cunningham, C., Perry, V.H., 2007. Systemic infections and inflammation affect chronic neurodegeneration. Nat. Rev. Immunol. 7 (2), 161–167. https://doi.org/10.1038/nri2015.

Hong, X., Cui, B., Wang, M., Yang, Z., Wang, L., Xu, Q., 2015. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J. Exp. Med. 236 (4), 297–304. https://doi.org/10.1620/tjem.236.297.

Hoyle, R.H., 1995. The Structural Equation Modeling Approach. In: Hoyle, R.H. (Ed.), Structural equation modeling: Concepts, issues, and applications (Vol. 1). Sage, pp. 1–15.

Hutton, C., Draganski, B., Ashburner, J., Weiskopf, N., 2009. A comparison between voxelbased cortical thickness and voxel-based morphometry in normal aging. Neuroimage 48 (2), 371–380. https://doi.org/10.1016/j.neuroimage.2009.06.043.

Hu, L.T., Bentler, P.M., 1999. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct. Equ. Model.: A Multidiscip. J. 6 (1), 1–55.

Hu, B., Yang, X.R., Xu, Y., Sun, Y.F., Sun, C., Guo, W., et al., 2014. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin. Cancer Res. 20 (23), 6212–6222.

James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Briggs, A.M., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392 (10159), 1789–1858.

Jacomb, I., Stanton, C., Vasudevan, R., Powell, H., Donnell, M.O., Lenroot, R., Weickert, T.W., 2018. C-reactive protein: higher during acute psychotic episodes and related to cortical thickness in schizophrenia and healthy controls. Front. Immunol. 9, 2230. https://doi.org/10.3389/fimmu.2018.02230.

Jeckel, C.M., Lopes, R.P., Berleze, M.C., Luz, C., Feix, L., Argimon, I.I., Stein, L.M., Bauer, M.E., 2010. Neuroendocrine and immunological correlates of chronic stress in 'strictly healthy' populations. Neuroimmunomodulation 17 (1), 9–18. https://doi.org/10.1159/000243080.

Jefferson, A.L., Massaro, J.M., Wolf, P.A., Seshadri, S., Au, R., Vasan, R.S., DeCarli, C., 2007. Inflammatory biomarkers are associated with total brain volume - the Framingham heart study. Neurology 68 (13), 1032–1038.

Juster, R.-P., McEwen, B.S., Lupien, S.J., 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci. Biobehav. Rev. 35 (1), 2–16. https://doi.org/10.1016/j.neubiorev.2009.10.002.

Kajantie, E., Phillips, D.I., 2006. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 31, 151–178.

Kaur, S.S., Gonzales, M.M., Eagan, D.E., Goudarzi, K., Tanaka, H., Haley, A.P., 2015. Inflammation as a mediator of the relationship between cortical thickness and metabolic syndrome. Brain Imaging and Behavior 9 (4), 737–743. https://doi.org/10.1007/s11682-014-9330-z.

Kern, P.A., Ranganathan, S., Li, C., Wood, L., Ranganathan, G., 2001. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am. J. Physiol. Endocrinol. Metabol. 280 (5), E745–E751. https://doi.org/10.1152/ajpendo.2001.280.5.E745.

Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B., Glaser, R., 2003. Chronic stress and age-related increases in the proinflammatory cytokine il-6. Proc. Natl. Acad. Sci. U.S.A. 100 (15), 9090–9095. https://doi.org/10.1073/pnas.1531903100.

Kim, Y.-K., Won, E., 2017. The influence of stress on neuroinflammation and alterations in brain structure and function in major depressive disorder. Behav. Brain Res. 329, 6–11. https://doi.org/10.1016/j.bbr.2017.04.020.

Kremen, W.S., O'Brien, R.C., Panizzon, M.S., Prom-Wormley, E., Eaves, L.J., Eisen, S.A., Franz, C.E., 2010. Salivary cortisol and prefrontal cortical thickness in middle- aged men: a twin study. Neuroimage 53 (3), 1093–1102. https://doi.org/10.1016/j.neuroimage.2010.02.026.

Kubera, M., Obuchowicz, E., Goehler, L., Brzeszcz, J., Maes, M., 2011. In animal models, psychosocial stress-induced (neuro)inflammation, apoptosis and reduced neurogenesis are associated to the onset of depression. Progress in Neuropsychopharmacology & Biological Psychiatry 35 (3), 744–759. https://doi.org/10.1016/j.pnpbp.2010.08.026.

Kulaga-Yoskovitz, J., Bernhardt, B.C., Hong, S.J., Mansi, T., Liang, K.E., Van Der Kouwe, A.J., et al., 2015. Multi-contrast submillimetric 3 Tesla hippocampal subfield segmentation protocol and dataset. Sci. Data 2 (1), 1–9.

Lebedeva, A., Sundström, A., Lindgren, L., Stomby, A., Aarsland, D., Westman, E., Nyberg, L., 2018. Longitudinal relationships among depressive symptoms, cortisol, and brain atrophy in the neocortex and the hippocampus. Acta Psychiatr. Scand. 137 (6), 491–502. https://doi.org/10.1111/acps.12860.

Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: Nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol. Aging 33 (3), 617.e1–617.e9. https://doi.org/10.1016/j.neurobiolaging.2010.07.013.

Licastro, F., Candore, G., Lio, D., Porcellini, E., Colonna-Romano, G., Franceschi, C., Caruso, C., 2005. Innate immunity and inflammation in ageing: a key for understanding age-related diseases. Immun. Ageing : I & A 2 (1), 8. https://doi.org/10.1186/1742-4933-2-8.

Little, T.D., Bovaird, J.A., Widaman, K.F., 2006. On the merits of orthogonalizing powered and product terms: implications for modeling interactions among latent variables. Struct. Equal. Model. : A Multidiscip. J. 13 (4), 497–519. https://doi.org/10.1207/s15328007sem1304.

Liu, X., Kakeda, S., Watanabe, K., Yoshimura, R., Abe, O., Ide, S., 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 (9), 702–708. https://doi.org/10.1002/da.22401.

Lupien, S., Thakur, M., de Leon, M., de Santi, S., Hauger, R., Convit, A., Nair, N.P.V., 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat. Neurosci. 1 (4), 329. https://doi.org/10.1038/1149.

Lupien, S.J., Lepage, M., 2001. Stress, memory, and the hippocampus: can't live with it, can't live without it. Behav. Brain Res. 127 (1), 137–158. https://doi.org/10.1016/S0166-4328(01)00361-8.

MacCallum, R.C., Browne, M.W., Sugawara, H.M., 1996. Power analysis and determination of sample size for covariance structure modeling. Psychol. Methods 1 (2), 130–149. https://doi.org/10.1037/1082-989X.1.2.130.

MacLullich, A.M.J., Ferguson, K.J., Wardlaw, J.M., Starr, J.M., Deary, I.J., Seckl, J.R., 2006. Smaller left anterior cingulate cortex volumes are associated with impaired hypothalamicpituitary- adrenal axis regulation in healthy elderly men. J. Clin. Endocrinol. Metabol. 91 (4), 1591–1594. https://doi.org/10.1210/jc.2005-2610.

Maes, M., Song, C., Lin, A., de Jongh, R., van Gastel, A., Kenis, G., Smith, R.S., 1998. The effects of psychological stress on humans: increased production of pro- inflammatory cytokines and th1-like response in stress-induced anxiety. Cytokine 10 (4), 313–318. https://doi.org/10.1006/cyto.1997.0290.

Maes, M., Yirmyia, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., et al., 2009. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab. Brain Dis. 24, 27–53.

Marsland, A.L., Gianaros, P.J., Abramowitch, S.M., Manuck, S.B., Hariri, A.R., 2008. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. Biol. Psychiatr. 64 (6), 484–490. https://doi.org/10.1016/j.biopsych.2008.04.016.

Marsland, A.L., Gianaros, P.J., Kuan, D.C.-H., Sheu, L.K., Krajina, K., Manuck, S.B., 2015. Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain Behav. Immun. 48, 195–204. https://doi.org/10.1016/j.bbi.2015.03.015.

Massuda, R., Pedrini, M., Panizzutti, B., Duarte, J., Polita, S., Sodre, L., Gama, C.S., 2014. Poster #t156 decreased cortical and right prefrontal cortex volumes are correlated with an inflammatory marker(il-6) in patients with schizophrenia. Schizophr. Res. 153, S345–S346. https://doi.org/10.1016/S0920-9964(14)70973-9.

Mazariegos, M., Wang, Z.-m., Gallagher, D., Baumgartner Jr., R.N., Allison, D.B., Wang, J., Heymsfield, S.B., 1994. Differences between young and old females in the five levels of body composition and their relevance to the two-compartment chemical model. J. Gerontol. 49 (5), M201–M208.

McCarrey, A.C., Pacheco, J., Carlson, O.D., Egan, J.M., Thambisetty, M., An, Y., Resnick, S.M., 2014. Interleukin-6 is linked to longitudinal rates of cortical thinning in aging. Transl. Neurosci. 5 (1), 1–7. https://doi.org/10.2478/s13380-014-0203-0.

McEwen, B.S., 1993. Stress and the individual. Arch. Intern. Med. 153 (18), 2093. https://doi.org/10.1001/archinte.1993.00410180039004.

McEwen, B.S., 1982. Glucocorticoids and hippocampus: receptors in search of a function. In: Ganten, D., Pfaff, D. (Eds.), Adrenal Actions on Brain (Current Topics in Neuroendocrinology(2). Springer, Berlin, Heidelberg, pp. 1–22.

McEwen, B.S., Biron, C.A., Brunson, K.W., Bulloch, K., Chambers, W.H., Dhabhar, F.S., Weiss, J.M., 1997. The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine and immune interactions. Brain research. Brain research reviews 23 (1–2), 79.

McEwen, B.S., 1999. Stress and hippocampal plasticity. Annu. Rev. Neurosci. 22 (1), 105–122. https://doi.org/10.1146/annurev.neuro.22.1.105.

McEwen, B.S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 22 (2), 108–124.

McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. 87 (3), 873–904.

McEwen, B.S., 2008. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. Eur. J. Pharmacol. 583 (2), 174–185. https://doi.org/10.1016/j.ejphar.2007.11.071.

McEwen, B.S., Gould, E., 1990. Adrenal steroid influences on the survival of hippocampal neurons. Biochem. Pharmacol. 40 (11), 2393–2402. https://doi.org/10.1016/0006-2952(90)90079-Z.

Miller, G.E., Chen, E., Sze, J., Marin, T., Arevalo, J.M.G., Doll, R., Cole, S.W., 2008. A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased nf-kappab signaling. Biol. Psychiatr. 64 (4), 266–272. https://doi.org/10.1016/j.biopsych.2008.03.017.

Miller, G.E., Cohen, S., Ritchey, A.K., 2002. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. Health Psychol. 21 (6), 531–541. https://doi.org/10.1037/0278-6133.21.6.531.

Mohamed-Ali, V., Goodrick, S., Rawesh, A., Katz, D.R., Miles, J.M., Yudkin, J.S., Coppack, S.W., 1997. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J. Clin. Endocrinol. Metabol. 82 (12), 4196–4200. https://doi.org/10.1210/jcem.82.12.4450.

Munck, A., Náray-Fejes-Tóth, A., 1994. Glucocorticoids and stress: permissive and suppressive actions. Ann. N. Y. Acad. Sci. 746 (1), 115–130. https://doi.org/10.1111/j.1749-6632.1994.tb39221.x.

Nijm, J., Jonasson, L., 2009. Inflammation and cortisol response in coronary artery disease. Ann. Med. 41 (3), 224–233. https://doi.org/10.1080/07853890802508934.

Ottino-Gonzalez, J., Jurado, M.A., Garcia-Garcia, I., Segura, B., Marques-Iturria, I., Sender- Palacios, M.J., Garolera, M., 2017. Allostatic load is linked to cortical thickness changes depending on body-weight status. Front. Hum. Neurosci. 11, 639. https://doi.org/10.3389/fnhum.2017.00639.

Pervanidou, P., Chrousos, G.P., 2012. Metabolic consequences of stress during childhood and adolescence. Metabolism 61 (5), 611–619. https://doi.org/10.1016/j.metabol.2011.10.005.

Piras, F., Salani, F., Bossù, P., Caltagirone, C., Spalletta, G., 2012. High serum levels of transforming growth factor b1 are associated with increased cortical thickness in

cingulate and right frontal areas in healthy subjects. J. Neuroinflammation 9 (1), 42. https://doi.org/10.1186/1742-2094-9-42.

Prado-Gascó, V., de la Barrera, U., Sancho-Castillo, S., de la Rubia-Ortí, J.E., Montoya-Castilla, I., 2019. Perceived stress and reference ranges of hair cortisol in healthy adolescents. PLoS One 14 (4), e0214856.

Puhlmann, L.M.C., Valk, S.L., Engert, V., Bernhardt, B.C., Lin, J., Epel, E.S., Vrtička, P., Singer, T., 2019a. Association of short-term change in leukocyte Telomere length with cortical thickness and outcomes of mental training among healthy adults: a randomized clinical trial. JAMA Netw. Open 2 (9). https://doi.org/10.1001/jamanetworkopen.2019.9687.

Puhlmann, L.M.C., Engert, V., Apostolakou, F., Papassotiriou, I., Chrousos, G.P., Vrtička, P., Singer, T., 2019b. Only vulnerable adults show change in chronic low-grade inflammation after contemplative mental training: evidence from a randomized clinical trial. Sci. Rep. 9 (1) https://doi.org/10.1038/s41598-019-55250-3.

Puhlmann, L., Linz, R., Valk, S.L., Vrtička, P., Vos de Wael, R., Bernasconi, A., Bernasconi, N., Caldairou, B., Papassotiriou, I., Chrousos, G.P., Bernhardt, B.C., Singer, T., Engert, V., 2021a. Association between hippocampal structure and serum Brain- Derived Neurotrophic Factor (BDNF) in healthy adults: a registered report. Neuroimage 236, 118011. https://doi.org/10.1016/j.neuroimage.2021.118011.

Puhlmann, L.M.C., Vrtička, P., Linz, R., Stalder, T., Kirschbaum, C., Engert, V., Singer, T., 2021b. Contemplative mental training reduces hair glucocorticoid levels in a randomized clinical trial. Psychosom. Med. 83 (8), 894–905. https://doi.org/10.1097/PSY.0000000000000970.

Qiu, Z., Sweeney, D.D., Netzeband, J.G., Gruol, D.L., 1998. Chronic interleukin-6 alters nmda receptor-mediated membrane responses and enhances neurotoxicity in developing cns neurons. J. Neurosci. 18 (24), 10445–10456. https://doi.org/10.1523/JNEUROSCI.18-24-10445.1998.

Ridker, P.M., Hennekens, C.H., Buring, J.E., Rifai, N., 2000. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N. Engl. J. Med. 342 (12), 836–843. https://doi.org/10.1056/NEJM200003233421202.

Rink, L., Kruse, A., Haase, H., 2015. Immunologie für Einsteiger (2., neu bearbeitete und aktualisierte Auflage. Springer Spektrum.

Robles, T.F., Glaser, R., Kiecolt-Glaser, J.K., 2016. Out of balance. Curr. Dir. Psychol. Sci. 14 (2), 111–115. https://doi.org/10.1111/j.0963-7214.2005.00345.x.

Rohleder, N., 2014. Stimulation of systemic low-grade inflammation by psychosocial stress. Psychosom. Med. 76 (3), 181–189. https://doi.org/10.1097/PSY.0000000000000049.

Rohleder, N., 2019. Stress and inflammation–The need to address the gap in the transition between acute and chronic stress effects. Psychoneuroendocrinology 105, 164–171.

Rosenblat, J.D., Cha, D.S., Mansur, R.B., McIntyre, R.S., 2014. Inflamed moods: a review of the interactions between inflammation and mood disorders. Progress in Neuropsychopharmacology & Biological Psychiatry 53, 23–34. https://doi.org/10.1016/j.pnpbp.2014.01.013.

Ross, K.M., Murphy, M.L.M., Adam, E.K., Chen, E., Miller, G.E., 2014. How stable are diurnal cortisol activity indices in healthy individuals? evidence from three multi-wave studies. Psychoneuroendocrinology 39, 184–193. https://doi.org/10.1016/j.psyneuen.2013.09.016.

Rosseel, Y., 2012. lavaan: an r package for structural equation modeling. J. Stat. Software 48 (2), 1–36.

Rungtusanatham, M., Miller, J.W., Boyer, K.K., 2014. Theorizing, testing, and concluding for mediation in scm research: tutorial and procedural recommendations. J. Oper. Manag. 32 (3), 99–113. https://doi.org/10.1016/j.jom.2014.01.002.

Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S., Busa, E., Fischl, B., 2004. Thinning of the cerebral cortex in aging. Cerebr. Cortex 14 (7), 721–730.

Sapolsky, R.M., Pulsinelli, W.A., 1985. Glucocorticoids potentiate ischemic injury to neurons: therapeutic implications. Science 229 (4720), 1397–1400. https://doi.org/10.1126/science.4035356.

Sapolsky, R.M., 1990. Glucocorticoids, hippocampal damage and the glutamatergic synapse. Prog. Brain Res. 86, 13–23.

Sapolsky, R.M., 2004. Social status and health in humans and other animals. Annu. Rev. Anthropol. 33, 393–418. https://doi.org/10.1146/annurev.anthro.33.070203.144000.

Savic, I., 2015. Structural changes of the brain in relation to occupational stress. Cerebr. Cortex 25 (6), 1554–1564. https://doi.org/10.1093/cercor/bht348.

Sheline, Y.I., 2003. Neuroimaging studies of mood disorder effects on the brain. Biol. Psychiatry. 54 (3), 338–352. https://doi.org/10.1016/S0006-3223(03)00347-0.

Short, S.J., Stalder, T., Marceau, K.P., Entringer, S., Moog, N.K., Shirtcliff, E.A., Buss, C., 2016. Correspondence between hair cortisol concentrations and 30-day integrated daily salivary and weekly urinary cortisol measures. Psychoneuroendocrinology 71, 12–18. https://doi.org/10.1016/j.psyneuen.2016.05.007.

Sigurdsson, S., Geerlings, M., Eiriksdottir, G., Garcia, M., Harris, T., Sigurdsson, T., Launer, L., 2012. Depression, salivary cortisol and brain atrophy in a population-based cohort of old persons without dementia: the ages-reykjavik study. Alzheimer's Dementia: The Journal of the Alzheimer's Association 8 (4), P731–P732. https://doi.org/10.1016/j.jalz.2012.05.1976.

Singer, T., Kok, B.E., Bornemann, B., Zurborg, S., Bolz, M., Bochow, C.A., 2016. The ReSource project. Background, design, samples, and measurements (2nd ed.). Max Planck Institute for Human Cognitive and Brain Sciences.

Slavich, G.M., 2020. Psychoneuroimmunology of stress and mental health. In: Harkness, K., Hayden, E.P. (Eds.), The Oxford Handbook of Stress and Mental Health. Oxford University Press, Oxford, pp. 519–546.

Sorrells, S.F., Sapolsky, R.M., 2007. An inflammatory review of glucocorticoid actions in the cns. Brain Behav. Immun. 21 (3), 259–272. https://doi.org/10.1016/j.bbi.2006.11.006.

Soper, D.S., 2022. A-Priori sample size calculator for structural equation models [Software]. Retrieved 2019-11-03 from. https://www.danielsoper.com/statcalc.

Stalder, T., Kirschbaum, C., 2012. Analysis of cortisol in hair – state of the art and future directions. Brain Behav. Immun. 26 (7), 1019–1029. https://doi.org/10.1016/j.bbi.2012.02.002.

Stalder, T., Steudte, S., Miller, R., Skoluda, N., Dettenborn, L., Kirschbaum, C., 2012. Intraindividual stability of hair cortisol concentrations. Psychoneuroendocrinology 37 (5), 602–610. https://doi.org/10.1016/j.psyneuen.2011.08.007.

Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., Miller, R., 2017. Stress-related and basic determinants of hair cortisol in humans: a metaanalysis. Psychoneuroendocrinology 77, 261–274. https://doi.org/10.1016/j.psyneuen.2016.12.017.

Stark, J.L., Avitsur, R., Padgett, D.A., Campbell, K.A., Beck, F.M., Sheridan, J.F., 2001. Social stress induces glucocorticoid resistance in macrophages. Am. J. Physiol. Regul. Integr. Comp. Physiol. 280 (6), 1799–1805. https://doi.org/10.1152/ajpregu.2001.280.6.R1799.

Steinmetz, H., Davidov, E., Schmidt, P., 2011. Three approaches to estimate latent interaction effects: intention and perceived behavioral control in the theory of planned behavior. Methodological Innovations Online 6 (1), 95–110. https://doi.org/10.4256/mio.2010.0030.

Stojanovic, A., Martorell, L., Montalvo, I., Ortega, L., Monseny, R., Vilella, E., Labad, J., 2014. Increased serum interleukin-6 levels in early stages of psychosis: associations with at-risk mental states and the severity of psychotic symptoms. Psychoneuroendocrinology 41, 23–32. https://doi.org/10.1016/j.psyneuen.2013.12.005.

Thayer, J.F., Yamamoto, S.S., Brosschot, J.F., 2010. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int. J. Cardiol. 141, 122–131.

Ugur, M.G., Kutlu, R., Kilinc, I., 2018. The effects of smoking on vascular endothelial growth factor and inflammation markers: a case-control study. The clinical respiratory journal 12 (5), 1912–1918. Retrieved from. https://onlinelibrary.wiley.com/doi/10.1111/crj.12755.

Vallieres, L., Campbell, I.L., Gage, F.H., Sawchenko, P.E., 2002. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin- 6. J. Neurosci. 22 (2), 486–492. https://doi.org/10.1523/JNEUROSCI.22-02-00486.2002.

van Velzen, L.S., Schmaal, L., Milaneschi, Y., van Tol, M.-J., van der Wee, N.J., Veltman, D.J., Penninx, B.W.J.H., 2017. Immunometabolic dysregulation is associated with reduced cortical thickness of the anterior cingulate cortex. Brain Behav. Immun. 60, 361–368. https://doi.org/10.1016/j.bbi.2016.10.019.

Valk, S.L., Bernhardt, B.C., Böckler, A., Trautwein, F.M., Kanske, P., Singer, T., 2017. Socio-cognitive phenotypes differentially modulate large-scale structural covariance networks. Cerebr. Cortex 27 (2), 1358–1368.

Valk, S.L., Engert, V., Puhlmann, L., Linz, R., Caldairou, B., Bernasconi, A., Bernasconi, N., Bernhardt, B.C., Singer, T., 2023. Hippocampal subfield CA1-3 shows differential structural and functional network plasticity after stress-reducing socio-affective mental training. Elife. https://doi.org/10.7554/eLife.87634.1.

Veit, R., Kullmann, S., Heni, M., Machann, J., Häring, H.-U., Fritsche, A., Preissl, H., 2014. Reduced cortical thickness associated with visceral fat and bmi. Neuroimage: Clinical 6 (C), 307–311. https://doi.org/10.1016/j.nicl.2014.09.013.

Vgontzas, A.N., Bixler, E.O., Lin, H.-M., Prolo, P., Trakada, G., Chrousos, G.P., 2005. Il-6 and its circadian secretion in humans. Neuroimmunomodulation 12 (3), 131–140. https://doi.org/10.1159/000084844.

Waage, A., Slupphaug, G., Shalaby, R., 1990. Glucocorticoids inhibit the production of il 6 from monocytes, endothelial cells and fibroblasts. Eur. J. Immunol. 20 (11), 2439–2443. https://doi.org/10.1002/eji.1830201112.

Weaver, J.D., Huang, M.H., Albert, M., Harris, T., Rowe, J.W., Seeman, T.E., 2002. Interleukin-6 and risk of cognitive decline - macarthur studies of successful aging. Neurology 59 (3), 371–378.

Wei, J., Xu, H., Davies, J.L., Hemmings, G.P., 1992. Increase of plasma il-6 concentration with age in healthy subjects. Life Sci. 51 (25), 1953–1956. https://doi.org/10.1016/0024-3205(92)90112-3.

Westland, J.C., 2010. Lower bounds on sample size in structural equation modeling. Electron. Commer. Res. Appl. 9 (6), 476–487.

Winkler, A.M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P.T., Glahn, D.C., 2010. Cortical thickness or grey matter volume? the importance of selecting the phenotype for imaging genetics studies. Neuroimage 53 (3), 1135–1146. https://doi.org/10.1016/j.neuroimage.2009.12.028.

Wittchen, H.U., Pfister, H., 1997. DIA-X-interviews: manual für screening-Verfahren und interview; Interviewheft.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Steinhausen, H.C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol 21 (9), 655–679.

Wright, C.B., Sacco, R.L., Rundek, T.R., Delman, J.B., Rabbani, L.E., Elkind, M.S.V., 2006. Interleukin-6 is associated with cognitive function: the northern manhattan study. J. Stroke Cerebrovasc. Dis. 15 (1), 34–38. https://doi.org/10.1016/j.jstrokecerebrovasdis.2005.08.009.

Wu, Y., Chen, Y., Chen, L., Yang, Y., Yang, X., 2016. Neutrophil-to-lymphocyte ratio (nlr) and platelet-to-lymphocyte ratio (plr) were associated with disease activity in

patients with systemic lupus erythematosus. Int. Immunopharm. 36, 94–99. https://doi.org/10.1016/j.intimp.2016.04.006.

Ye, S.-M., Johnson, R.W., 1999. Increased interleukin-6 expression by microglia from brain of aged mice. J. Neuroimmunol. 93 (1), 139–148. https://doi.org/10.1016/S0165-5728(98)00217-3.

Zhong, J.-H., Huang, D.-H., Chen, Z.-Y., 2017. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget 8 (43), 75381–75388. https://doi.org/10.18632/oncotarget.18856.