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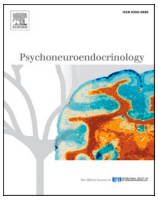

Psychosocial health modifies associations between HPA-axis function and brain structure in older age

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ABSTRACT

Background: Dysregulation of the negative feedback loop of the hypothalamic-pituitary-adrenal (HPA) axis may have damaging effects on the brain, potentially under influence of psychosocial health factors. We studied associations between functioning of the negative feedback loop of HPA-axis, measured with a very low-dose dexamethasone suppression test (DST), and brain structure in middle-aged and older adults, and whether these associations were modified by psychosocial health.

Methods: From 2006 to 2008, 1259 participants (mean age 57.6 ± 6.4, 59.6 % female) of the population-based Rotterdam Study completed a very low-dose DST (0.25 mg) and underwent magnetic resonance imaging (MRI) of the brain. Self-reported psychosocial health (depressive symptoms, loneliness, marital status, perceived social support) were assessed in the same time period. Multivariable linear and logistic regression were used to study cross-sectional associations between cortisol response and brain volumetrics, cerebral small vessel disease markers and white matter structural integrity. To assess the effect of psychosocial health on these associations, analyses were further stratified for psychosocial health markers.

Results: Cortisol response was not associated with markers of global brain structure in the overall study sample. However, in participants with clinically relevant depressive symptoms, a diminished cortisol response was associated with smaller white matter volume (mean difference: − 1.00 mL, 95 %CI = − 1.89;− 0.10) and smaller white matter hyperintensity volume (mean difference: − 0.03 mL (log), 95 %CI = − 0.05;0.00). In participants with low/moderate perceived social support compared to those with high social support, a diminished cortisol response was associated with larger gray matter volume (mean difference: 0.70 mL, 95 %CI = 0.01;1.39) and higher fractional anisotropy (standardized mean difference 0.03, 95 %CI = 0.00;0.06).

Conclusion: Diminished function of the HPA-axis is differently associated with brain structure in community-dwelling middle-aged and older adults with clinically relevant depressive symptoms or suboptimal social support, but not in adults without depressive symptoms or with optimal social support.

1. Introduction

With aging populations worldwide, healthy brain aging is considered a societal priority (Cole et al., 2019). Stress may be critical in healthy brain aging as it may play a role in structural and functional brain changes (Banasr et al., 2021). One factor contributing to these changes in relation to stress may be dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Byers and Yaffe, 2011), a key part of the stress response system which coordinates the biological stress response by releasing cortisol after a perceived stressor, but also

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initiates a negative feedback loop to down-regulate this release.

Inadequate activation of the HPA-axis, with resulting mismanaged cortisol levels, can have adverse effects on the brain (Kinlein and Karatsoreos, 2020; McEwen and Gianaros, 2010). Several population-based studies have reported on associations between higher cortisol levels and unfavorable global brain structure, with mixed results for morning and evening cortisol levels in association with total brain and white matter volumes (Cox et al., 2015; Echouffo-Tcheugui et al., 2018; Geerlings et al., 2015; Lebedeva et al., 2018). However, cortisol levels are known to vary widely between and within individuals, and respond to acute stressors (Almeida et al., 2009). Therefore, single cortisol values may reflect many aspects of the functioning of the HPA-axis. The very low-dose dexamethasone-suppression-test (DST) allows us to assess a specific aspect of the HPA-axis: the functioning of the negative feedback loop (Direk et al., 2016). With this method, the cortisol response is estimated by comparing cortisol levels before and after intake of a pharmacological stressor (dexamethasone). Although the DST cannot estimate the duration of long-term dysregulation of the negative feedback loop, it gives a more stable estimate of functioning of the stress system than single cortisol values. As such, functioning of the negative feedback loop of HPA-axis can be studied in relation to global brain structure in large population-based samples, on which information is currently lacking.

Dysregulation of the HPA-axis is common in mental health disorders and both enhanced and diminished activity of the HPA-axis can occur (Kinlein and Karatsoreos, 2020; Maripuu et al., 2014). With a diminished response, negative feedback sensitivity of the HPA-axis is reduced, resulting in a smaller decrease in cortisol after a stressor. Conversely, in an enhanced state, sensitivity to negative feedback in the HPA-axis is increased, leading to a larger decrease in cortisol in response to a stressor (Maripuu et al., 2014). In depression, both diminished and enhanced HPA-axis responses have been reported, although the diminished response is more prevalent (Maripuu et al., 2014). Aspects of social health, such as loneliness (Hackett et al., 2012; Johar et al., 2021; Montoliu et al., 2019; Steptoe et al., 2004), living alone (Zilioli and Jiang, 2021), marital status (Chin et al., 2017) and negative experiences of social support (Iob et al., 2018), can also induce dysregulation of the cortisol response. Neuroendocrine dysregulation has been suggested to be involved in associations of depression and social health with structural brain changes (Cacioppo et al., 2015; Rafnsson et al., 2020), but current literature is still inconclusive. Importantly, associations between neuroendocrine dysregulation and brain structure may differ within and between psychosocial states, since these psychosocial states may modify stress regulation and brain health in different ways: the associations between HPA-axis function and brain structure may differ in people with and without depression, loneliness, social support or a current partner.

We determined the associations between the negative feedback loop of the HPA-axis, using a very low-dose DST, and brain structure in community-dwelling older adults, and whether these associations differ across psychosocial factors (clinically relevant depressive symptoms, loneliness, partner status and perceived social support). Since the diminished cortisol response is known to more prevalent in depressive syndromes, we hypothesized that a diminished negative feedback response is associated with worse brain structure, especially in participants with suboptimal psychosocial health.

2. Methods

2.1. Study design and population

This study was part of the Rotterdam Study, a prospective population-based cohort that started in 1990 and is ongoing (Ikram et al., 2020). Inhabitants aged $\geq$ 40 years from the neighborhood Ommoord in Rotterdam were invited to participate and followed-up every 3–4 years. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; https://apps.who.int/trialsearch/) under shared catalog number NL6645/NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Data on the very-low dose dexamethasone-suppression test (DST) and Magnetic Resonance Imaging (MRI) of the brain were collected from 2006 to 2008 with a median of 1 day apart [IQR: 1.0–1.0]. Of the 3247 participants invited to participate in the DST, 2076 agreed (63.9 %). Participants with incomplete cortisol measurements (n = 188) and a between cortisol sampling time difference of > 3 h from the specified 24 h (n = 59) were excluded. Cortisol data pre- and post- DST were complete for 1829 participants. Of this group, 1657 participants underwent an MRI scan. Participants with missing structural MRI segmentation or visual ratings (n = 27), or insufficient segmentation quality were excluded (n = 36). In total, 1594 participants had complete data for both the DST and the MRI. After exclusion of participants with prevalent dementia (n = 25), cortical brain infarcts on MRI (n = 37), use of corticosteroids within one year prior to the DST (self-reported use or prescribed under Anatomical Therapeutic Chemical Classification (ATC) code H02: oral, inhalation or dermal) (n = 257), and outlier removal for MRI outcomes (n = 16, see image acquisition and processing for outlier definition), the final sample comprised 1259 participants.

2.2. Measurement of the negative feedback loop of the HPA-axis

A very-low dose DST was used to assess the negative feedback loop of the HPA-axis. Dexamethasone is a synthetic glucocorticoid which mimics the effect of cortisol and induces the HPA-axis negative feedback loop. With a normal HPA-axis response, adrenal cortisol secretion is reduced after dexamethasone intake. Although no reference values are available for the post-DST cortisol values, a larger difference between pre-DST and post-DST salivary cortisol indicates an enhanced HPA-axis response and a smaller difference indicates a diminished response. The DST procedure in the Rotterdam Study has been described in detail elsewhere (Direk et al., 2016). In brief, participants were instructed to collect saliva samples at home, using Salivette sampling devices (Sarstedt, Nümbrecht, Germany). Oral and written instructions were given with emphasis on the importance of adhering to the sampling time. Participants were asked to collect the first saliva sample at 8 a.m., take the dexamethasone pill (0.25 mg orally) at 11 p.m. the same day, and take the second saliva sample the next morning at 8 a.m. Participants were asked to report the exact times of their saliva sampling and dexamethasone intake. Salivettes were stored at − 80 °C until they were sent to the Laboratory of Biopsychology, Technical University of Dresden, Germany. Salivary cortisol concentrations were measured using a commercial immunoassay with chemiluminescence detection (CLIA; IBL Hamburg, Hamburg, Germany).

2.3. Brain MRI acquisition and processing

MRI scanning of the brain was performed with a 1.5 Tesla MRI unit (Signa Excite II, General Electric Healthcare, Milwaukee, USA) with an eight-channel head coil. The scan protocol included a T1-weighted sequence, proton density-weighted sequence, fluid-attenuated inversion recovery (FLAIR) sequence and 3D T2*-weighted gradient recalled echo (GRE) sequence. Detailed information on the Rotterdam Scan Study, including scan parameters and quality control, can be found elsewhere (Ikram et al., 2015). Automated brain tissue segmentation based on a k-nearest neighbor algorithm was used to quantify

volumetric measures (Vrooman et al., 2007). All scans were inspected for artefacts, image quality and segmentation quality. Segmentations were manually corrected when necessary. Amygdala and hippocampal volumes were obtained using FreeSurfer (version 5.1) segmentation on T1-weighted images (Fischl et al., 2004). Volumetric outcomes in our study were total brain, gray matter, white matter, hippocampal and amygdala volumes. Total brain volume was defined as the sum of supratentorial gray and white matter volume. White matter volume consisted of normal-appearing white matter volume and white matter hyperintensity (WMH) volume. Cerebral small vessel disease markers were defined as WMH volume, presence of lacunar infarcts and presence of cerebral microbleeds. Trained raters assessed all scans for cortical infarcts, lacunar infarcts and cerebral microbleeds (Vernooij et al., 2007). White matter microstructural integrity measures were obtained using diffusion tensor imaging (DTI). Processing was performed with a standardized pipeline to quantify global fractional anisotropy (FA) and global mean diffusivity (MD) in normal-appearing white matter (Koppelmans et al., 2014). Lower FA and higher MD values indicate worse white matter microstructural integrity. Due to failed segmentations for some participants, hippocampus and amygdala volumes were available in a subset of the sample (n = 1253), as were white matter microstructure markers (n = 1240). Outliers were defined as > 2 * IQR for total brain, gray matter, white matter and amygdala volumes and > 3 * IQR for FA, MD and hippocampal and WMH volumes (Osborne and Overbay, 2004).

2.4. Psychosocial health

Depressive symptoms were assessed with the Dutch version Center for Epidemiological Studies – Depression (CES-D) scale. A cut-off score of ≥ 16 out of a total 60 points was used to identify participants with clinically relevant depressive symptoms (Beekman et al., 1997; Radloff, 1977). CES-D scores were weighted to account for missing responses in case < 25% of items were missing. For responses with > 25 % missing, CES-D sum scores were set to missing. Loneliness was assessed with a single-item question from the CES-D. Reponses were dichotomized into lonely (loneliness ≥ 1 day during the past week) and not lonely (loneliness < 1 day during the past week). Partner status was categorized as having a current partner (married or unmarried) or not having a current partner (including participants who were widowed, divorced or never married and did not have partner at the time). Perceived social support was assessed using a 5-item questionnaire modified from the Health and Lifestyle Survey (Cox et al., 1987), with the following items: “I know people, among my family and friends, 1) who do things that make me happy; 2) whom I can always count on; 3) who would make sure that I would get help if I would need it; 4) who give me the feeling that I am important in their lives; 5) who accept me for who I am.” Scores were weighted to account for scores with one missing item. Scores with < 4 responses were set to missing. Categories of perceived social support scores were defined as high support (agree on all 5 items), moderate support (agree on 3–4 items) or low support (agree on 0–2 items).

2.5. Other measurements

Covariable selection was based on a variable being a potential cause of the determinant (negative feedback loop of the HPA-axis) or the outcome (brain structure) (VanderWeele, 2019). Intracranial volume was defined as the sum of total brain volume and cerebrospinal fluid on MRI. Educational attainment based on UNESCO classification, smoking habits (never, former or current smoker) and alcohol consumption were assessed during home interview. Alcohol consumption was classified into none (no alcoholic beverages), moderate (≤ 1 beverage/day) and heavy (> 1 beverage/day). Weight and height were measured at the research center and used to calculate body mass index (BMI). We calculated a morbidity score based on the Rotterdam Study’s Healthy Aging Score’s chronic disease domain (Jaspers et al., 2017). Eight diseases were included based on chronicity and burden: cancer, chronic obstructive pulmonary disease, chronic kidney disease, coronary heart disease, heart failure, diabetes mellitus type 2, Parkinson’s Disease and stroke. Morbidity scores were classified as low (no diseases), moderate (1 disease) or high (> 1 disease). The ascertainment of each chronic disease was based on medical records and has been described in detail elsewhere (Jaspers et al., 2017). Use of psycholeptic or psychoanaleptic medication (ATC code: N05 or N06) was based on self-report. Average wake-up time was assessed using the Pittsburgh Sleep Quality Index question “At what time do you usually wake up?”, and was used to calculate the time difference between average wake-up time and time of taking the cortisol saliva sample(Buysse et al., 1991).

2.6. Statistical analyses

Missing covariate data (< 5 %) was imputed with fivefold multiple imputation. WMH volumes were natural log-transformed to obtain a normal distribution. FA and MD were standardized to ease interpretation of the outcomes. We used multivariable linear regression models to study the associations between cortisol response and continuous outcomes (total brain, gray matter, white matter, amygdala and hippocampus volumes, FA and MD), and logistic regression models for dichotomous outcomes (lacunar infarcts, cerebral microbleeds). Cortisol response was defined as post-DST cortisol level adjusted for pre-DST cortisol as a covariable (Direk et al., 2016). As such, basic multivariable models were adjusted for age, sex, intracranial volume and pre-DST cortisol. A quadratic term for age at baseline was added as covariable to adjust for the non-linear effect of age on brain outcomes (Vinke et al., 2018). Basic models of white matter microstructure were additionally adjusted for normal-appearing white matter volume, WMH volume and phase encoding direction of the DTI sequence. In the final models, we additionally adjusted for BMI, smoking status, alcohol consumption, morbidity score, education, depressive symptoms total sum score, use of psycholeptic or psychoanaleptic medication, and time difference between waking up and taking the saliva sample. Since both diminished and enhanced HPA responses may be associated with brain outcomes, we explored non-linear associations using a quadratic term for post-DST cortisol and tertiles of HPA-axis suppression (enhanced suppression (lowest tertile of post-DST cortisol), reference/medium suppression and diminished suppression (highest tertile of post-DST cortisol)).

Analyses with brain volumes and white matter microstructure were next stratified on psychosocial markers (presence of clinically relevant depressive symptoms, loneliness, partner status and perceived social support score). Low and moderate social support categories were grouped, with high social support as reference. Stratified analyses for lacunar infarcts and cerebral microbleeds were not possible due to limited power. Additive interaction was assessed by adding an interaction term for the product of post-DST cortisol with the stratification variable (i.e. clinically relevant depressive symptoms, loneliness, partner status, perceived social support score) to each model.

We performed three additional analyses to ensure the consistency of our findings. First, to compare our findings to previous studies using baseline cortisol levels, we repeated our main analyses with pre-DST cortisol level as the determinant instead of cortisol response (Echouffo-Tcheugui et al., 2018; Geerlings et al., 2015). Second, we repeated the analyses for cortisol response after exclusion of participants with non-suppression of cortisol post-DST (n = 137, remaining sample size n = 1122). Non-suppression was defined as post-DST cortisol levels being higher than pre-DST cortisol levels. Finally, since cortisol metabolism differs for males and females, we stratified our main analyses on sex.

3. Results

Characteristics for 1259 participants are presented in Table 1. Mean age was 57.6 (SD 6.4) and 59.6 % was female. Median cortisol levels were 13.6 nmol/L pre-DST [IQR: 9.3–19.8] and median 5.0 nmol/L post-

Table 1
Study sample characteristics.

	Overall (N = 1259)
Age (years), Mean (SD)	57.4 (6.40)
Sex, Female	750 (59.6 %)
Education	
Primary education	118 (9.4 %)
Lower/intermediate general education or lower vocational education	477 (37.9 %)
Intermediate vocational education or higher general education	352 (28.0 %)
Higher vocational education or university	312 (24.8 %)
Smoking status	
Never	412 (32.7 %)
Former	590 (46.9 %)
Current	257 (20.4 %)
Alcohol use	
None	136 (10.8 %)
Moderate (0–1 units per day)	816 (64.8 %)
Heavy (> 1 unit per day)	307 (24.4 %)
Number of chronic illnesses, score	
Low (no chronic illness)	1054 (83.7 %)
Moderate (1 chronic illness)	179 (14.2 %)
High (> 1 chronic illness)	26 (2.1 %)
Body Mass Index (kg/m^2), Mean (SD)	27.5 (4.4)
Perceived social support categories, weighted score	
Low (agree on 0–2 items)	30 (2.4 %)
Moderate (agree on 3–4 items)	166 (13.2 %)
High (agree on 5 items)	1060 (84.2 %)
Marital status	
Married or has partner	998 (79.3 %)
Never married	62 (4.9 %)
Widowed or divorced	197 (15.6 %)
Loneliness, Lonely ≥ 1 day per week	158 (12.5 %)
Depressive symptoms sum score, Median [Q1–Q3]	3.00 [1.00–7.00]
Clinically relevant depressive symptoms, (CESD ≥ 16)	118 (9.4 %)
Psychoanaleptics usage, Yes	84 (6.7 %)
Psycholeptics usage, Yes	115 (9.1 %)
Cortisol pre-DST (nmol/L), Median [Q1–Q3]	13.6 [9.33–19.8]
Cortisol post-DST (nmol/L), Median [Q1–Q3]	4.96 [1.99–9.50]
Intracranial volume (mL), Mean (SD)	1140 (113)
Total brain volume (mL), Mean (SD)	956 (96.9)
Gray matter volume (mL), Mean (SD)	536 (51.3)
White matter volume (mL), Mean (SD)	420 (57.1)
Normal appearing white matter volume (mL), Mean (SD)	417 (57.3)
Mean hippocampal volume (mL), Mean (SD)	4.02 (0.440)
Mean amygdala volume (mL), Mean (SD)	1.39 (0.176)
White matter hyperintensities volume (mL), Median [Q1–Q3]	2.10 [1.35–3.53]
Cerebral microbleeds, Present	150 (11.9 %)
Lacunar infarcts, Present	49 (3.9 %)
Fractional anisotropy, Mean (SD)	0.34 (0.014)
Mean diffusivity (10E-3 mm^2/s), Mean (SD)	0.73 (0.021)

Perceived social support score, categories: responses of somewhat agree were grouped with disagree. Abbreviations: DST: dexamethasone suppression test; IQR: interquartile range; SD: standard deviation.

DST [IQR: 2.0–9.5]. In Table A.1, characteristics for participants versus participants not included in the analyses are presented. Compared to Rotterdam Study participants not included in the analyses, more participants were female, were less often a current smoker and were overall slightly healthier.

There were no statistically significant associations between cortisol response and markers of global brain structure in the overall study sample (Tables 2 and 3). We did not find indications of non-linear associations between cortisol response and brain structure using a quadratic term or tertiles of HPA-axis suppression (data not shown).

However, associations between cortisol response and markers of global brain structure were found for specific strata of psychosocial health (Fig. 1). In participants with clinically relevant depressive symptoms (n = 118) (CES-D ≥ 16), a diminished cortisol response was associated with smaller white matter volume (mean difference per nmol/L increase in post-DST cortisol − 1.00 mL, 95 %CI − 1.89; − 0.10)

Table 2
Associations between cortisol response and brain volumes.

	Total brain volume (mL) Mean difference (95 %CI)	**Gray matter volume (mL)** Mean difference (95 %CI)	**White matter volume (mL)** Mean difference (95 %CI)
Cortisol response, Model 1	0.00 (− 0.24; 0.24)	-0.10 (− 0.31; 0.12)	0.10 (− 0.15; 0.34)
Model 2	0.01 (− 0.23; 0.24)	-0.09 (− 0.31; 0.13)	0.10 (− 0.15; 0.34)
	WMH (mL) (log) Mean difference (95 %CI)	**Hippocampus volume (mL)** Mean difference (95 %CI)	**Amygdala volume (mL)** Mean difference (95 %CI)
Cortisol response, Model 1	0.00 (− 0.00; 0.01)	0.00 (−0.01; 0.00)	0.00 (0.00; 0.00)
Model 2	0.00 (− 0.00; 0.01)	0.00 (− 0.01; 0.00)	0.00 (0.00; 0.00)

Cortisol response: post-DST cortisol level (nmol/L) adjusted for pre-DST cortisol level.
Model 1: adjusted for age, age^2, sex, intracranial volume, pre-DST cortisol.
Model 2: model 1 + adjusted for body mass index, smoking, alcohol consumption, morbidity score, education, depressive symptoms score, psycholeptics/psychoanaleptics use, time difference between waking up and saliva sample.
Sample size for: global volumes: n = 1259; hippocampus and amygdala volumes: n = 1253. Abbreviations; CI: confidence interval; DST: dexamethasone suppression test. Log: natural logarithm; WMH: white matter hyperintensity.

Table 3
Associations between cortisol response and focal brain lesions and white matter microstructural integrity.

	Microbleeds (presence)	**Lacunar infarcts (presence)**
	Odds ratio (95 %CI)	Odds ratio (95 %CI)
Cortisol response, Model 1	0.99 (0.96; 1.01)	1.00 (0.97; 1.04)
Model 2	0.99 (0.96; 1.01)	1.00 (0.96; 1.04)
	Fractional anisotropy	**Mean diffusivity (10^{-3} mm^2/s)**
	Standardized mean difference (95 %CI)	Standardized mean difference (95 %CI)
Cortisol response, Model 1	0.00 (− 0.01; 0.01)	0.00 (− 0.01; 0.01)
Model 2	0.00 (− 0.01; 0.01)	0.00 (− 0.01; 0.01)

Cortisol response: post-DST cortisol level (nmol/L) adjusted for pre-DST cortisol level.
Model 1: adjusted for age, age^2, sex, intracranial volume. Model for fractional anisotropy and mean diffusivity additionally adjusted for phase encoding direction, normal-appearing white matter volume and white matter hyperintensity volume.
Model 2: model 1 + adjusted for body mass index, smoking, alcohol consumption, morbidity score, education, depressive symptoms score, psycholeptics/psychoanaleptics use, time difference between waking up and saliva sample.
Sample size for: focal lesions: n = 1259; white matter microstructure: n = 1240. Standardized mean differences represent mean difference per standard deviation increase in fractional anisotropy or mean diffusivity. Abbreviations: CI: confidence interval; DST: dexamethasone suppression test.

and smaller WMH volume (− 0.03 mL (log), 95 %CI − 0.05; 0.00, p for interaction term = 0.07). Additionally, the effect size for the association of a diminished cortisol response with a smaller total brain volume was relatively large, but with a wide 95 % confidence interval (− 0.87 mL, 95 %CI − 1.85; 0.12) in those with clinically relevant depressive symptoms. These associations were not present in participants without clinically relevant depressive symptoms. Conversely, in participants with moderate/low perceived social support (n = 196), a diminished cortisol response was associated with larger gray matter volume (0.70 mL, 95 %CI 0.01; 1.39), but not in those with high perceived social support. Again, the effect size for the association of a diminished cortisol

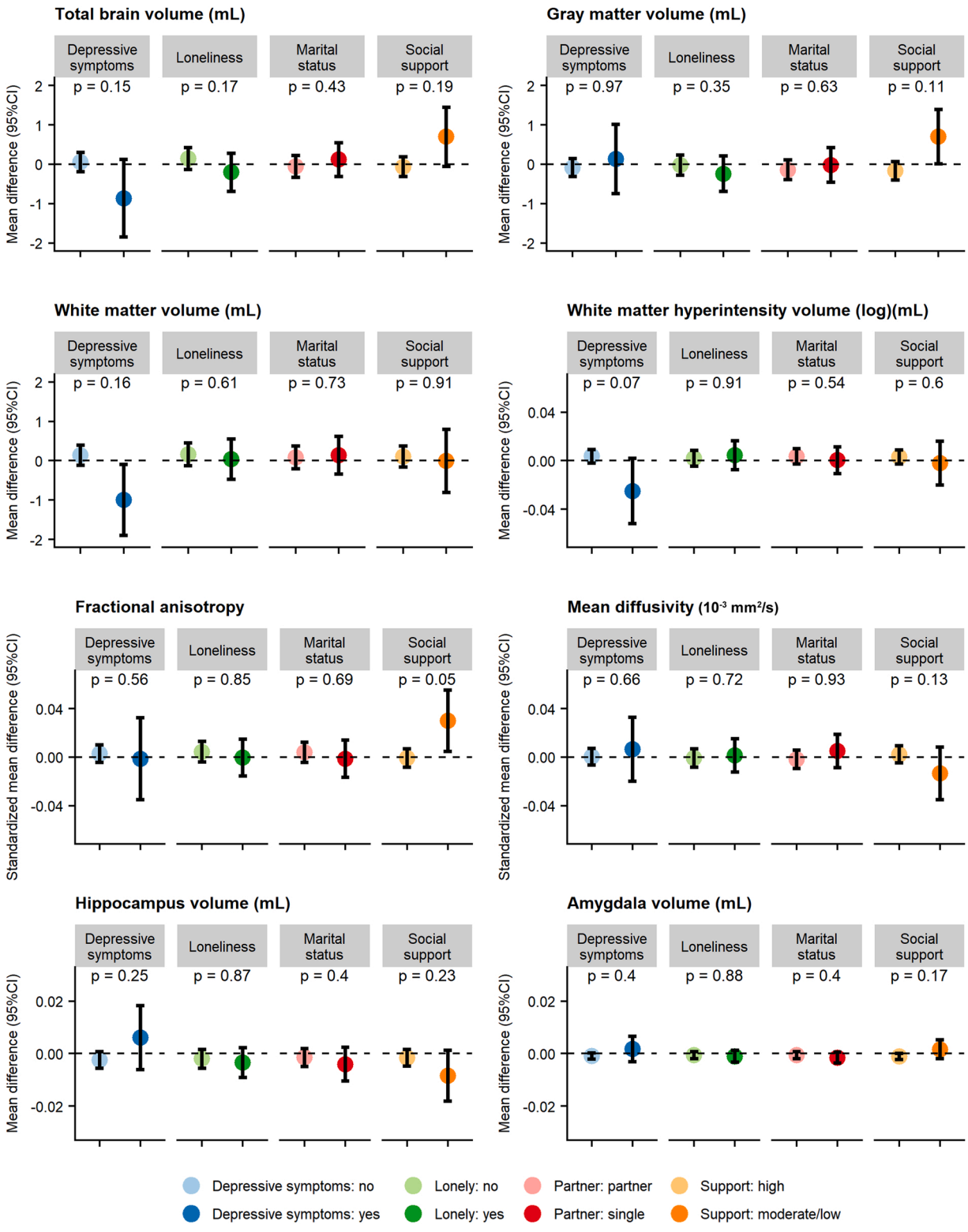

Fig. 1. Associations between post-DST cortisol and brain structure stratified for psychosocial health markers. Associations between cortisol response (post-DST cortisol level (nmol/L) adjusted for pre-DST cortisol level) and brain structure, stratified for depression, loneliness, partner status and perceived social support score. Points represent mean differences in mL of brain volumes. Standardized mean differences represent mean difference per standard deviation increase in fractional anisotropy or mean diffusivity. P represents p-value for the interaction term of post-DST cortisol and psychosocial health marker. All analyses are adjusted for age, age^2, sex, intracranial volume, pre-DST cortisol, body mass index, smoking, alcohol consumption, morbidity score, education, depressive symptoms score, psycholeptics/psychoanaleptics use and time difference between waking up and saliva sample. Models for fractional anisotropy and mean diffusivity additionally adjusted for phase encoding direction, normal-appearing white matter volume and white matter hyperintensity volume. Abbreviations: CI: confidence interval; DST: dexamethasone suppression test. Log: natural logarithm; WMH: white matter hyperintensity.

response with larger total brain volume was relatively large, but with a wide 95 % confidence interval (0.70 mL, 95 %CI − 0.05; 1.44) in those with moderate/low perceived social support. For white matter microstructural integrity, a diminished cortisol response was associated with higher FA (0.03 SD per unit increase, 95 %CI 0.00; 0.06) also only in participants with moderate/low perceived social support (p for interaction term = 0.05). Stratification on partner status and loneliness did not demonstrate differences between strata.

3.1. Additional analyses

Sample characteristics for participants with high perceived social support versus moderate/low support are presented in Table A.2. Higher pre-DST cortisol levels were associated with larger white matter volume (0.16 mL, 95 %CI 0.00; 0.33), but not with any other structural brain changes after adjustment for all covariates (Tables A.3–A.4). Excluding participants with non-suppression of cortisol after DST (n = 137) did not change the interpretation of the results (Tables A.5–A.6). We did not find any differences between male and female participants after stratification on sex (data not shown).

4. Discussion

In this study, we found that cortisol response after a very low-dose DST was not associated with brain structure in the overall sample of community-dwelling middle-aged and older adults. In participants with clinically relevant depressive symptoms, a diminished cortisol response was associated with smaller total brain, white matter and WMH volumes. Conversely, a diminished cortisol response was associated with larger total brain and gray matter volumes and lower global FA in participants with low/moderate perceived social support, but not in those with high perceived social support. This suggests that the HPA-axis negative feedback response is associated with brain structure differently in persons with depression and low/moderate perceived social support.

We did not find any associations between functioning of the HPA-axis negative feedback loop and brain structure in our overall study sample. To our knowledge, no other studies in general populations have described the specific association between the HPA-axis negative feedback loop and brain structure before. Two recent large population-based studies in middle-aged and older adults did study cortisol levels in relation to brain structure, where one study found that morning salivary cortisol level was associated with larger white matter volume, and the other study found that morning serum cortisol was associated with smaller total brain volumes and lower regional FA (Echouffo-Tcheugui et al., 2018; Geerlings et al., 2015). Importantly, these single-time point measures of cortisol levels do not reflect functioning of the negative feedback loop of the HPA-axis per se and are thus not directly comparable to our main findings. While we did find that higher pre-DST (morning salivary) cortisol was associated with larger white matter volume, we did not find any other associations between pre-DST cortisol and brain structure. The differences between these studies and ours suggest that age, cortisol sampling method and sample size and may influence subtle associations between cortisol metabolism and brain structure in healthy adults. Power and variation in our study sample for determinants and outcomes may have been too limited to pick up these subtle differences in cortisol response and brain structure, particularly since the mean age of our sample was middle-aged and brain changes are typically more prominent at later ages. Studies on functioning of the HPA-axis negative feedback loop in larger study populations are needed to further explore etiological associations with global brain structure in older adults. Another potential explanation however may be that the association between functioning of the HPA-axis negative feedback loop and brain structure is present only in persons under psychosocial stress.

Indeed, we found that diminished function of the HPA-axis negative feedback loop was associated with smaller total brain and white matter volume in participants with clinically relevant depressive symptoms. These associations were accompanied by a smaller WMH volume, suggesting that these findings may be explained by global tissue loss rather than vascular brain pathology. Dysregulation of the HPA-axis in depression has been studied extensively. As a result of glucocorticoid resistance due to chronically elevated cortisol levels, an altered (often diminished) function of the negative feedback loop is thought to induce a hyperactive HPA-axis with hypersecretion of cortisol (Cheiran Pereira et al., 2021; Pariante and Lightman, 2008). These dysregulated cortisol levels may affect brain structure through several mechanisms. First, excess glucocorticoids in the central nervous system may activate microglia, inducing neuroinflammation that may lead to neuronal damage (Cheiran Pereira et al., 2021). Alternatively, dysregulated cortisol levels may affect cardiovascular activity and induce cerebral endothelial dysfunction that can lead to neuronal damage and tissue loss (Burrage et al., 2018). Of note, stress-related structural brain changes have been described in depressed individuals, in particular remodeling of the hippocampus, amygdala and prefrontal cortex in response to HPA-axis dysregulation (McEwen, 2005; McEwen and Akil, 2020). Since HPA-axis dysfunction is a prominent feature of depression, the association between HPA-axis dysfunction and brain structure might have been more prominent in this subgroup in our study sample.

Unexpectedly, we found that in participants with low/moderate perceived social support, a diminished cortisol response was associated with larger total brain volume, larger gray matter volume and better white matter microstructural integrity, compared to those with high social support. Previous studies have found that better social support is typically associated with better brain health (Sherman et al., 2016; van der Velpen et al., 2021). and better overall health (Uchino, 2006). Our contrasting findings can be interpreted in two ways. First, the direction of the association in this subgroup is positive: higher post-DST cortisol is associated with larger brain volumes. This means that lower post-DST cortisol in this subgroup is associated with smaller brain volumes. Lower post-DST cortisol values may signal an enhanced cortisol response, which has also been associated with adverse health outcomes and is known to occur in stress-related disorders (Kinlein and Karatsoreos, 2020; Maripuu et al., 2014). This indicates that an enhanced cortisol response may be associated with worse brain structure. Within an enhanced state, higher post-DST cortisol may reflect a situation closer to normal HPA-axis function. However, since validated cut-offs are not available for the very low dose-DST this remains difficult to determine. Alternatively, higher post-DST cortisol levels may reflect an adaptive response. A previous study found that higher cortisol levels moderated whom lonely individuals befriended, suggesting cortisol serves as an adaptive response to engage resources needed to develop new social connections (Kornienko et al., 2020). Similarly, in participants with low/moderate social support, higher post-DST cortisol levels may reflect that these participants are able to regulate the HPA-axis response as a coping response. Being able to regulate and cope may in turn be associated with better brain health. Our findings show that the association between stress, social support and the brain is highly complex and that social support may affect the brain through a different mechanism than depression.

The cross-sectional nature of our study prohibits conclusions on the direction of the associations. Although our hypothesis was that HPA-axis dysfunction is associated with worse brain structure, it is plausible that worse brain structure actually affects HPA-axis function. Brain aging may occur in regions that are crucial to HPA-axis regulation, and damage in these areas may consequently lead to dysregulation of the stress response. In fact, HPA-axis dysfunction is common after traumatic brain injury, partially as a result of neuronal damage in these crucial brain areas (Tapp et al., 2019). In states of depressive symptomatology or suboptimal social support, brain changes affecting the hypothalamus or pituitary may add onto existing stress (dys)regulation and modify the association between HPA-axis function and brain structure. The association between the HPA-axis, the brain and other neuroendocrine and

immune systems are very complex, and causal relationships in this field are yet to be determined (Yiallouris et al., 2019).

Several limitations should be considered in our study. First, persons with serious psychosocial health problems might be less likely to participate in research, and might not have been included in our sample. This could have led to an underestimation of our results. Second, since we considered cross-sectional associations only, we cannot infer causality in our findings. Third, the lack of reference values limits our interpretation of the HPA-axis response. In addition, we performed a large number of analyses, which increases the probability of spurious findings. Although the outcomes and subgroups are correlated and the associations point generally in the same direction, future studies will have to show whether our findings are robust. Strengths of our study include the intersection of HPA-axis function and brain structure in a population-based setting while taking into account psychosocial health and adjusting for a large number of covariates. We were able to explore effect modification and interaction between psychosocial health and HPA-axis function, but further research is necessary to study whether the HPA-axis could be a mediator in the association between psychosocial health and brains structure. Future research should focus on studying sex-differences in these associations and establishing the direction of the association in longitudinal imaging studies, while taking into account specifically the role of the hippocampus in the glucocorticoid cascade hypothesis (Sapolsky et al., 1986).

5. Conclusions

In conclusion, a diminished negative feedback loop of the HPA-axis is associated with worse brain structure in community-dwelling older adults with clinically relevant depressive symptoms, but with better brain structure in older adults with suboptimal perceived social support. Our results suggest that dysregulation of the HPA-axis is associated with brain structure only in specific psychosocial conditions in which the cortisol response to a stressor is altered. Although mental, social and physical wellbeing are often considered as separate domains of health, these systems closely interact to constantly adapt to changing circumstances(Huber et al., 2011). In elucidating the mechanisms linking the HPA-axis stress response and brain structure in adverse psychosocial circumstances, these interactions should be taken into account.

CRediT authorship contribution statement

Isabelle F. van der Velpen: Formal analysis, Writing – original draft, Conceptualization. **Maud de Feijter:** Formal analysis, Writing – review & editing. **Rutika Raina:** Formal analysis, Writing – review & editing. **Fatih Özel:** Supervision, Writing – review & editing. **Marieke Perry:** Supervision, Funding acquisition, Writing – review & editing. **M. Arfan Ikram:** Supervision, Funding acquisition, Writing – review & editing. **Meike W. Vernooij:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing. Annemarie I. Luik: Conceptualization, Supervision, Writing – review & editing.

Declarations of interest

None.

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Disclosures

Isabelle van der Velpen: none.
Maud de Feijter: none.
Rutika Raina is currently employed by Open Health, a healthcare consultancy firm.
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Arfan Ikram: none.
Meike Vernooij: none.
Annemarie Luik: none.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106106.

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