Archival Report

Biological Psychiatry: GOS

Circulating Stress Hormones, Brain Health, and Cognition in Healthy Older Adults: Cross-Sectional Findings and Sex Differences in Age-Well

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ABSTRACT

BACKGROUND: Increased stress is a proposed risk factor for Alzheimer's disease (AD). We examined cross-sectional associations between circulating stress biomarkers and multimodal measures of brain health and cognition susceptible to AD in older adults and sex-specific subgroups.

METHODS: Baseline data from 132 cognitively unimpaired participants without depression (age, mean ± SD = 74.0 ± 4.0 years, women: n = 80) in the Age-Well trial (NCT02977819) were included. Stress hormone levels were measured in overnight fasting blood serum (cortisol, dehydroepiandrosterone sulfate) and blood plasma (epinephrine, norepinephrine) samples. AD-sensitive measures of brain health, including glucose metabolism (n = 89), cerebral perfusion, gray matter volume, amyloid deposition in a priori regions of interest, and cognitive markers were evaluated. Models were adjusted for age, sex, education, trait anxiety, and depressive symptoms.

RESULTS: Higher epinephrine levels were associated (false discovery rate–corrected $p < .05$) with lower glucose metabolism in the anterior cingulate cortex ($\beta = -0.26$, $p = .008$), posterior cingulate cortex ($\beta = -0.32$, $p = .006$), and precuneus ($\beta = -0.27$, $p = .021$) and lower perfusion in the posterior cingulate cortex ($\beta = -0.23$, $p = .013$). Interactions between stress hormones and sex showed (false discovery rate–corrected $p < .05$) that in women only, higher epinephrine was associated with larger anterior cingulate cortex volume (interaction: $\beta = 0.32$, $p = .016$), whereas in men only, higher cortisol was associated with lower episodic memory performance (interaction: $\beta = 0.98$, $p = .012$).

CONCLUSIONS: The current study demonstrates the involvement of circulating stress hormones, particularly epinephrine and cortisol, in greater resilience or vulnerability of brain health and cognitive indicators of susceptibility to AD in older adults. The identification of sex-specific patterns in these associations may inform the development of more effective and tailored interventions.

https://doi.org/10.1016/j.bpsgos.2024.100431

The stress response, or fight-or-flight reaction, involves a powerful interplay between the brain, nervous system, and secretory organs. Dysfunction/dysregulation of the stress response can lead to systemic physiological changes that are thought to be associated with accelerated brain and cognitive aging and increased risk of cognitive impairment and Alzheimer's disease (AD) [for review, see (1,2)] (3,4). Elevated stress levels have been identified as a potentially modifiable risk factor for dementia [for review, see (5)]. Several studies have shown that stress biomarker levels, as measured in blood, saliva, or cerebrospinal fluid (CSF), are altered in AD dementia and associated risk states with regard to cortisol (6–10), dehydroepiandrosterone sulfate (DHEAS) (6,11), and catecholamines, including epinephrine and norepinephrine (12) [for review, see (13)], although there have been some inconsistent findings across studies (14). Here, we aimed to better understand the relationships between multiple stress biomarkers, which reflect the two key axes of the stress response system, and brain health and cognition in healthy older adults.

Stress as a Risk Factor

There is growing evidence that even subtle elevations of the stress response system may be linked to indicators of brain and cognitive health that are susceptible to AD in older adults. Mainly, two axes are involved in the physiological stress response, i.e., the sympathetic-adrenal-medullary (SAM) and the hypothalamic-pituitary-adrenal (HPA) axes, and they appear to act on different temporal scales (15) [for review, see

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ISSN: 2667-1743

(16)]. The SAM axis represents the immediate stress response of the nervous system, promptly increasing circulating catecholamine (epinephrine and norepinephrine) levels. The HPA axis, acting via the activation of hypothalamus and pituitary and adrenal glands, stimulates the elevation of circulating cortisol as well as DHEA and its sulfate ester DHEAS, which may counteract the neurotoxic effects of cortisol through neuroprotective actions [for review, see (17)]. Nevertheless, circulating catecholamines can be associated with chronic stress [for review, see (18,19)] by reflecting increased underlying sympathetic nervous system activity that may be triggered by prolonged/chronic stress.

Stress Biomarkers and Brain Health. Stress biomarkers have been associated with poorer brain health in regions vulnerable to AD. Specifically, studies have shown associations between higher cortisol levels measured in blood, CSF, or saliva of middle-aged and older adults (with and without dementia) and smaller brain structure in the hippocampus (8,20–26) and in medial prefrontal areas including the anterior cingulate cortex (ACC) (27); lower glucose metabolism in lateral and medial parietal brain regions including the posterior cingulate cortex (PCC) and precuneus (22); as well as increased brain amyloid-β (Aβ) deposition (28). Another study linked smaller left ACC volumes to HPA axis dysregulation in a sample of healthy older men (N = 20) (29). The Age-Well trial has also demonstrated a correlation between plasma epinephrine levels and brain function (30), namely altered functional connectivity between hypothalamic and hippocampal subfields in healthy older adults with subclinical depression (N = 73).

Stress Biomarkers and Cognition. Stress biomarkers have been associated with lower cognitive functioning in domains that are vulnerable to AD. Specifically, higher cortisol levels, as measured in blood, CSF, saliva, or hair, have been associated with lower performance in working and short-term verbal memory (26,31) and/or lower executive functioning in middle-aged and older adults at baseline (23,32) and over time, either alone [for review, see (33)] (34) or in synergy with Aβ burden (35). Longitudinal studies have further linked altered baseline DHEAS levels (both decreased and increased) measured in blood serum or CSF to a faster decline in AD-sensitive global cognitive performance during a 3-year follow-up period in independent cohorts comprising 755 (36) and 145 (34) older adults, respectively. Higher levels of CSF norepinephrine have been associated with lower executive functioning in healthy adults across the lifespan (N = 258, ages 21–100 years) (37) and age-related cognitive deficits (38) [for review, see (39)].

Sex Specificities

Only a few studies reported to date have examined potential sex differences in the association between stress markers and indicators of brain health and cognition that are susceptible to AD in older adults. This is surprising given the growing evidence that men and women respond differently to stress across the life course [for review, see (40,41)], which may be relevant to sex differences in age-related disease risks including AD [for review, see (42)]. A previous cross-sectional study of middle-aged adults without dementia (N = 2018) showed sex-specific differences in the susceptibility of brain structure to stress (26), with higher levels of serum cortisol being related to less total brain volume in women but not in men. These findings collectively suggest the potential for sex differences in stress hormone–related associations, which warrants further investigation.

The Present Study

To date, most studies have examined potentially adverse effects of a single stress biomarker, primarily cortisol, in older populations. Less is known about the associations of other circulating stress hormones with brain health and cognition in older adults with particular attention paid to potential sex specificities in this context. The main objective of the current study was to better understand the links between circulating stress biomarkers that reflect the two main axes of the stress response system and multimodal indicators of brain health and cognition that are susceptible to AD. We hypothesized that overnight fasting blood serum (cortisol, DHEAS) and plasma (epinephrine, norepinephrine) stress hormone levels would be associated with predetermined indicators of brain health and cognition in older adults. We also hypothesized that older women and men might demonstrate differential stress hormone–related associations.

METHODS AND MATERIALS

General Methodological Approach

In this cross-sectional study, we analyzed baseline data from the Age-Well trial (NCT02977819) (43), a community-based study of well-characterized older adults. Positron emission tomography (PET) and magnetic resonance imaging were used to assess brain glucose metabolism, cerebral perfusion, and gray matter volume in a set of a priori regions of interest (ROIs) that are part of the stress-regulatory system and that are also susceptible to AD, including the ACC, PCC, precuneus, and hippocampus, as well as neocortical Aβ deposition. Cognitive performance was measured using a global composite score of AD risk, namely the Preclinical Alzheimer's Cognitive Composite 5 (PACC-5) (44), and a domain composite score of episodic memory (45). We examined the associations between multiple stress biomarkers (i.e., epinephrine, norepinephrine, cortisol, DHEAS, and the DHEAS/cortisol ratio) measured in blood and multimodal AD-sensitive measures of brain health and cognition in the total sample and in sex-specific subgroups.

Study Participants

The current study included 132 cognitively unimpaired older adults from the Age-Well trial (NCT02977819) (43). Participants were enrolled between November 24, 2016, and March 5, 2018. Detailed inclusion and exclusion criteria for the Age-Well trial have been described previously (43). Briefly, all participants were 65 years or older, had received at least 7 years of education, and showed no evidence of neurological or psychiatric disorders. The participants had no chronic disease or acute unstable illness, no history of cerebrovascular disease, and no current or recent medication that might have interfered with cognitive performance. The absence of clinical depression was assessed using a clinician-administered questionnaire,

the Montgomery–Åsberg Depression Rating Scale (46). The participation selection process is depicted in Figure 1 and detailed in the Supplement.

Protocol Approval, Registration, and Patient Consent

The Age-Well randomized clinical trial was approved by the local ethics committee (Comité de Protection des Personnes Nord-Ouest III, Caen, France; trial registration number: EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819). All participants gave written informed consent prior to the examinations.

Stress Biomarkers

We analyzed levels of stress biomarkers derived from blood sampling that reflect the two main axes of the stress response system, including plasma epinephrine and norepinephrine, serum cortisol and DHEAS, and the DHEAS/cortisol ratio. Detailed extraction procedures have been described previously (43,47). Details are provided in the Supplement.

Neuroimaging Assessments

All participants were scanned at Cyceron Center in Caen, France on the same magnetic resonance imaging scanner (Philips Achieva 3T) and PET scanner (Discovery RX VCT 64 PET-CT; GE Healthcare). Details on neuroimaging acquisition and preprocessing procedures have been described in our previous publications (43,47–49). Structural magnetic resonance imaging scans and PET scans of early and late ^{18}F-florbetapir (AV45; Amyvid) and ^{18}F-fluorodeoxyglucose PET were assessed. The images were processed to obtain gray matter volume, glucose metabolism, and cerebral perfusion, as well as Aβ deposition in a priori ROIs that are sensitive to AD. Details are provided in the Supplement.

In addition, standard procedures (50,51) were used to obtain Centiloid values from the ^{18}F-florbetapir PET. To categorize participants as amyloid positive, a threshold of >12 Centiloid was used to indicate the presence of moderate-to-frequent neuritic plaques (52).

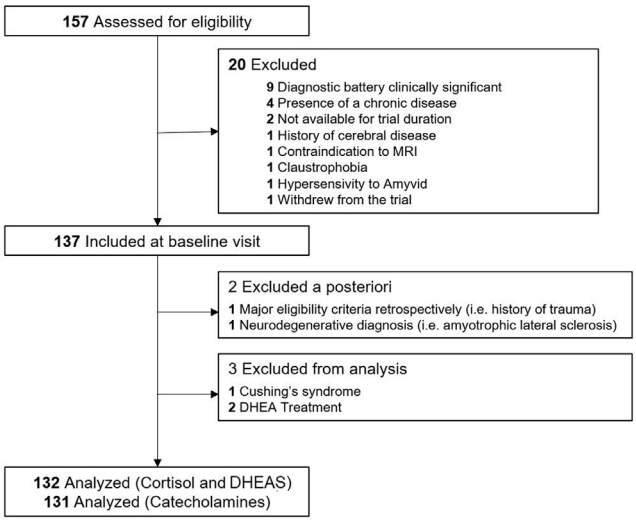

Figure 1. Flow diagram. The flow diagram shows the inclusion process from the baseline dataset of the Age-Well trial. DHEA, dehydroepiandrosterone; MRI, magnetic resonance imaging.

Cognitive Assessments

All participants underwent comprehensive neuropsychological assessments. For this study, we assessed the association between stress biomarkers and a priori cognitive composite scores that are sensitive to AD, namely the PACC-5 (44) and a verbal episodic memory composite (45). Details are provided in the Supplement.

Assessment of Other Variables

We assessed a number of additional variables, including the State-Trait Anxiety Inventory part B (STAI-B) (53), the Geriatric Depression Scale (GDS-15) (54), and the AD risk score Lifestyle for Brain Health (LIBRA) (49,55). Details are provided in the Supplement.

Statistical Analysis

All statistical analyses were performed and plots were generated using R Studio (version 1.4.1106 for Mac and version 4.3.2 for Windows; https://posit.co/products/open-source/rstudio/). To facilitate interpretation, we considered p values $< .05$ as statistically significant and applied correction for multiple comparisons using false discovery rate (FDR). First, the entire sample as well as sex-stratified subgroups (women, men) were characterized using baseline demographic, clinical, health risk, biological, and neuroimaging markers as well as cognitive composite scores. Sex-stratified subgroups were compared using t tests for continuous variables or χ^2 statistics for categorical variables.

Multiple linear regression analyses were conducted to investigate the association between each of the selected circulating stress hormones (i.e., plasma epinephrine and norepinephrine, serum cortisol and DHEAS, and the DHEAS/cortisol ratio) as independent variables and the multimodal brain markers (cerebral glucose metabolism, cerebral perfusion, gray matter volume in the a priori ROIs, and neocortical amyloid deposition) and cognitive composite scores (PACC-5 and episodic memory) as dependent variables. In follow-up analyses, interaction analyses were carried out to assess whether stress-related associations were moderated by sex. For this purpose, the interaction term stress hormone × sex was modeled as an independent variable for each stress biomarker and included in statistical models with each brain marker and cognitive scores as dependent variables. If a significant interaction was found, post hoc sex-stratified regression analyses were carried out.

Statistical analyses were conducted using models with and without adjustment for covariates of no interest. Models were adjusted for age, sex, education, trait anxiety (STAI-B), and depressive symptoms (GDS). We have reported unadjusted and adjusted outcomes in the respective result tables.

Additional Analyses

We conducted a series of follow-up analyses that included additional dependent variables (i.e., glucose metabolism,

cerebral perfusion, and gray matter volume in the insula as well as executive function). Details are provided in the Supplement.

RESULTS

Participant Characteristics

Demographic data and other sample information are provided in Table 1 for the total sample and sex-stratified subgroups. The Age-Well participants showed low levels of anxiety/depression symptoms (measured by the STAI-B/GDS) and intermediate dementia risk (measured by the AD risk score LIBRA). Women differed significantly from men in education, depressive symptoms, stress biomarker levels, episodic memory performance, and brain measures related to cerebral perfusion and gray matter volume (all $ps < .05$).

Associations Between Stress Biomarkers and Brain Health

Cerebral Glucose Metabolism. Total sample: Results of the analyses are shown in Table 2 and Figure 2. In the total sample, higher epinephrine was significantly ($p_{FDR} < .05$)

Table 1. Descriptive Baseline Characteristics

	Total Sample, *N*	Women, *n* = 80	Men, *n* = 52	*p* Value
Demographics, *N* = 132				
Age, Years	74.0 (4.0)	74.0 (3.9)	74.0 (4.2)	.943
Education, Years	13.1 (3.1)	12.5 (3.0)	14.1 (3.1)	.003
Psychological and Lifestyle Risk Markers, *N* = 132				
STAI-B	34.4 (6.97)	35.0 (6.91)	33.6 (7.04)	.239
GDS	1.30 (1.75)	1.56 (1.98)	0.81 (1.21)	.015
LIBRA	0.90 (2.41)	1.05 (2.24)	0.67 (2.65)	.375
Stress Biomarkers				
Epinephrine, μg/L, Plasma, *n* = 131	0.04 (0.03)	0.03 (0.02)	0.05 (0.04)	<.001
Norepinephrine, μg/L, Plasma, *n* = 131	0.58 (0.22)	0.59 (0.22)	0.56 (0.21)	.509
Cortisol, nmol/L, Serum, *N* = 132	438 (103)	463 (104)	400 (91)	<.001
DHEAS, μmol/L, Serum, *N* = 132	2548 (1571)	1986 (969)	3412 (1905)	<.001
DHEAS/Cortisol Ratio, *N* = 132	6.32 (4.70)	4.57 (2.75)	9.01 (5.72)	<.001
Cognitive Composite Scores, *N* = 132				
Verbal Episodic Memory	0.013 (0.981)	0.305 (0.945)	−0.437 (0.864)	<.001
PACC-5	0.003 (0.997)	0.183 (0.989)	−0.273 (0.954)	.010
Multimodal Neuroimaging Markers				
Glucose Metabolism, SUV Ratio, *n* = 89				
Posterior cingulate cortex	1.38 (0.12)	1.39 (0.12)	1.37 (0.13)	.387
Precuneus	1.24 (0.09)	1.24 (0.09)	1.24 (0.10)	.850
Anterior cingulate cortex	0.99 (0.07)	0.99 (0.06)	0.98 (0.08)	.411
Cerebral Perfusion, SUV Ratio, *n* = 130				
Posterior cingulate cortex	1.25 (0.08)	1.26 (0.08)	1.24 (0.09)	.118
Precuneus	1.14 (0.07)	1.15 (0.07)	1.14 (0.06)	.331
Anterior cingulate cortex	1.02 (0.06)	1.03 (0.05)	1.00 (0.07)	.026
MRI Volumes, mm^3, *N* = 132				
Anterior cingulate cortex	10,033 (732)	10,239 (653)	9717 (741)	<.001
Hippocampus	3371 (376)	3231 (316)	3585 (361)	<.001
Amyloid Deposition				
Neocortex, SUV ratio, *n* = 131	1.24 (0.15)	1.24 (0.13)	1.25 (0.18)	.717
Neocortex, Centiloid units, *n* = 130	7.39 (24.97)	6.27 (21.50)	9.10 (26.62)	.528
Amyloid status, positive/negative, *n* = 131	35/96	21/58	14/38	.966
Timing of Assessments				
Time Interval, Blood to MRI, Days, *N* = 132	11.53 (20.72)	12.17 (21.86)	10.58 (19.03)	.670
Time Interval, Blood to FDG-PET, Days, *n* = 89	37.56 (23.84)	36.54 (23.90)	39.30 (24.00)	.600
Time Interval, Blood to AV45-PET, Days, *n* = 131	31.21 (23.83)	32.06 (22.71)	29.89 (25.64)	.610
Time Interval, Blood to Cognition, Days, *N* = 132	25.63 (19.53)	25.03 (20.25)	26.56 (18.52)	.661

Values are presented as mean (SD) or *n*. MRI volumes were adjusted for total intracranial volume.

AD, Alzheimer's disease; AV45, florbetapir; DHEAS, dehydroepiandrosterone sulfate; FDG, fluorodeoxyglucose; GDS, Geriatric Depression Scale; LIBRA, Lifestyle for Brain Health; MRI, magnetic resonance imaging; PACC-5, Preclinical Alzheimer's Cognitive Composite 5; PET, positron emission tomography; STAI-B, State-Trait Anxiety Inventory part B; SUV, standardized uptake value.

Table 2. Associations Between Stress Biomarkers and Cerebral Glucose Metabolism

	ACC		PCC		Precuneus	
Stress Biomarkers	Beta Coefficient	*p* Value	Beta Coefficient	*p* Value	Beta Coefficient	*p* Value
Epinephrine, *n* = 88						
Unadjusted model	−0.23	.035[a]	−0.28	.008[a,b]	−0.22	.042[a]
Adjusted model	−0.26	.008[a,b]	−0.32	.006[a,b]	−0.27	.021[a,b]
Norepinephrine, *n* = 88						
Unadjusted model	0.15	.162	0.13	.227	0.15	.178
Adjusted model	0.12	.283	0.11	.320	0.13	.252
Cortisol, *n* = 89						
Unadjusted model	−0.00	.995	−0.01	.921	−0.01	.930
Adjusted model	−0.04	.709	−0.02	.880	−0.02	.893
DHEAS, *n* = 89						
Unadjusted model	0.02	.877	−0.12	.269	0.00	.964
Adjusted model	0.05	.688	−0.14	.296	−0.01	.917
DHEAS/Cortisol, *n* = 89						
Unadjusted model	−0.00	.989	−0.14	.197	−0.03	.803
Adjusted model	0.03	.821	−0.18	.169	−0.06	.631

Results of the linear regression models. Models were adjusted for sex, age, education, trait anxiety (STAI-B), and depressive symptoms (GDS).

ACC, anterior cingulate cortex; DHEAS, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; PCC, posterior cingulate cortex; STAI-B, State-Trait Anxiety Inventory part B.

[a]$p < .05$, uncorrected.

[b]$p < .05$, false discovery rate adjusted.

associated with lower glucose metabolism in the ACC (adjusted $\beta = -0.26$, $p = .008$), PCC (adjusted $\beta = -0.32$, $p = .006$), and precuneus (adjusted $\beta = -0.27$, $p = .021$). No other significant associations were found.

Interaction analysis: As shown in Figure 2 and Table S5, follow-up analysis showed no significant interactions between stress hormones and sex on cerebral glucose metabolism in the ROIs (interactions: all $ps \geq .09$).

Cerebral Perfusion. Total sample: Results of the analyses are displayed in Table 3 and Figure 2. In the total sample, higher epinephrine levels were significantly associated

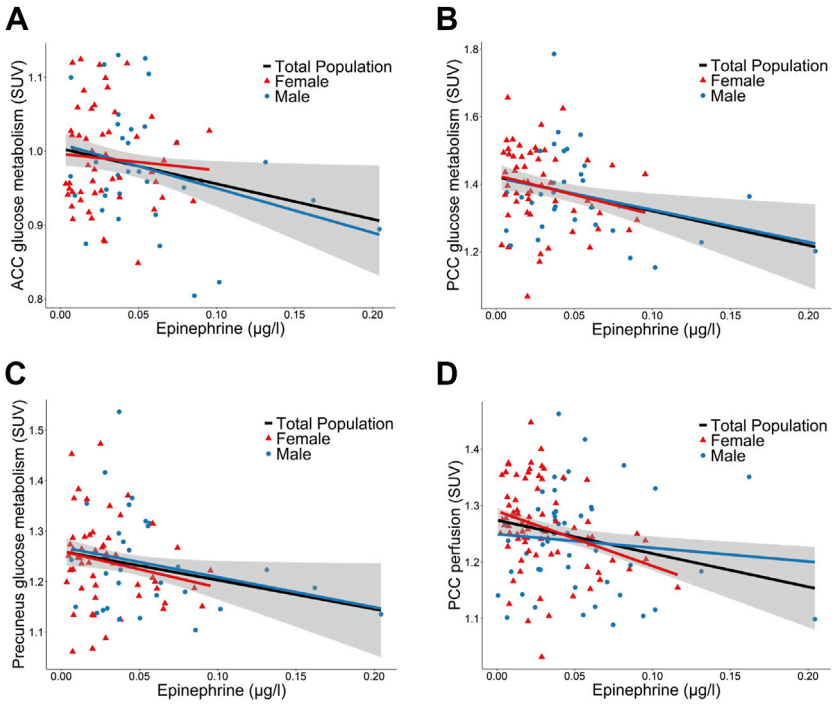

Figure 2. Associations between plasma epinephrine and brain health. Scatter plots show the association between epinephrine and cerebral glucose metabolism in the anterior cingulate cortex (ACC) **(A)**, posterior cingulate cortex (PCC) **(B)**, and precuneus **(C)** as well as between epinephrine and cerebral perfusion in the PCC **(D)** for the total sample and stratified by sex. Higher epinephrine levels were associated (false discovery rate–corrected $p < .05$) with lower glucose metabolism and lower cerebral perfusion in these brain regions independent of sex. Black lines indicate regression lines with shaded areas showing the 95% CI for the total sample, red dots and lines indicate data points and regression lines for the subgroup with women, blue dots and lines indicate data points and regression lines for the subgroup with men. SUV, standardized uptake value.

Table 3. Associations Between Stress Biomarkers and Cerebral Perfusion

	ACC		PCC		Precuneus	
Stress Biomarkers	Beta Coefficient	*p* Value	Beta Coefficient	*p* Value	Beta Coefficient	*p* Value
Epinephrine, *n* = 129						
Unadjusted model	−0.12	.167	−0.23	.008[a,b]	−0.08	.355
Adjusted model	−0.06	.491	−0.23	.013[a,b]	−0.08	.364
Norepinephrine, *n* = 129						
Unadjusted model	0.04	.631	0.04	.637	0.07	.460
Adjusted model	0.01	.901	0.02	.864	0.04	.617
Cortisol, *n* = 130						
Unadjusted model	0.06	.496	0.13	.130	0.13	.130
Adjusted model	−0.01	.909	0.12	.209	0.13	.167
DHEAS, *n* = 130						
Unadjusted model	0.00	.993	−0.18	.040[a]	0.11	.228
Adjusted model	0.05	.604	−0.19	.063	0.11	.258
DHEAS/Cortisol, *n* = 130						
Unadjusted model	−0.03	.844	−0.22	.013[a]	0.06	.480
Adjusted model	0.03	.862	−0.25	.015[a]	0.06	.571

Results of the linear regression models. Models were adjusted for sex, age, education, trait anxiety (STAI-B), and depressive symptoms (GDS).

ACC, anterior cingulate cortex; DHEAS, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; PCC, posterior cingulate cortex; STAI-B, State-Trait Anxiety Inventory part B.

[a]$p < .05$, uncorrected.

[b]$p < .05$, false discovery rate adjusted.

($p_{FDR} < .05$) with lower cerebral perfusion in the PCC (adjusted $\beta = -0.23$, $p = .013$). In addition, a higher DHEAS/cortisol ratio was associated with lower perfusion in the PCC (adjusted $\beta = -0.25$, $p = .015$); however, this association was not significant with FDR correction.

Interaction analysis: As shown in Figure 2 and Table S6, follow-up analysis showed an interaction between sex and norepinephrine on precuneus perfusion (interaction: adjusted $\beta = 0.59$, $p = .034$) that was not significant with FDR correction. Post hoc sex-stratified analysis showed no significant associations between norepinephrine and precuneus perfusion among women (adjusted $\beta = 0.17$, $p = .132$) or men (adjusted $\beta = -0.19$, $p = .167$).

Brain Volume. Total sample: Results of the analyses are shown in Table S2. In the total sample, higher stress hormone levels were not significantly associated with regional brain volumes in the ACC or hippocampus in the adjusted models (all $ps \geq .1$).

Interaction analysis: As shown in Figure 3, Table 4, and Table S7, follow-up analysis showed a significant interaction ($p_{FDR} < .05$) between sex and epinephrine on ACC volume (interaction: adjusted $\beta = 0.32$, $p = .016$). Post hoc sex-stratified analysis indicated that in women, higher epinephrine levels were associated with greater ACC volume (adjusted $\beta = 0.29$, $p = .011$). This association was not found in men (adjusted $\beta = -0.04$, $p = .808$). An observed interaction between norepinephrine and sex on the hippocampal volume (interaction: unadjusted $\beta = 0.53$, $p = .036$) was not significant after FDR correction. Post hoc sex-stratified analysis showed no significant associations between norepinephrine and hippocampal volume in women (unadjusted $\beta = 0.20$, $p = .085$) or men (unadjusted $\beta = -0.18$, $p = .198$).

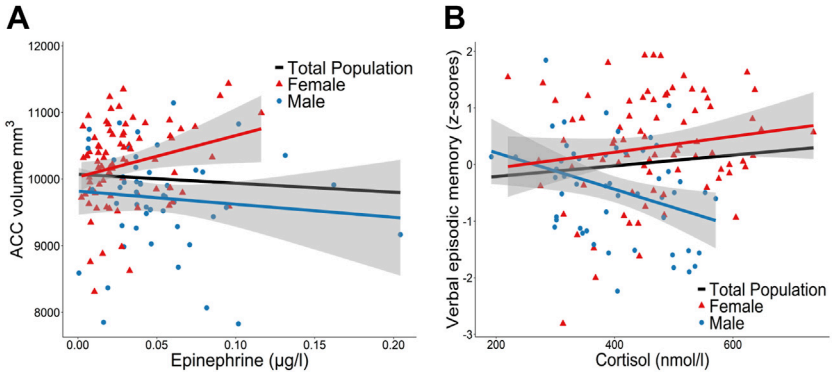

Figure 3. Interactions between sex and stress biomarkers on brain health and cognition. **(A)** The scatter plot shows the interaction (false discovery rate–corrected $p < .05$) between sex and plasma epinephrine on anterior cingulate cortex (ACC) brain volume. In women, but not in men, higher epinephrine was associated with greater ACC volume. **(B)** Interaction (false discovery rate–corrected $p < .05$) between serum cortisol and sex on verbal episodic memory. In men, but not in women, higher cortisol levels were associated with lower memory performance. Black lines indicate regression slopes for the total sample; red dots and lines indicate data points and regression lines, with shaded areas showing the 95% CI for the subgroup with women; blue dots and lines indicate data points and regression lines, with shaded areas showing the 95% CI for the subgroup with men.

Table 4. Selected Interactions Between Stress Biomarkers and Sex on Cognition and Brain Volume

	Verbal Episodic Memory		PACC-5		ACC Brain Volume, mm^3	
Stress Biomarkers	Beta Coefficient	*p* Value	Beta Coefficient	*p* Value	Beta Coefficient	*p* Value
Epinephrine × Sex, *n* = 131						
Unadjusted model	0.01	.931	−0.20	.144	0.28	.040[a]
Adjusted model	0.07	.608	−0.10	.421	0.32	.016[a,b]
Norepinephrine × Sex, *n* = 131						
Unadjusted model	−0.04	.873	−0.25	.363	0.49	.067
Adjusted model	0.01	.978	−0.17	.497	0.50	.058
Cortisol × Sex, *N* = 132						
Unadjusted model	1.14	.005[a,b]	0.94	.034[a,b]	0.38	.376
Adjusted model	0.98	.012[a,b]	0.77	.057	0.30	.483
DHEAS × Sex, *N* = 132						
Unadjusted model	−0.15	.351	0.07	.690	−0.05	.763
Adjusted model	−0.12	.424	0.07	.641	−0.03	.830
DHEAS/Cortisol × Sex, *N* = 132						
Unadjusted model	−0.23	.095	−0.04	.809	−0.11	.418
Adjusted model	−0.17	.197	0.00	.984	−0.09	.512

Results of the linear regression models. Brain volumes were adjusted for total intracranial volume. Models were adjusted for age, education, trait anxiety (STAI-B), and depressive symptoms (GDS).

ACC, anterior cingulate cortex; DHEAS, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; PACC-5, Preclinical Alzheimer's Cognitive Composite 5; STAI-B, State-Trait Anxiety Inventory part B.

[a]$p < .05$, uncorrected.

[b]$p < .05$, false discovery rate adjusted.

Amyloid Deposition. Total sample: Results of the analyses are displayed in Table S3. In the total sample, stress hormone levels were not significantly associated with neocortical amyloid deposition (all *p*s ≥ .1). Follow-up analysis showed no significant interactions between stress hormone levels and sex on amyloid deposition (all *p*s ≥ .5) (Table S8).

Associations Between Stress Biomarkers and Cognition

Total sample: Results of the analyses are displayed in Figure 3 and Table S4. In the total sample, stress hormone levels were not significantly associated with the cognitive composite scores (all *p*s ≥ .06).

Interaction analysis: As shown in Table 4 and Figure 3, follow-up analysis showed a significant interaction between sex and cortisol on verbal episodic memory performance (interaction: adjusted $\beta = 0.98$, $p = .012$, $p_{FDR} < .05$) that was maintained after FDR correction. Post hoc sex-stratified analysis showed that in men, higher cortisol was associated with lower verbal episodic memory (adjusted $\beta = -0.33$, $p = .020$). This association was not found in women (adjusted $\beta = 0.08$, $p = .459$). For the PACC-5, we observed a significant interaction between cortisol levels and sex with a similar directionality (interaction: $\beta = 0.94$, $p = .034$). However, this interaction was reduced to trend level after adjustment for covariates (interaction: adjusted $\beta = 0.77$, $p = .057$).

Additional Analyses

Results of the additional analyses are presented in the Supplement. In summary, follow-up analyses showed no significant associations between stress biomarkers and neuroimaging measures in the insula as well as executive function (all *p*s > .1). In further follow-up analyses, in which an additional adjustment was made for the time interval between individual measurements, the primary results remained significant (all *p*s < .05). Finally, post hoc analyses showed no significant interactions between amyloid status (positive/negative) and stress hormone levels (epinephrine) in the significant models of the main analysis (all *p*s > .5).

DISCUSSION

In the present study, we systematically examined cross-sectional correlations between circulating stress biomarkers that reflect SAM activation (plasma epinephrine and norepinephrine) and HPA activation (serum cortisol and DHEAS) and multimodal indicators of brain health and cognition susceptible to AD. We investigated baseline data from cognitively unimpaired older adults without clinical depression/anxiety and intermediate dementia risk who were enrolled in the Age-Well trial (43). Our findings highlight that levels of circulating stress hormones, particularly epinephrine and cortisol, were linked to greater resilience or vulnerability of certain indicators of brain health and cognition that are susceptible to AD in older people. Importantly, we found sex-specific patterns in these associations, which may assist in the design of more effective and tailored intervention strategies.

Association Between Stress Biomarkers and Brain Health

Our findings suggest a link between circulating stress hormones and functional measures of brain health, namely glucose metabolism and cerebral perfusion, in brain regions susceptible to AD. In our study, higher plasma epinephrine was associated with lower glucose metabolism in the ACC, PCC,

and precuneus and lower cerebral perfusion in the PCC. A post hoc analysis demonstrated that these associations were observed irrespective of brain Aβ deposition in our sample. In contrast with our initial hypothesis, no significant associations were identified between circulating stress biomarkers and hippocampal volume or brain Aβ deposition (for discussion, see the Supplement). Previously, we documented an association between higher plasma cortisol and lower glucose metabolism in AD-sensitive lateral and medioparietal brain regions in a mixed cohort of individuals along the cognitive continuum (22). Lower glucose metabolism and lower cerebral perfusion in temporo-parietal and/or medial prefrontal brain regions have been documented in older adults at increased risk of AD (56–58) and may in turn contribute to accelerated cognitive decline and clinical progression of the disease (59,60).

Multiple physiological pathways may be involved in the association between circulating epinephrine and indicators of brain health. Epinephrine is primarily associated with short-term stress responses via activation of the sympathetic nervous system. However, circulating epinephrine can be associated with chronic stress [for review, see (18,19)] because catecholamines are indicative of the baseline activity of the autonomic nervous system, which can be affected by prolonged/chronic stress and anxiety. The sympathetic nervous system integrates a multitude of brain regions involved in the detection and interpretation of potential threats and the activation of physiological stress responses [for review, see (19)]. While the rapid up- and downregulation of epinephrine can contribute to stress adaptation, long-term sustained epinephrine elevation may facilitate maladaptation and disease. Although circulating epinephrine does not cross the blood-brain barrier, catecholamines may have indirect effects on the central nervous system via visceral efferent fibers of the vagus nerve [for review, see (61)]. Indirect effects of elevated circulating epinephrine on the brain could also be related to changes in glycemic (i.e., hyperglycemia), cardiovascular (i.e., hypertension), and inflammatory activity [for review, see (19)]. Studies have demonstrated a negative association between vascular risk factors and functional measures of brain health, including glucose metabolism, cerebral perfusion, and functional connectivity (62,63). This may contribute to an increased vulnerability of the aging brain.

Sex Specificities in Stress Biomarker Associations

We found that higher epinephrine levels were associated with a larger ACC volume in women but not in men. This observation is surprising given that higher levels of chronic stress have been linked to reduced ACC volume in animal (64) and human (65,66) studies. The current finding is of interest for several reasons. First, the ACC is a key brain region involved in cognitive, emotional, and affective processing [for review, see (67)]. Deficits in ACC structure and function have been implicated in mood and anxiety disorders (68) and in the development of AD (69). Conversely, preserved or enhanced ACC structure and function have been linked to greater brain resilience [for review, see (70)] and cognitive reserve mechanisms (71,72) in older adults. An increased ACC volume has also been associated with positive coping styles. Additionally, greater ACC volume and positive coping styles have been linked to lower levels of anxiety and depression in women but not in men in the same study (73). Moreover, larger medial prefrontal brain structures involved in emotion regulation (including the ACC) have been associated with stress resilience in animal and human studies [for review, see (74)]. Given these findings, the positive correlation between circulating epinephrine and ACC volume in older women may reflect a beneficial structural adaptation associated with greater resilience in this group.

Our data also showed that higher serum cortisol was associated with lower verbal episodic memory performance in men but not in women (a similar effect for the PACC-5 was not significant after covariate adjustment). A previous study did not find a significant interaction between serum cortisol and sex on cognitive (global and domain specific) performance (26). However, numerous studies in rodent models [for review, see (75)] have demonstrated that stress impairs memory in male mice (76–78). In contrast, female mice frequently show resilience or even improvement in learning and memory abilities following stress exposure (79–81). In a longitudinal study on older adults, greater perceived stress was associated with faster age-related cognitive decline only in men and not in women (82). The lack of a significant association between stress markers and cognitive ability in older women may reflect a greater resilience of the cognitive system in this group. In contrast, the cognitive functioning of older men appears to be more vulnerable to the effects of stress, which could be addressed in tailored intervention programs.

Synopsis and Future Research

Taken together, our results substantiate the notion that levels of circulating stress hormones can be linked to the resilience or vulnerability of brain health and cognition indicators that are susceptible to AD, even in cognitively unimpaired older adults without depression. Longitudinal studies will help to clarify whether elevated stress hormone levels increase susceptibility to pathological brain aging. Some stress-related associations were only observed in older men or women, suggesting that the effects of stress hormones differ between the sexes, and different physiological pathways may be involved (for discussion, see the Supplement). Given that stress and its broad systemic impact [for review, see (83)] is considered a potentially modifiable risk factor for AD and other health conditions (4), the physiological effects of stress hormones in older women and men and the effectiveness of sex-specific interventions need to be investigated further.

Strengths and Limitations

Our study has several strengths. First, multiple stress biomarkers indicative of SAM and HPA axis activations were measured and analyzed together with multimodal measures of brain health and cognition in the same well-characterized sample of older adults, which may outweigh limitations in sample size. Second, blood levels of stress hormone may not provide the same information as CSF concentrations, but their use in clinical settings represents a practical approach that supports the potential future translation of our findings. Third, we considered various potential confounding variables in our

analyses, and FDR correction was applied to the *p* values. Despite this strict methodological approach, several statistical models remained significant, highlighting the validity of our results.

The following limitations of the current study need to be acknowledged. First, the current study used a cross-sectional design, which does not allow us to interpret causalities. Additional investigation is required using intervention studies and randomized clinical studies to elucidate the causal relationships between stress biomarkers and indicators of brain health and cognition in older adults. Second, our study included only healthy, cognitively unimpaired participants, which may limit the generalizability of the results. Third, a single blood measurement of stress biomarkers was used rather than multiple biomarker measurements over time and/or other measurement types. This limits the interpretation of longer-term effects of elevated stress hormone levels on brain health and cognition. Long-term effects of increased stress may be captured better by composite measures of allostatic load [for review, see (83,84)]. In addition, repeated low-threshold saliva or hair sampling could be used in future studies, with the latter reflecting long-term stress exposure (85).

Conclusions

Our results demonstrate an association between circulating stress hormones and certain indicators of brain health and cognition that are vulnerable to AD in older adults. Furthermore, the current study shows that older women and men may differ in their resilience or vulnerability to elevated stress hormone levels, particularly epinephrine and cortisol. Future research is needed to elucidate the underlying physiological pathways and address these sex differences in tailored intervention programs.

ACKNOWLEDGMENTS AND DISCLOSURES

The Age-Well randomized clinical trial is part of the Medit-Ageing project and is funded through the European Union's Horizon 2020 Research and Innovation Program (Grant No. 667696), Institut National de la Santé et de la Recherche Médicale (INSERM), Région Normandie, and Fondation MMA des Entrepreneurs du Futur.

GC, GP, and MW were responsible for conceptualization. AC, FM, BL, MD, OH, ALT, ML, SW, OK, GP, and MW were responsible for acquisition, methodology, or validation. ML, SW, OK, GP, and MW were responsible for writing the original draft of the article. ML, SW, SH, AC, FM, NLM, GC, OK, GP, and MW were responsible for writing, reviewing, and editing the article. ML, SW, SH, and MW were responsible for statistical analysis. GC, GP, OK, and NLM were responsible for funding acquisition. AC, BL, FM, MD, NLM, and OH were responsible for project administration. OK, GP, and MW were responsible for supervision. Other principal investigators: Vincent De La Sayette (Medit-Ageing Research Group).

We thank A. Cognet, C. Gaubert, T. Jorand, M. Botton, M.Sc., A. Joret Philippe, M.Sc., S. Egret, M.Sc., P. Lacheray, M.Sc., J. Lebahar, Ph.D., L. Paly, M.Sc., C. Tomadesso, Ph.D., H Espérou, M.D., E. Frison, M.D., Ph.D., and the Cyceron MRI-PET staff members for their help with recruitment and data acquisition or administrative support. We acknowledge the Euclid team, the sponsor (INSERM Pôle de Recherche Clinique), and all the participants of the study for their contribution. We acknowledge the Medit-Ageing Research Group.

The data underlying this study are made available on request following approval by the executive committee and a formal data-sharing agreement (https://silversantestudy.eu/2020/09/25/data-sharing). The data can be mobilized, under the conditions and modalities defined in the Medit-Ageing Chartery, by any research team that belongs to an academic institution for carrying out a scientific research project related to the scientific theme of mental health and wellbeing in older people. The data may also be mobilized by nonacademic third parties, under conditions, in particular financial, which will be established by separate agreement between INSERM and said third party. Data-sharing policies described in the Medit-Ageing Charter are in compliance with the ethics approval and guidelines of our funding body. Data contain potentially identifying or sensitive patient information. To request data, please contact the data access committee via the official project website (https://silversantestudy.eu/2020/09/25/data-sharing). The R scripts that were used for the analyses for the current study are available via the Open Science Framework (https://osf.io/4vp8g/).

GC, GP, OK, and NLM report support from European Union's Horizon 2020 Research and Innovation Program (Grant No. 667696). All other authors report no biomedical financial interests or potential conflicts of interest.

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Received Jul 16, 2024; revised Oct 24, 2024; accepted Nov 27, 2024.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsgos.2024.100431.

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