Psychoneuroendocrinology 115 (2020) 104601

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Cortisol reactivity to a psychosocial stressor significantly increases the risk of developing Cognitive Impairment no Dementia five years later

Juliana Nery de Souza-Talarico[a,*], Andrea Regiani Alves[a], Sonia Maria Dozzi Brucki[b], Ricardo Nitrini[b], Sonia J. Lupien[c], Deborah Suchecki[d]

[a] Department of Medical-Surgical Nursing, School of Nursing, Universidade de São Paulo, São Paulo, 05403 000, Brazil
[b] Department of Neurology, Faculty of Medicine, Universidade de São Paulo, São Paulo, 05403 000, Brazil
[c] Centre for Studies on Human Stress, Mental Health Research Centre Fernand Seguin, Hospital Louis H. Lafontaine, Université de Montréal, Montréal, QC, H1N 3V2, Canada
[d] Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, 04023-062, Brazil

ARTICLE INFO

Keywords:
Psychological stress
Cortisol
Cognitive impairment not dementia
Dementia
Aging

ABSTRACT

Alzheimer's disease (AD) patients show high cortisol levels suggesting that biological mediators of stress may play a role in the neurodegenerative process of cognitive disorders. However, there is no consensus as to whether cortisol concentrations represent a risk factor for the development of cognitive impairment. We analyzed the potential association between the incidence of cognitive impairment and cortisol concentrations under basal and acute stress conditions in 129 individuals aged 50 years or older, with preserved cognitive and functional abilities. All participants were recruited in 2011 for assessment of cognitive performance and cortisol levels. Cortisol was analyzed in saliva samples collected during two typical and consecutive days, in the morning, afternoon, and night, and also during exposure to an acute psychosocial stressor (Trier Social Stress Test – TSST). After a five-year follow-up, 69 of these volunteers were reassessed for cognitive performance, functional evaluation, memory complaints, and depression. The incidence of cognitive impairment not dementia (CIND) was 26.1 %, and was positively associated with greater TSST-induced cortisol release (responsiveness) [(95 % CI = 1.001–1.011; B = 0.006), p = 0.023]. Moreover, five years before diagnosis, participants who later developed CIND had greater responsiveness to TSST (p = 0.019) and lower cortisol awakening response (CAR: p = 0.018), as compared to those who did not develop CIND. These findings suggest that higher psychosocial stress responsiveness profiles may represent a preclinical sign of cognitive impairment.

1. Introduction

More than three decades have passed by since the association between glucocorticoids and memory performance was established in animals (Landfield et al., 1978) and humans (Lupien et al., 1994), giving rise to a remarkable area of investigation for risk factors to cognitive disorders. Several studies have been conducted since, aiming to identify stress — especially stress hormones — as a potential risk factor for the development of forms of dementia, such as Alzheimer's disease (AD). However, this relationship is still under debate and investigation (see Matos and Souza-Talarico, 2019) for review).

The presence of glucocorticoid receptors in the hippocampus and prefrontal cortex, areas intrinsically related to learning and memory, and their role in regulating the negative feedback of the hypothalamic-pituitary-adrenal axis (HPA) have been the basis for the association between stress and cognition (Diorio et al., 1993; Reul and de Kloet, 1985). Under acute stress, the occupancy of glucocorticoid receptors in the hippocampus triggers the inhibition of the HPA axis, which in turn causes glucocorticoids to return to basal levels (Joëls and de Kloet, 1989). However, chronic exposure to high levels of glucocorticoids damages hippocampal neurons, producing a failure of the HPA axis negative feedback, as well as memory decline (Sapolsky et al., 1986b). Animal experiments demonstrate that aged rats chronically exposed to sustained stress-induced elevated glucocorticoid levels exhibit hippocampal neuron loss and a delay to return to baseline corticosterone levels after the end of the stressor (Sapolsky et al., 1986a). This loss of sensitivity to negative feedback inhibition can progressively elevate corticosterone levels, which in turn leads to permanent neurodegenerative changes in hippocampal neurons and consequently memory decline. Altogether, these findings demonstrate that hippocampal

* Corresponding author.
E-mail address: junery@usp.br (J.N. de Souza-Talarico).

https://doi.org/10.1016/j.psyneuen.2020.104601
Received 14 October 2019; Received in revised form 8 January 2020; Accepted 1 February 2020

damage followed by cognitive impairment during aging can be triggered by HPA axis dysregulation induced by prolonged stress (Sapolsky et al., 1986b).

Similar findings in humans show an association between basal cortisol levels and low memory performance, such that cognitively healthy older adults with sustained high cortisol concentrations over a period of six years have worse declarative memory performance and 14 % lower hippocampal volume than those with lower cortisol concentrations (Lupien et al., 1998). Recently, cortisol awakening response (CAR) was associated to cognitive performance in healthy older adults (Evans et al., 2012; Hidalgo et al., 2016). Evans and colleagues reported that both earlier peak and greater magnitude of the CAR were associated with better executive function, but not with verbal declarative memory performance (Evans et al., 2012). In contrast, another study showed that higher CAR was associated with lower declarative memory performance, but not with working memory test scores (Hidalgo et al., 2016).

Regarding pathological aging, several studies report higher basal cortisol concentrations and worse memory performance in patients with Mild Cognitive Impairment (MCI) or dementia compared to healthy older adults (Arsenault-Lapierre et al., 2010; Davis et al., 1986; Hartmann et al., 1997; Lind et al., 2007; Maeda et al., 1991; O'Brien et al., 1996; Popp et al., 2009; Souza-Talarico et al., 2010; Umegaki et al., 2000). The few available longitudinal studies demonstrate that high cortisol concentrations can accurately predict AD (Ennis et al., 2017; Lehallier et al., 2016; Popp et al., 2015; Schrijvers et al., 2011; Udeh-Momoh et al., 2019). Furthermore, conversion of older adults with MCI to AD or from mild to moderate AD is also associated with increased cortisol concentrations (Csernansky et al., 2006; Huang et al., 2009; Popp et al., 2015). However, this outcome is not consensual, since other studies failed to find such an association (Schrijvers et al., 2011; Swanwick et al., 1998).

Methodological differences between studies, mainly regarding the biological specimens and the condition (acute or basal) of cortisol measurement constitutes one of the reasons for discrepant findings and, therefore, a relevant obstacle to consistently ascertain whether stress or dysregulation of stress regulatory systems represent a risk factor for cognitive impairment. For instance, the abovementioned longitudinal studies have evaluated cortisol concentrations in a single biological sample, under basal conditions, hindering any conclusion as to whether HPA axis dysregulation constitutes a risk factor for cognitive impairments. Data based on cortisol reactivity to acute psychosocial stress and CAR, which is an important indicator of HPA axis reactivity to endogenous demands of waking up (Clow et al., 2004) could generate findings more closely related to the functioning of the HPA axis. Despite the extensive literature linking cortisol to cognitive impairment and dementia, no evidence has been published on cortisol reactivity to acute stress and only one analyzed CAR as a predictor of MCI (Peavy et al., 2012). Specifically, lower CAR was associated to conversion from cognitively normal status to MCI (Peavy et al., 2012).

Considering the above, we performed a longitudinal study with cognitively healthy older adults to test the hypothesis that changes in cognitive status can be associated with lower CAR and greater responsiveness to acute stress. Testing of this hypothesis can contribute to the understanding of how the HPA axis may influence the development of cognitive impairment.

2. Methods

2.1. Ethics statement and participants recruitment

This study was approved by the Ethical Committee of the Federal University of *Universidade Federal de São Paulo* (Brazil) (number 0823/09). All participants provided written informed consent. Participants were recruited from the metropolitan community of São Paulo City, Brazil, using media advertisements (radio, internet and television). One hundred and thirty-four older adults completed a face-to-face interview for eligibility assessment. Participants were 50 years-old or older, with preserved cognitive and functional abilities evaluated by the Mini-Mental State Examination – MMSE (Folstein et al., 1975) and the Informant Questionnaire on Cognitive Decline – IQCODE (Jorm and Jacomb, 1989), both adapted and validated for Brazilian Portuguese (Brucki et al., 2003; Bustamante et al., 2003). Exclusion criteria included diagnoses of neurological or psychiatric disorders (e.g., dementia, depression, anxiety, bipolarity, schizophrenia, post-traumatic stress disorder), history of alcohol or drug abuse, currently smoking or having smoked in the previous 10 years, use of psychoactive, synthetic glucocorticoids or steroids medications, and dental treatment at the time of assessment. All female participants were postmenopausal and were not under hormone replacement therapy. Five individuals with MMSE and IQCODE scores below the educational-level cutoff (Brucki et al., 2003) and one under dental treatment were excluded.

2.2. Study design

The target sample was comprised of one hundred and twenty-nine cognitively healthy older adults who enrolled in the study in 2011 (baseline). The baseline assessment included cognitive evaluation, diurnal and stress-induced cortisol concentrations, and cardiac reactivity to psychosocial stress test. After five-years follow-up, participants were invited for a cognitive reevaluation in order to analyze changes in cognitive status (Fig. 1). Among the 129 participants initially enrolled, twenty-five were unable to be located even after three telephone call attempts, thirty-four refused to be reevaluated, and one had passed away. Thus, sixty-nine individuals were evaluated for cognitive impairment in 2016. There were no reports of stroke, myocadiac infarction, heart failure or any other medical diagnoses during the follow-up period. No changes in smoking or alcohol abuse status were reported either. As shown in Table 1, no differences regarding sociodemographic characteristics, medical history, cognitive and functional performance, perceived stress and depressive symptoms were observed in the comparison between participants who completed the follow-up (n = 69) and those who did not (n = 60).

2.3. Measurements

2.3.1. Diurnal cortisol concentration

Cortisol concentration was determined from saliva samples taken at the participants' homes. All individuals were asked to collect the saliva samples using a cotton swab (Salivette®) placed in the mouth for two minutes and stored in a plastic tube in the refrigerator. Detailed oral and written instructions were given to participants, including: not to practice exercise on the day of collection; not to eat or drink anything or brush your teeth one hour prior to saliva sampling. They were instructed to collect the saliva on two consecutive days right after waking up, 30 min after waking up, 2 PM, 4 PM, and at bedtime. The Medical Event Monitoring System (MEMS®) device was used to assure compliance regarding saliva sampling timing (Kudielka et al., 2003).

2.3.2. Stress-induced cortisol concentration and cardiac reactivity

Saliva samples were also collected before and after the *Trier Social Stress Test* (TSST), which is a laboratory acute psychosocial stressor capable of inducing a stress response (Kirschbaum et al., 1993). The TSST consists of a 5-min public speech followed by a 5-min period of mental arithmetic task in front of a nonresponsive "behavioral experts" panel. Participants underwent the TSST in the afternoon, between 2 PM and 4 PM in order to control for the circadian cycle of cortisol. A total of eight saliva samples for cortisol determination were obtained before the TSST (-20 min = baseline), after speech preparation (0 min = anticipation phase), and after the TSST (10 min, 25 min for reactivity phase; 40 min, 55 min, 70 min and 100 min for recovery phase). Heart rate and blood pressure were also measured before (0 min) and after the

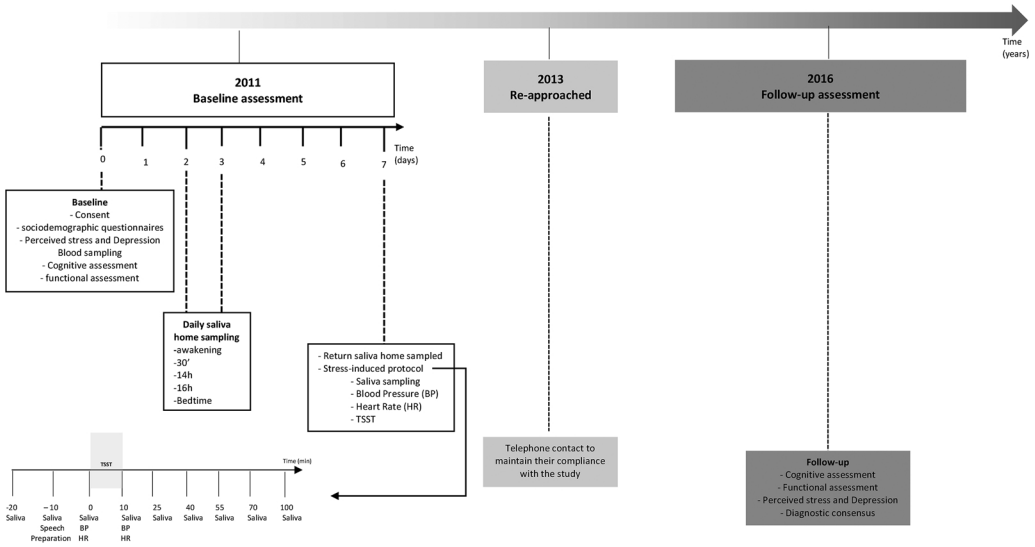

Fig. 1. Flowchart representing the study design and procedures.

TSST (10 min) using a wristwatch digital blood pressure monitor (Microlife, Corporation, Taipei, Taiwan) to analyze cardiac reactivity to acute stress (Fig. 1).

Saliva samples were stored at −20 °C until the cortisol assay, which was performed using a commercially available enzyme immunoassay kit (Salimetrics®, State College, PA, USA) manufactured by a certified research laboratory whose assay technique has been previously validated. The cortisol limit of detection was 0.01 μg/dl, and the intra- and inter-assay variability was considered to be 7.4 % and 12.4 % (within a 0.1–10 μg/dl dosage range).

2.3.3. Perceived stress

Chronic perceived stress was evaluated using the Perceived Stress Scale (PSS), composed of 14 items to measure how unpredictable, uncontrollable and overloaded the respondents considered their daily lives to be in the previous month (Cohen et al., 1983). Each item presents response options ranging from zero to four points (0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, 4 = always). Items with positive connotations (4, 5, 6, 7, 9, 10 and 13) have their score inverted (0 = 4, 1 = 3, 2 = 2, 3 = 1 and 4 = 0). The other items have a negative connotation and are therefore added directly. The total score is performed by adding up the results of the 14 questions, and can range from zero to 56. The PSS was previously adapted and validated to the Brazilian population (Luft et al., 2007).

2.3.4. Cognitive and functional assessment

All participants were submitted to the neuropsychological tests assessing global cognition, attention, declarative memory, working memory, verbal fluency and visuo-constructional ability at baseline and in the follow-up phase. The following tests were employed: the MMSE recommended for use in Brazil (Brucki et al., 2003); the Brief Cognitive Screening Battery (BCSB), which involves immediate and a 5-min

Table 1
Sample characteristic according to follow-up and prevalence of cognitive impairment.

Variables	Baseline N = 129	*Follow-up*		*p*-value*	*Cognitive Impairment no Dementia*		*p*-value**
		Uncomplete N = 60	Complete N = 69		Yes N = 18	No N = 51	
Age, mean (± SD)[a]	65.9 (8.0)	65.2 (7.9)	66.5 (8.2)	0.374	73.7 (8.4)	70.9 (8.0)	0.215
Education in years, mean (± SD) [a]	9.8 (4.4)	9.7 (4.7)	9.9 (4.3)	0.809	8.6 (3.9)	10.4 (4.3)	0.132
Woman, N (%) [b]	106 (82.2)	47 (78.3)	59 (85.5)	0.358	14 (77.8)	45 (88.2)	0.279
Retired (% yes) [b]	53 (76.8)	0 (0)	53 (76.8)	–	14 (77.8)	39 (76.5)	0.910
Socioeconomic status, N (%) [b]							
High			3 (4.3)		1 (5.6)	2 (3.9)	
Medium			28 (39.1)		4 (22.3)	23 (45.1)	0.376
Low			28 (40.6)		9 (50.0)	19 (37.3)	
Extremely low			11 (15.9)		4 (22.3)	7 (13.7)	
BMI, N (%) [b]	26.0 (4.3)	26.6 (4.4)	25.4 (4.1)	0.106	25.2 (3.5)	26.2 (4.5)	0.438
DM, N (%) [b]	12 (9.4)	4 (6.9)	8 (11.6)	0.544	8 (11.6)	6 (11.8)	0.941
Hypertension, N (%) [b]	52 (40.9)	24 (41.4)	28 (40.6)	1.000	28 (40.6)	18 (35.3)	0.132
Previous smoking, N (%) [b]	31 (24.6)	14 (24.6)	17 (24.6)	1.000	3 (16.7)	15 (83.3)	0.340
Previous alcohol abuse, N (%) [b]	0 (0)	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Stroke, N (%) [b]	1 (0.78)	0 (0)	1 (1.4)	–	1 (5.6)	0 (0)	0.090
MMSE, mean (± SD) [a]	27.6 (1.5)	27.6 (1.4)	26.0 (5.0)	0.740	25.4 (2.7)	26.7 (4.2)	0.207
MACQ, mean (± SD) [a]	24.0 (3.1)	23.8 (3.1)	24.5 (5.4)	0.442	24.7 (7.5)	24.9 (3.1)	0.881
IQCODE, mean (± SD) [a]	2.8 (0.6)	2.7 (0.6)	3.2 (0.3)	0.539	3.4 (0.6)	3.1 (0.1)	0.076
PSS score, mean (± SD) [a]							
GDS score, mean (± SD) [a]			3.0 (2.8)		4.1 (3.3)	2.7 (2.6)	0.075

BMI = Body mass index; DM = Diabetes Mellitus; MACQ = Memory Assessment Complain Questionnaire; MMSE = Mini Mental State Exam; PSS = Perceived Stress Scale; GDS = Geriatric Depression Scale. * difference between complete and uncomplete follow-up groups. ** difference between individuals with and without cognitive impairment no dementia. [a]t-Student test; [b]Qui-square test. Values in bold indicate p ≤ 0.05.

delayed recall of ten printed drawings (shoe, house, comb, plane, turtle, book, spoon, tree and bucket) presented to the participant three times—one point being attributed for each correctly recalled figure, in a total score of 10 points for both immediate and delayed recall (Nitrini et al., 2007); the Digit Span Forward (DSF) and Backward (DSB), which entails the repetition of six numerical sequences, each containing two to seven digits, to be repeated by the participant in forward (DSF) and reverse order (DSB)—the test's score corresponds to the number of digits in the complete sequence repeated correctly (0–6 points); the Semantic Verbal Fluency Test (words beginning with FAS letters, corresponding to animals and fruits), entailing the production of as many words, animals and fruits as possible in 60 s. All tests have been validated for use in the Brazilian population and holds discriminatory sensitivity for identifying cognitive impairment in individuals with low educational level (Caramelli et al., 2007; Nitrini et al., 2007).

Functional performance was evaluated by the Questionnaire of Instrumental Activities of Daily Living (QIADL, (Pfeffer et al., 1982)), comprised of 10 questions, which are answered by a relative. The relative evaluates the participant's performance in managing his/her own finances, shopping, heating water and then turning off the stove, preparing meals, staying up to date with the news, watching the news and then discussing it, remembering appointments, taking care of their own medication, keeping oriented when walking in the neighborhood, and staying home alone. The instrument's score ranges from 0 to 30. The lower the score, the higher the individual's independence and autonomy. The instrument was adapted and validated to use in the Brazilian population (Dutra et al., 2015) and applied to the participant's relative via telephone interview.

2.3.5. Criteria for determination of cognitive impairment

Data regarding cognitive and functional assessment was independently reviewed by two neurologists to reach a diagnostic consensus, based on the National Institute on Aging–Alzheimer's Association (NIAA) guidelines for the diagnosis of cognitive impairment no dementia (CIND), and the DSM-IV, for dementia diagnosis. The diagnostic consensus was established to classify participants into the following categories: no cognitive impairment; CIND; and with dementia. This classification was based on the following criteria: 1) MMSE scores ≤ 20 for illiterate individuals, ≤ 25 for those with 1–4 years of education, ≤ 26 for those with 5–8 years of education, ≤ 28 for those with 9–11 years of education and ≤ 29 for those with more than 11 years of education; 2) scores ≤ 6 for BCSB delayed recall; 3) category fluency scores ≤ 9 for illiterate individuals, ≤ 12 for those with 1–7 years of education, and ≤ 13 for those with more than 7 years of education; 4) scores ≥ 3 on QIADL Pfeffer (Pfeffer et al., 1982). Analysis of performance on the other cognitive tests was performed according to a case-by-case observation. Subjective memory decline using the Memory Assessment Complaint Questionnaire – MAC-Q (Crook et al., 1992) and depressive symptoms using the Geriatric Depression Scale - GDS (Yesavage et al., 1982) were also considered in the classification. In the event of a divergence between specialists regarding the diagnosis, a third specialist reviewed the data.

2.3.6. Assessment of potential confounding variables

Information regarding sociodemographic and clinical variables were recorded to characterize the sample and adjust the statistical analyses for possible confounding effects. The following variables were considered: age, sex, years of education, retirement status, social economic status (high, medium, and low level, per *Associação Brasileira de Pesquisas* criteria), hypertension (medical diagnosis), diabetes mellitus (medical diagnosis), stroke, previous alcohol or tobacco abuse, body mass index, depressive symptoms using GDS scores, and reported waking-up time.

2.4. Procedures

2.4.1. Baseline assessment

Eligible participants were tested through an individual face-to-face interview for sociodemographic and medical history characterization. Cognitive performance, perceived stress and depressive symptoms were evaluated and instructions for saliva sampling delivered. One week after the saliva sampling, participants returned to the research setting to perform the TSST stress-induced protocol (Fig. 1). On that occasion, participants were encouraged to take part in the follow-up study and received explanations about the importance of communicating changes of address or medical status, whenever possible, to the research team. Participants were re-approached two years after the baseline assessment, so as to maintain their compliance with the study.

2.4.2. Reassessment: cognitive status evaluation

Five years after the baseline assessment, participants were contacted to schedule a new individual face-to-face interview. They were asked to perform the same cognitive tasks, and to respond to the same perceived stress and depressive symptom instruments applied during the baseline (Fig. 1). Their performance was independently analyzed by two neurologists, in order to reach a diagnostic consensus. Participants who showed cognitive and functional performance within the CIND spectrum were schedule for a medical appointment in the Neurology Unit of FMUSP's *Hospital das Clínicas*.

2.5. Statistical analysis

For data presenting normal distribution, Student's *t*-test was used to compare the means, whereas the Chi-squared test was used to compare frequencies between the two groups (with and without CIND). Cortisol levels were not normally distributed and therefore logarithm transformations were performed. Two-way analyses of variance (ANOVAs) for repeated measures were conducted to investigate possible effects of Time and Group and interactions on diurnal and reactive cortisol levels. Greenhouse and Geisser (1959) method to correct the degrees of freedom was used when sphericity was not met. CAR was calculated using the area of trapezoid from awakening to 30 min after waking (Pruessner et al., 2003). Cortisol reactivity was measured using the cortisol percentage of change [100 x (cortisol level at 25 min - cortisol level at 0 min)/ cortisol level at 0 min]. To analyze the association between the incidence of CIND and cortisol concentration under basal and stressful condition, logistic regression was used, with the dependent categorical variable being CIND (with x without), independent variables (CAR, Cortisol reactivity) and confounding variables (age, education, sex, HAS, DM, smoking, GDS and PSS score). In the logistic regression analysis, the variance inflation factor (VIF) was used to analyze the multi-collinearity between the variables, in addition to the Lasso method of variable selection. The level of significance adopted for all statistical tests was 5 % ($p \leq 0.05$) with a 95 % confidence interval.

3. Results

3.1. Sociodemographic characteristics, medical history, perceived stress, depressive symptoms, and cognitive impairment no dementia (CIND) prevalence

A total of 135 older adults without cognitive impairment were screened between January and June of 2011, and 129 were eligible. These volunteers (105 woman and 24 men) consented to and completed the baseline assessment (Table 1). Five years later, a total of 69 participants completed the follow-up assessment (59 women and 10 men); among them, 18 participants (26.1 %) had developed CIND. No participant fulfilled the criteria for dementia. No significant differences regarding sociodemographic characteristics, medical history, perceived stress, and depressive symptoms were observed between participants

Table 2
Scores of cognitive and functional tests for each group.

Variables	Follow-up N = 69	*Cognitive Impairment no Dementia*		*p*-value*
		Yes N = 18	No N = 51	
Category fluency, mean (± SD)				
Words (F)	13.1 (4.5)	9.2 (4.1)	14.5 (3.8)	< **0.001**
Words (A)	12.5 (4.8)	8.8 (4.6)	13.8 (4.2)	< **0.001**
Words (S)	12.7 (4.9)	8.1 (5.1)	14.3 (3.7)	< **0.001**
Animals	14.6 (4.5)	10.7 (3.7)	16.0 (3.9)	< **0.001**
Fruits	13.9 (3.1)	11.1 (1.9)	14.0 (3.1)	< **0.001**
Digit spam forward, mean (± SD)	4.9 (0.9)	4.4 (0.8)	5.0 (0.9)	**0.024**
Digit spam backward, mean (± SD)	3.7 (0.85)	3.2 (0.7)	3.8 (0.8)	**0.003**
BBSC Delayed recall, mean (± SD)				
ADL Pfeffer	0.8 (1.3)	1.3 (2.0)	0.6 (0.9)	0.149

ADL = Questionnaire of Instrumental Activities of Daily Living. * t-Student test. Values in bold indicate p ≤ 0.05.

with and without CIND (Table 1). Similarly, no differences were found between the participants who completed the follow-up and those who did not (Table 1).

3.2. Cognitive and functional performance

Controlling for age and education, the participants with CIND showed worse performance at follow-up assessment in all cognitive tasks in comparison with those without CIND. No differences were observed between groups regarding their capacity to perform daily activities (Table 2).

3.3. Diurnal and stress-induced cortisol concentration

Controlling for age, sex, waking-up time and GDS scores, ANOVAs for repeated measures showed a Time × Group interaction in regard to diurnal cortisol levels ($F_{(2,156)}$ = 3.04, p = 0.041) at baseline study assessment, whereby individuals with CIND showed lower cortisol concentrations 30 min. after waking up (mean: 0.35 ± 0.22 μg/dL) than participants without CIND (mean: 0.50 ± 0.21 μg/dL; p = 0.023; see Fig. 2A). No main effect of Group was observed ($F_{(1,65)}$ = 1.2, p = 0.143) demonstrating that diurnal average cortisol concentration did not differ between groups. CAR was lower in the CIND group (mean: 9.8 ± 4.6 μg/dL) in comparison to participants without CIND (mean: 13.2 ± 5.1 μg/dL; p = 0.018).

Regarding TSST reactive cortisol at baseline study assessment, controlling for age, sex and GDS scores, ANOVAs for repeated measures showed neither a significant Time × Group interaction ($F_{(2,154)}$ = 0.84, p = 0.451) nor a main effect of Group ($F_{(1,65)}$ = 1.64; p = 0.205; Fig. 2B). Participants with CIND showed lower cortisol concentration at 25 min after the beginning of the TSST (0.232 ± 0.186) compared to individuals without CIND (0.258 ± 0.180; p < 0.03). No significant difference was observed in the other TSST time points (Fig. 2B). Nonetheless, the percentage of cortisol increase to TSST (from 0 min to 25 min in Fig. 2B), that is, the cortisol reactivity to TSST was higher in individuals with CIND (percentage of cortisol increase - mean: 174.5 ± 164.9 μg/dL) compared to individuals without CIND (mean: 83.4 ± 127.9 μg/dL; p < 0.02).

3.4. Cardiac reactivity to psychosocial stress

Controlling for age and sex, ANOVAS for repeated measures showed no Time × Group interaction or main effect of Group on systolic blood pressure (interaction: p = 0.943; main effect: p = 0.760), diastolic blood pressure (interaction: p = 0.604; main effect: p = 0.440) and heart rate (interaction: p = 0.260; main effect: p = 0.486) during the TSST protocol.

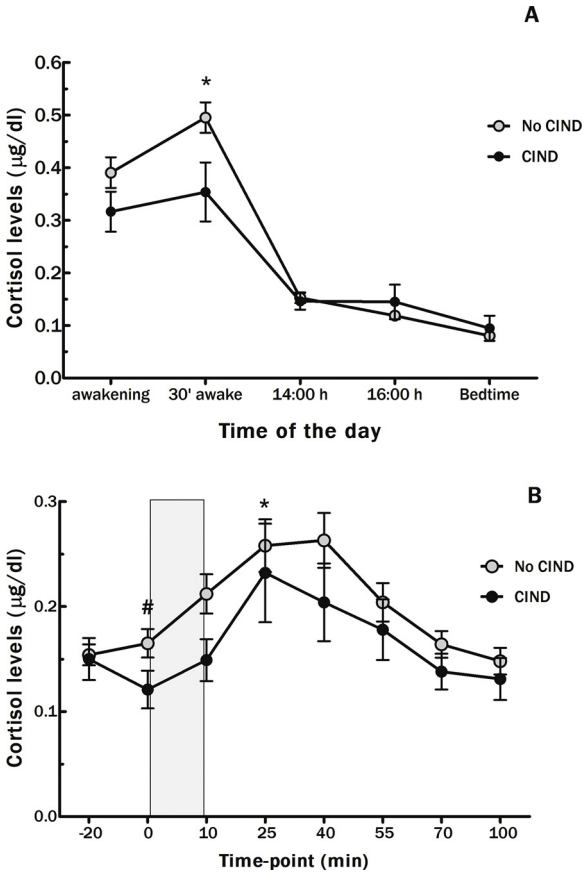

Fig. 2. Diurnal and reactive cortisol concentration of older adults with and without cognitive impairment no dementia (CIND). **A**: CIND patients (n = 18) showed lower diurnal cortisol concentration 30 min. after waking up than participants without CIND (n = 51). **B**: CIND (n = 18) showed lower cortisol concentration right after the TSST (10 min) than participants without CIND (n = 51). A tendency toward significance was observed in cortisol concentration immediately before the TSST between groups. * p < 0.05; # p = 0.06. Data is presented as mean ± s.e.m; Time-point: -20 min (baseline), 0 min = immediately before TSST, 10 min = immediately after TSST; 25 min; 40 min; 55 min; 70 and 100 min after the end of the TSST.

3.5. Influence of cortisol concentration on cognitive impairment prevalence

Controlling for age, sex, education, previous smoking, diabetes, hypertension and depressive symptoms, logistic regression showed a main effect of cortisol reactivity on CIND prevalence. The probability of CIND increased 6 % for each 10 units of TSST-induced cortisol concentration increase, suggesting that the higher the cortisol reactivity, the higher the probability to develop cognitive impairment (Table 3).

4. Discussion

The current results demonstrated that higher cortisol reactivity to a psychosocial stressor significantly increased the risk of developing cognitive impairment five years later. Moreover, participants who developed CIND showed lower CAR and more than two-fold higher cortisol reactivity compared to cognitively healthy individuals. No significant changes in cardiac reactivity were observed. These findings suggest that a defective HPA axis response, as indirectly evaluated by cortisol reactivity to both endogenous and acute stressors, may represent a vulnerability factor for cognitive impairment in older adults.

Table 3
Prevalence of cognitive impairment no dementia and associated factors.

Variables	B	EXP(B)	95 %CI		*p*
			Min.	Max.	
Age	0.104	1.110	0.977	1.260	0.109
Sex	2.629	13.856	1.006	190.912	**0.050**
Education	0.055	1.056	0.824	1.354	0.667
Previous smoking	−0.171	0.843	0.069	10.293	0.894
DM	−0.243	0.784	0.020	30.511	0.896
Hypertension	1.457	4.294	0.546	33.755	0.166
PSS	−0.218	0.804	0.615	1.051	0,111
GDS	0.047	1.049	1.049	0.633	0.854
CAR	−0.109	0.896	0.896	0.659	0.486
Cortisol reactivity	0.006	1.006	1.001	1.011	**0.023**

DM = Diabetes mellitus; PSS = Perceived Stress Scale; GDS = Geriatric Depression Scale; CAR = cortisol awakening response. Values in bold indicate p ≤ 0.05.

Our result showing that CAR was lower in participants with cognitive impairment replicates previous transversal studies (Johar et al., 2015; Venero et al., 2013). Using a cross-sectional study design, Johar and colleagues demonstrated lower CAR and lower salivary cortisol concentrations 30 min after awakening in patients with probable dementia and MCI, whose cognitive diagnosis were based on assessment via telephone interview (Johar et al., 2015). In accordance to these results, salivary cortisol concentrations at awakening were significantly higher in non-amnestic and multidomain MCI, but not in amnestic MCI (Venero et al., 2013). Longitudinal findings demonstrate that both diurnal salivary cortisol concentrations and CAR can predict decline in cognitive tasks over time (Beluche et al., 2010; Peavy et al., 2012). For instance, slow diurnal rhythm (flatter slope) is associated with decline in visuo-spatial performance and visual memory in men, and in verbal fluency in women, over 4 years (Beluche et al., 2010). In addition, lower CAR was associated with diagnostic change to MCI (Peavy et al., 2012). Conversely, in the Whitehall II study no significant longitudinal association was observed between diurnal cortisol patterns and decline in short-term verbal memory, reasoning and verbal fluency (Singh-Manoux et al., 2014). As an original contribution to these longitudinal studies, in which both diurnal salivary cortisol levels and CAR appear related to decline in cognitive performance, our study shows that CIND is associated with lower CAR five years earlier the neurologic consensus diagnosis. CAR is a distinctive feature of the HPA axis, potentially regulated by the hippocampus and the frontal lobe (Clow et al., 2004; Fries et al., 2009), which responds to the endogenous stimulation of waking up and light (Petrowski et al., 2019); this response is characterized by a peak occurring 30–45 min after waking up (Clow et al., 2004). Deviations from this expected standard have been recognized as potential biomarkers of unhealthy states (Chida and Steptoe, 2009). Specifically, the state variation in the CAR has been proposed to be the key to understand its role in healthy functioning (Law et al., 2013). Increased CAR magnitude has been suggested to play a preparatory role in response to challenges or workload of the day ahead (Adam et al., 2006; Stalder et al., 2010), while lack of CAR variation to anticipated physical or psychosocial challenges suggests abnormal functioning (Law et al., 2013). Interestingly, lower or no CAR is observed in individuals with amnesia and hippocampus damage (Buchanan et al., 2004; Wolf et al., 2005), whereas greater CAR is obtained in young individuals with larger hipocampal volume (Pruessner et al., 2007). In this line of view, the current study provides interesting findings to enhance the understanding of the relationship between state variation in the CAR and cognitive functioning.

Our findings also demonstrated that greater cortisol reactivity to psychosocial stressor increased the risk of developing cognitive impairment five years later. Participants with CIND exhibited higher cortisol reactivity than cognitively healthy older adults five years before the cognitive evaluation. A cross-sectional study showed that lower cortisol reactivity to the TSST is associated with poorer declarative and working memory performance (Almela et al., 2014). Conversely, it has been shown that higher cortisol reactivity to TSST is associated with poorer delayed recall in healthy older adults (Dos Santos et al., 2018). Although these data demonstrate the association between stress reactivity and cognitive performance, they are based on cross-sectional findings that do not allow the measurement of cognitive impairment over a long period of time, and therefore, can only indicate the possible impact of stress and cortisol reactivity on immediate memory. Our findings are unique in demonstrating that higher cortisol reactivity to stress, five years before the medical diagnosis, is associated with CIND.

A possible mechanism by which low or high cortisol response may represent a risk for cognitive disorders may be related to the HPA axis disfunction induced by chronic exposure to stress (McEwen, 1998). Repeated and sustained exposure to cortisol cumulatively produces neurotoxic effects, primarily in the hypothalamus, prefrontal cortex and hippocampus. These effects are mediated by neuroinflammation and hyperglycemic states (Matos and Souza-Talarico, 2019; Picard et al., 2014). Chronically, damage induced by stress alters the binding sites of mineralocorticoid and glucocorticoid receptors in the hippocampus and prefrontal cortex, affecting the inhibition of the HPA axis and, consequently, the negative feedback process. This maintains glucocorticoid secretion at high (or sustained) levels, leading to a vicious cycle, further impairing HPA axis regulation (Sapolsky et al., 1986b). These effects may progressively affect HPA axis functioning, likely resulting in heightened or blunted response to both endogenous demands, such as the awakening response, and acute stress, such as psychosocial threats or challenges. Interestingly, hypercortisolemic and hypocortisolemic profiles associated with low cognitive performance have been reported in both normal and pathological aging (see Matos and Souza-Talarico, 2019 for review). On the one hand, cognitively healthy older adults with low CAR display worse memory performance (Evans et al., 2011; Gerritsen et al., 2011). On the other hand, individuals with subjective memory decline, which may represent an earlier sign of dementia (Studart and Nitrini, 2016), display higher cortisol concentration in comparison with those without memory complaints (Fiocco et al., 2006). AD or MCI patients also exhibit higher cortisol concentration and worse cognitive performance than cognitively healthy elderly (Arsenault-Lapierre et al., 2010; Davis et al., 1986; Hartmann et al., 1997; Lara et al., 2013; Lind et al., 2007; Maeda et al., 1991; O'Brien et al., 1996; Popp et al., 2009; Souza-Talarico et al., 2010; Umegaki et al., 2000). In the present study, we showed that lower CAR and higher cortisol reactivity to acute stress were hallmarks of older adults who developed CIND, whereas no such features were seen in volunteers without changes in cognitive status across the five-year follow-up. Overall, it seems that the relationship between cortisol levels and cognitive performance follows a continuum from normal to pathological aging, suggesting that HPA axis functioning may represent a preclinical sign of cognitive impairment.

Interestingly, the current study also demonstrated that five years before the diagnosis, individuals who developed CIND simultaneously exhibited lower CAR and higher cortisol reactivity to acute stress. It has been argued that CAR is regulated by a complex process that involves not only HPA axis functioning, but also extra-pituitary structures through hippocampal and suprachiasmatic nucleus pathways (Clow et al., 2004). Our findings raise the question of whether the HPA reactivity to endogenous and exogenous demands interact with each other. Future studies should investigate whether a sustained abnormal CAR functioning may progressively increase the HPA axis reactivity to external stimuli and vice-versa.

Regarding the subjective stress perception, no significant association between perceived stress scores and CIND prevalence was observed. In contrast, Turner et al. (2017) observed, in a large sample of older African Americans, that those with higher levels of perceived

stress displayed faster decline in global cognition, episodic memory and visuospatial ability than those with lower levels (Turner et al., 2017). The low variability in the PSS scores allied to smaller sample size may explain the absence of significant relationship between perceived stress and the development of cognitive impairment.

Although this study has provided some important findings, certain limitations must be considered in the interpretation of results. First, there was a considerable loss in follow-up participants, which may have led to an underestimation of the current findings. The development of cognitive deficits by itself may explain this loss. A similar loss rate was previously reported in one of the largest population-based longitudinal studies regarding health, well-being and aging (the SABE study) in Latin America (Lebrão et al., 2019). Those who failed to be followed-up presented lower cognitive and functional performance in the baseline assessment compared to those who were reassessed years later (Dias et al., 2015). Moreover, periodical cognitive and cortisol assessment over time could have led to a more detailed overview of cortisol change and cognitive decline.

Despite these limitations, our study is unique in regards to several relevant aspects. After cortisol measurement, participants were followed-up for five years, and this was sufficient to detect cognitive changes which resulted in a CIND prevalence similar to previous studies (César et al., 2016; Plassman et al., 2011). Additionally, cognitive impairment was evaluated through a neurologic diagnostic consensus by behavior and cognition experts, based on traditional, validated, and reliable neuropsychological assessments. Basal and stress-induced cortisol were analyzed using several saliva samples, following the recommended method of detecting change over time, as well as assessing free-cortisol concentration, which is the hormone fraction most representative of the brain hormonal levels (Hammond, 1990; Lewis et al., 2005). Previous longitudinal studies that analyzed cortisol concentration as a predictor of cognitive impairment were based on plasma cortisol (Lehallier et al., 2016; Umegaki et al., 2000), which is mostly bound to cortisol-binding globulin and, therefore, unable to cross the blood-brain barrier, representing indirect estimates of brain cortisol levels (Hammond, 1990; Lewis et al., 2005). An additional advantage of the present study, was the assessment of cortisol levels on several time-points during the day, instead of a single time point in the morning and under basal conditions, which hinders any conclusion regarding HPA axis reactivity and the development of cognitive impairment. Finally, our findings were obtained in participants with low educational levels, from a low to middle-income country, where the prevalence of dementia is projected to dramatically increase in the next few years (Ferri and Jacob, 2017). Therefore, this study may represent an initial attempt to establish a simple and reliable predictive assessment for cognitive impairment, using the cortisol response to endogenous and exogenous sources of stress reaction.

5. Conclusions

Our study revealed that, compared to cognitively healthy individuals, participants who developed CIND showed lower change in cortisol concentration after waking up and a two-fold higher cortisol reactivity to acute stress five years before the medical diagnosis. Furthermore, a main effect of cortisol reactivity on CIND prevalence was observed, showing that the higher the cortisol reactivity, the greater the probability to develop cognitive impairment. These findings support future studies to investigate whether the HPA axis dysfunction may represent a preclinical sign of cognitive impairment during aging.

Role of funding source

This research study was supported by a grant from the São Paulo Research Foundation (FAPESP) for the financial support (#2009/13911-6) in Brazil, pilot project competition to Deborah Suchecki. The authors wish to declare that FAPESP had no involvement in the study design, collection, analysis and interpretation of data, in the writing of the report and in the decision to submit the paper for the publication.

Declaration of Competing Interest

None.

Acknowledgements

We would like to thank Deborah de Souza Almeida Santos and Vinicius Bunscheit who kindly provided assistance in the data collection and to São Paulo Research Foundation (FAPESP) for the financial support (#2009/13911-6, Brazil, to D. Suchecki). Deborah Suchecki is the recipient of a Research Fellowship from Conselho Nacional de Pesquisa e Desenvolvimento Tecnológico (CNPq, grant # 303449/2015-2).

References

Adam, E.K., Hawkley, L.C., Kudielka, B.M., Cacioppo, J.T., 2006. Day-to-day dynamics of experience – cortisol associations in a population-based sample of older adults. Proc. Natl. Acad. Sci. 103, 17058–17063.

Almela, M., Hidalgo, V., van der Meij, L., Pulopulos, M.M., Villada, C., Salvador, A., 2014. A low cortisol response to acute stress is related to worse basal memory performance in older people. Front. Aging Neurosci. 6, 157.

Arsenault-Lapierre, G., Chertkow, H., Lupien, S., 2010. Seasonal effects on cortisol secretion in normal aging, mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 31, 1051–1054.

Beluche, I., Carrière, I., Ritchie, K., Ancelin, M.L., 2010. A prospective study of diurnal cortisol and cognitive function in community-dwelling elderly people. Psychol. Med. 40, 1039–1049.

Brucki, S.M., Nitrini, R., Caramelli, P., Bertolucci, P.H., Okamoto, I.H., 2003. [Suggestions for utilization of the mini-mental state examination in Brazil]. Arq. Neuropsiquiatr. 61, 777–781.

Buchanan, T.W., Kern, S., Allen, J.S., Tranel, D., Kirschbaum, C., 2004. Circadianregulation of cortisol after hippocampal damage in humans. Biol. Psychol. Bull. 56, 651–656.

Bustamante, S.E., Bottino, C.M., Lopes, M.A., Azevedo, D., Hototian, S.R., Litvoc, J., Jacob Filho, W., 2003. [Combined instruments on the evaluation of dementia in the elderly: preliminary results]. Arq. Neuropsiquiatr. 61, 601–606.

Caramelli, P., Carthery-Goulart, M.T., Porto, C.S., Charchat-Fichman, H., Nitrini, R., 2007. Category fluency as a screening test for Alzheimer disease in illiterate and literate patients. Alzheimer Dis. Assoc. Disord. 21, 65–67.

César, K.G., Brucki, S.M., Takada, L.T., Nascimento, L.F., Gomes, C.M., Almeida, M.C., Oliveira, M.O., Porto, F.H., Senaha, M.L., Bahia, V.S., Silva, T.B., Ianof, J.N., Spíndola, L., Schmidt, M.T., Jorge, M.S., Vale, P.H., Cecchini, M.A., Cassimiro, L., Soares, R.T., Gonçalves, M.R., Martins, A.C., Daré, P., Smid, J., Porto, C.S., Carthery-Goulart, M.T., Yassuda, M.S., Mansur, L.L., Nitrini, R., 2016. Prevalence of cognitive impairment without dementia and dementia in Tremembé, Brazil. Alzheimer Dis. Assoc. Disord. 30, 264–271.

Chida, Y., Steptoe, A., 2009. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. Biol. Psychol. 80, 265–278.

Clow, A., Thorn, L., Evans, P., Hucklebridge, F., 2004. The awakening cortisol response: methodological issues and significance. Stress 7, 29–37.

Crook, T.H., Feher, E.P., Larrabee, G.J., 1992. Assessment of memory complaint in age-associated memory impairment: the MAC-Q. Int. Psychogeriatr. 4, 165–176.

Csernansky, J.G., Dong, H., Fagan, A.M., Wang, L., Xiong, C., Holtzman, D.M., Morris, J.C., 2006. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am. J. Psychiatry 163, 2164–2169.

Davis, K.L., Davis, B.M., Greenwald, B.S., Mohs, R.C., Mathé, A.A., Johns, C.A., Horvath, T.B., 1986. Cortisol and Alzheimer's disease, I: Basal studies. Am. J. Psychiatry 143, 300–305.

Dias, E.G., Andrade, F.B., Duarte, Y.A.O., Santos, J.L.F., Lebrão, M.L., 2015. Advanced activities of daily living and incidence of cognitive decline in the elderly: the SABE Study. Cad. Saúde Pública 31, 1–13.

Diorio, D., Viau, V., Meaney, M.J., 1993. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. J. Neurosci. 13, 3839–3847.

Dos Santos, A.T., Leyendecker, D.M.D., Costa, A.L.S., de Souza-Talarico, J.N., 2018. Relationship between cortisol reactivity to psychosocial stress and declarative memory decline during aging: impact of age and sex. Geriatr. Gerontol. Int. 18, 169–176.

Dutra, M.C., Ribeiro, R.D.S., Pinheiro, S.B., de Melo, G.F., Carvalho, G.A., 2015. Accuracy and reliability of the Pfeffer Questionnaire for the Brazilian elderly population. Dement. Neuropsychol. 9, 176–183.

Ennis, G.E., An, Y., Resnick, S.M., Ferrucci, L., O'Brien, R.J., Moffat, S.D., 2017. Long-term cortisol measures predict Alzheimer disease risk. Neurology 88, 371–378.

Evans, P.D., Fredhoi, C., Loveday, C., Hucklebridge, F., Aitchison, E., Forte, D., Clow, A., 2011. The diurnal cortisol cycle and cognitive performance in the healthy old. Int. J. Psychophysiol. 79, 371–377.

Evans, P., Hucklebridge, F., Loveday, C., Clow, A., 2012. The cortisol awakening response is related to executive function in older age. Int. J. Psychophysiol. 84, 201–204.
Ferri, C.P., Jacob, K.S., 2017. Dementia in low-income and middle-income countries: different realities mandate tailored solutions. PLoS Med. 14, e1002271.
Fiocco, A.J., Wan, N., Weekes, N., Pim, H., Lupien, S.J., 2006. Diurnal cycle of salivary cortisol in older adult men and women with subjective complaints of memory deficits and/or depressive symptoms: relation to cognitive functioning. Stress 9, 143–152.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Fries, E., Dettenborn, L., Kirschbaum, C., 2009. The cortisol awakening response (CAR): facts and future directions. Int. J. Psychophysiol. 72, 67–73.
Gerritsen, L., Comijs, H.C., Deeg, D.J., Penninx, B.W., Geerlings, M.I., 2011. Salivary cortisol, APOE-ε4 allele and cognitive decline in a prospective study of older persons. Neurobiol. Aging 32, 1615–1625.
Greenhouse, S., Geisser, S., 1959. On methods in the analysis of profile data. Psychometrika 24, 95–112.
Hammond, G.L., 1990. Molecular properties of corticosteroid binding globulin and the sex-steroid binding proteins. Endocr. Rev. 11, 65–79.
Hartmann, A., Veldhuis, J.D., Deuschle, M., Standhardt, H., Heuser, I., 1997. Twenty-four hour cortisol release profiles in patients with Alzheimer's and Parkinson's disease compared to normal controls: ultradian secretory pulsatility and diurnal variation. Neurobiol. Aging 18, 285–289.
Hidalgo, V., Almela, M., Pulopulos, M.M., Salvador, A., 2016. Memory performance is related to the cortisol awakening response in older people, but not to the diurnal cortisol slope. Psychoneuroendocrinology 71, 136–146.
Huang, C.W., Lui, C.C., Chang, W.N., Lu, C.H., Wang, Y.L., Chang, C.C., 2009. Elevated basal cortisol level predicts lower hippocampal volume and cognitive decline in Alzheimer's disease. J. Clin. Neurosci. 16, 1283–1286.
Joëls, M., de Kloet, E.R., 1989. Effects of glucocorticoids and norepinephrine on the excitability in the hippocampus. Science 245, 1502–1505.
Johar, H., Emeny, R.T., Bidlingmaier, M., Lacruz, M.E., Reincke, M., Peters, A., Heier, M., Ladwig, K.H., 2015. Lower morning to evening cortisol ratio is associated with cognitive impairment in men but not women: an analysis of 733 older subjects of the cross-sectional KORA-age study. Psychoneuroendocrinology 51, 296–306.
Jorm, A.F., Jacomb, P.A., 1989. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol. Med. 19, 1015–1022.
Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1993. The 'Trier Social Stress Test'—A tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28, 76–81.
Kudielka, B.M., Broderick, J.E., Kirschbaum, C., 2003. Compliance with saliva sampling protocols: electronic monitoring reveals invalid cortisol daytime profiles in non-compliant subjects. Psychosom. Med. 65, 313–319.
Landfield, P.W., Waymire, J.C., Lynch, G., 1978. Hippocampal aging and adrenocorticoids: quantitative correlations. Science 202, 1098–1102.
Lara, V.P., Caramelli, P., Teixeira, A.L., Barbosa, M.T., Carmona, K.C., Carvalho, M.G., Fernandes, A.P., Gomes, K.B., 2013. High cortisol levels are associated with cognitive impairment no-dementia (CIND) and dementia. Clin. Chim. Acta 423, 18–22.
Law, R., Hucklebridge, F., Thorn, L., Evans, P., Clow, A., 2013. State variation in the cortisol awakening response. Stress 16, 483–492.
Lebrão, M.L., Duarte, Y.A.O., Santos, J.L.F., Silva, N.N.D., 2019. 10 Years of SABE Study: background, methodology and organization of the study. Rev. Bras. Epidemiol. 21 (Suppl. 02), e180002.
Lehallier, B., Essioux, L., Gayan, J., Alexandridis, R., Nikolcheva, T., Wyss-Coray, T., Britschgi, M., Initiative, A.s.D.N, 2016. Combined plasma and cerebrospinal fluid signature for the prediction of midterm progression from mild cognitive impairment to Alzheimer disease. JAMA Neurol. 73, 203–212.
Lewis, J.G., Bagley, C.J., Elder, P.A., Bachmann, A.W., Torpy, D.J., 2005. Plasma free cortisol fraction reflects levels of functioning corticosteroid-binding globulin. Clin. Chim. Acta 359, 189–194.
Lind, K., Edman, A., Nordlund, A., Olsson, T., Wallin, A., 2007. Increased saliva cortisol awakening response in patients with mild cognitive impairment. Dement. Geriatr. Cogn. Disord. 24, 389–395.
Luft, C.D., Sanches, S., Mazo, G.Z., Andrade, A., 2007. [Brazilian version of the perceived stress scale: translation and validation for the elderly]. Rev. Saude Publica 41, 606–615.
Lupien, S., Lecours, A.R., Lussier, I., Schwartz, G., Nair, N.P., Meaney, M.J., 1994. Basal cortisol levels and cognitive deficits in human aging. J. Neurosci. 14, 2893–2903.
Lupien, S.J., de Leon, M., de Santi, S., Convit, A., Tarshish, C., Nair, N.P., Thakur, M., McEwen, B.S., Hauger, R.L., Meaney, M.J., 1998. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat. Neurosci. 1, 69–73.
Maeda, K., Tanimoto, K., Terada, T., Shintani, T., Kakigi, T., 1991. Elevated urinary free cortisol in patients with dementia. Neurobiol. Aging 12, 161–163.
Matos, T.M., Souza-Talarico, J.N., 2019. How stress mediators can cumulatively contribute to Alzheimer's disease an allostatic load approach. Dement. Neuropsychol. 13, 11–21.
McEwen, B.S., 1998. Stress, adaptation, and disease. Allostasis and allostatic load. Ann. N. Y. Acad. Sci. 840, 33–44.
Nitrini, R., Caramelli, P., Porto, C.S., Charchat-Fichman, H., Formigoni, A.P., Carthery-Goulart, M.T., Otero, C., Prandini, J.C., 2007. Brief cognitive battery in the diagnosis of mild Alzheimer's disease in subjects with medium and high levels of education. Dement. Neuropsychol. 1, 32–36.
O'Brien, J.T., Ames, D., Schweitzer, I., Colman, P., Desmond, P., Tress, B., 1996. Clinical and magnetic resonance imaging correlates of hypothalamic-pituitary-adrenal axis function in depression and Alzheimer's disease. Br. J. Psychiatry 168, 679–687.
Peavy, G.M., Jacobson, M.W., Salmon, D.P., Gamst, A.C., Patterson, T.L., Goldman, S., Mills, P.J., Khandrika, S., Galasko, D., 2012. The influence of chronic stress on dementia-related diagnostic change in older adults. Alzheimer Dis. Assoc. Disord. 26, 260–266.
Petrowski, K., Schmalbach, B., Niedling, M., Stalder, T., 2019. The effects of post-awakening light exposure on the cortisol awakening response in healthy male individuals. Psychoneuroendocrinology 108, 28–34.
Pfeffer, R.I., Kurosaki, T.T., Harrah, C.H., Chance, J.M., Filos, S., 1982. Measurement of functional activities in older adults in the community. J. Gerontol. 37, 323–329.
Picard, M., Juster, R.P., McEwen, B.S., 2014. Mitochondrial allostatic load puts the' gluc' back in glucocorticoids. Nat. Rev. Endocrinol. 10, 303–310.
Plassman, B.L., Langa, K.M., McCammon, R.J., Fisher, G.G., Potter, G.G., Burke, J.R., Steffens, D.C., Foster, N.L., Giordani, B., Unverzagt, F.W., Welsh-Bohmer, K.A., Heeringa, S.G., Weir, D.R., Wallace, R.B., 2011. Incidence of dementia and cognitive impairment, not dementia in the United States. Ann. Neurol. 70, 418–426.
Popp, J., Schaper, K., Kölsch, H., Cvetanovska, G., Rommel, F., Klingmüller, D., Dodel, R., Wüllner, U., Jessen, F., 2009. CSF cortisol in Alzheimer's disease and mild cognitive impairment. Neurobiol. Aging 30, 498–500.
Popp, J., Wolfsgruber, S., Heuser, I., Peters, O., Hüll, M., Schröder, J., Möller, H.J., Lewczuk, P., Schneider, A., Jahn, H., Luckhaus, C., Perneczky, R., Frölich, L., Wagner, M., Maier, W., Wiltfang, J., Kornhuber, J., Jessen, F., 2015. Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type. Neurobiol. Aging 36, 601–607.
Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916–931.
Pruessner, M., Pruessner, J.C., Hellhammer, D.H., Pike, G.B., Lupien, S.J., 2007. Theassociations among hippocampal volume, cortisol reactivity, and memor-yperformance in healthy young men. Psychiatry Res. Neuroim 155, 1–10.
Reul, J.M., de Kloet, E.R., 1985. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. Endocrinology 117, 2505–2511.
Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986a. The adrenocortical axis in the aged rat: impaired sensitivity to both fast and delayed feedback inhibition. Neurobiol. Aging 7, 331–335.
Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1986b. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr. Rev. 7, 284–301.
Schrijvers, E.M., Direk, N., Koudstaal, P.J., Kirschbaum, C., Hofman, A., Tiemeier, H., Breteler, M.M., 2011. Associations of serum cortisol with cognitive function and dementia: the Rotterdam Study. J. Alzheimers Dis. 25, 671–677.
Singh-Manoux, A., Dugravot, A., Elbaz, A., Shipley, M., Kivimaki, M., Kumari, M., 2014. No evidence of a longitudinal association between diurnal cortisol patterns and cognition. Neurobiol. Aging 35, 2239–2245.
Souza-Talarico, J.N., Chaves, E.C., Lupien, S.J., Nitrini, R., Caramelli, P., 2010. Relationship between cortisol levels and memory performance may be modulated by the presence or absence of cognitive impairment: evidence from healthy elderly, mild cognitive impairment and Alzheimer's disease subjects. J. Alzheimers Dis. 19, 839–848.
Stalder, T., Evans, P., Hucklebridge, F., Clow, A., 2010. State associations with the cortisol awakening response in healthy females. Psychoneuroendocrinology 35, 1245–1252.
Studart, A., Nitrini, R., 2016. Subjective cognitive decline: the first clinical manifestation of Alzheimer's disease? Dement. Neuropsychol. 10, 170–177.
Swanwick, G.R., Kirby, M., Bruce, I., Buggy, F., Coen, R.F., Coakley, D., Lawlor, B.A., 1998. Hypothalamic-pituitary-adrenal axis dysfunction in Alzheimer's disease: lack of association between longitudinal and cross-sectional findings. Am. J. Psychiatry 155, 286–289.
Turner, A.D., James, B.D., Capuano, A.W., Aggarwal, N.T., Barnes, L.L., 2017. Perceived stress and cognitive decline in different cognitive domains in a cohort of older African Americans. Am. J. Geriatr. Psychiatry 25, 25–34.
Udeh-Momoh, C.T., Su, B., Evans, S., Zheng, B., Sindi, S., Tzoulaki, I., Perneczky, R., Middleton, L.T., Initiative, A.s.D.N, 2019. Cortisol, Amyloid-β, and reserve predicts alzheimer's disease progression for cognitively normal older adults. J. Alzheimers Dis. 70, 551–560.
Umegaki, H., Ikari, H., Nakahata, H., Endo, H., Suzuki, Y., Ogawa, O., Nakamura, A., Yamamoto, T., Iguchi, A., 2000. Plasma cortisol levels in elderly female subjects with Alzheimer's disease: a cross-sectional and longitudinal study. Brain Res. 881, 241–243.
Venero, C., Díaz-Mardomingo, C., Pereda-Pérez, I., García-Herranz, S., Utrera, L., Valencia, A., Peraita, H., 2013. Increased morning salivary cortisol levels in older adults with nonamnestic and multidomain mild cognitive impairment. Psychoneuroendocrinology 38, 488–498.
Wolf, O.T., Fujiwara, E., Luwinski, G., Kirschbaum, C., Markowitsch, H.J., 2005. Nomorning cortisol response in patients with severe global amnesia. Psychoneuroendocrinology 30, 101–105.
Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O., 1982. Development and validation of a geriatric depression screening scale: a preliminary report. J. Psychiatr. Res. 17, 37–49.