

Cortisol Reactivity to a physical stressor in Patients with Depression and Alzheimer's disease

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ABSTRACT. Some prevalent mental disorders in the elderly, such as Alzheimer's disease (AD) and major depression disorder (MDD), are associated with chronic stress and consequently with possible dysregulation of hypothalamic–pituitary–adrenal (HPA) axis and cortisol levels in basal conditions or in the reactivity of an acute stressor. However, evidence of cortisol behavior after a physical stressor in patients with AD and MDD is scarce. **Objective:** This study aimed to investigate the cortisol reactivity to a single session of physical exercise in patients with MDD and AD and compare it to healthy control (HC) older individuals. **Methods:** HC individuals (n=10) and elderly with clinical diagnosis of MDD (n=08) and AD (n=13) were submitted to a single bout of aerobic exercise in a treadmill during 30 minutes of moderate intensity. Salivary cortisol was collected before and after acute stressor. A repeated-measure analysis of variance (ANOVA), spearman correlation, and linear regression were performed. **Results:** The repeated-measure ANOVA revealed no interaction for cortisol on the moment×group [$F(2.000, 28.000)=1.285$; $p=0.293$] and no effect for group ($F=0.323$; $p=0.727$). However, a significant effect for moment [$F(1.000, 28.000)=4.930$; $p=0.035$] was found, with a decreased cortisol levels in postexercise for all groups. The effect size (ES) of cortisol reduction was small for patients with MDD ($d=0.402$) and trivial for patients with AD ($d=0.166$) and HC group ($d=0.090$). **Conclusions:** All participants show a decreased cortisol reactivity to a physical stressor, which can be associated with an impairment in coping with an acute stressor.

Keywords: Hydrocortisone; Stress, Mechanical; Alzheimer Disease; Exercise; Depression.

REATIVIDADE DO CORTISOL A UM ESTRESSOR FÍSICO EM PACIENTES COM DEPRESSÃO E DOENÇA DE ALZHEIMER

RESUMO. A doença de Alzheimer (DA) e o transtorno depressivo maior (TDM) são transtornos que acometem idosos e estão associadas ao estresse crônico e à desregulação do eixo hipotálamo-hipófise-adrenal (HPA), que repercute em alterações nos níveis de cortisol (basal e reatividade). **Objetivo:** Investigar a reatividade do cortisol em uma única sessão de exercício físico em pacientes com TDM e com DA e compará-la com a de idosos saudáveis. **Métodos:** Indivíduos controle saudáveis (n=10) e idosos com diagnóstico clínico de TDM (n=08) e DA (n=13) foram submetidos a uma única sessão de exercício aeróbico em esteira rolante, durante 30 minutos, em intensidade moderada. O cortisol salivar foi coletado antes e depois do estressor agudo. Na estatística, foram realizadas as análises de variância (ANOVA) de medidas repetidas, correlação de spearman e regressão linear. **Resultados:** Não foi encontrada interação para momento x grupo [$F(2.000, 28.000)=1.285$; $p=0,293$] e tampouco efeito para o grupo ($F=0,323$; $p=0,727$). Todavia, foi observado efeito significativo para o momento [$F(1,000, 28,000)=4,930$; $p=0,035$], mostrando diminuição dos níveis de cortisol no pós-exercício para todos os grupos. O tamanho do efeito (TE) foi considerado pequeno para o grupo TDM ($d=0,402$) e trivial para o DA ($d=0,166$) e o saudável ($d=0,090$). **Conclusões:** Todos os participantes apresentaram diminuição da reatividade do cortisol a um estressor físico, o que pode estar associado a um comprometimento no enfrentamento de um estressor agudo.

Palavras-chave: Hidrocortisona; Estresse Mecânico; Doença de Alzheimer; Exercício Físico; Depressão.

This study was conducted by the Institute of Psychiatry, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

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INTRODUCTION

Life expectancy has increased in several countries in the past decades, impacting on the prevalence of some chronic diseases and even neuropsychiatric disorders related to aging such as major depressive disorder (MDD) and Alzheimer's disease (AD)^{1,2}. Although there is a genetic component for their development in late life, some modifiable risks are known^{3,4}, such as chronic stress⁵ and aggravation of the disease courses.

Stress system is regulated mainly by hypothalamic–pituitary–adrenal (HPA) axis resulting in cortisol release in the body, which involves the activation of autonomic nervous system and consequently an increase in blood pressure and heart rate (HR), preparing to a life-threatening situation. Moreover, cortisol crosses the blood–brain barrier, achieving some brain regions to promote negative feedback mechanism. High cortisol levels may cause consequent neuron apoptosis impacting in hippocampus atrophy, also observed in patients with MDD⁶ and AD⁷. This mechanism can be aggravated by some other physiological changes related to aging, such as inflammaging, which is a phenomenon with chronic and low-grade inflammation observed in elderly individuals⁸, and wear and tear of chronic exposure to cortisol in the body (allostatic load)⁹.

In this sense, some studies have observed HPA changes in psychiatric disorders, which may result in hypercortisolism or hypocortisolism at rest in older patients with MDD^{10,11} and hypercortisolism in patients with AD¹². Furthermore, chronic stress can also change HPA reactivity, causing blunted cortisol reactivity and increased cortisol levels after exposure to a stressor agent¹³. A previous meta-analysis with an adult sample observed higher cortisol reactivity in MDD individuals after the psychosocial stress task¹⁴. In this line, previous studies with older healthy adults have shown a higher cortisol response to pharmacological or psychological challenges compared to younger individuals¹⁵.

Specifically, to patients with AD, it is widely known to cause a hyperactivity of cortisol in basal conditions and a circadian cortisol hypersecretion in individuals with clinical diagnosis¹⁶. A recent study demonstrated that higher psychosocial stress reactivity may represent a preclinical sign of cognitive impairment¹⁷. It can explain some difficulty in these individuals to develop coping strategy to lead with stressor event¹⁸, mainly those with worsened cognitive performance¹⁹. Regarding patients with AD, it is also expected a difficulty in responding to a stressful stimulus due to failure to elaborate confrontational and problem-solving actions¹⁹.

Although previous studies have shown higher cortisol response for patients with MDD and AD, these

studies have investigated through psychological stressor tests. Perhaps, few studies in the older sample may be explained by the difficulty to introduce stressor tests for this population. In this sense, another type of stressor agent, such as physical exercise (PE), with a lower cognitive demand during the task, may be more efficient, which promotes already known changes in HPA axis²⁰. Most studies have observed higher cortisol levels after a single session of exercise in elderly individuals²¹, notwithstanding it is unknown if MDD and AD older adults show the same response for cortisol.

Thus, this study aimed to investigate the cortisol reactivity to a single session of PE in patients with MDD and AD and compare it to healthy control (HC) individuals. We expected an increase in cortisol hormone after acute PE among groups with more pronounced levels for patients with MDD and AD.

METHODS

Protocol and registration

This research is part of a major study entitled “Efficacy of physical exercise in the Treatment of Major Depression, Alzheimer's Disease and Parkinson's Disease” that evaluates the chronic effect of PE. It was approved by the Ethics Committee for Studies on Humans from the Institute of Psychiatry of Universidade Federal do Rio de Janeiro under registration in CAAE: 24904814.0.0000.5263 and was registered under the Brazilian Registry of Clinical Trials (REBEC) protocol RBR-4M3K2C.

Recruitment and eligibility criteria

We recruited 34 male and female older adults (≥60 years old) with at least 4 years of education attended on Centre for Alzheimer's Disease and Related Disorders in the Institute of Psychiatry at the Universidade Federal do Rio de Janeiro. In this recruitment, three individuals declined to participate in the research, one in MDD and two in HC group. Participants should be diagnosed with MDD and AD according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders).

All patients were taken medication, and patients with AD were classified into mild and moderate stages according to the Clinical Dementia Rating (CDR). The HC group was recruited through usually familiar patients, neighbors, or colleagues, with age ≥60 years old, at least 4 years of education, no psychiatric disorder, and cognitive decline confirmed by a psychiatric evaluation. The exclusion criteria were severe stage of AD, any other psychiatric disorder, the existence of any

musculoskeletal and audiovisual limitation, the use of corticoid medication, and who performed a dental procedure at least 7 days before saliva collection. In all, 10 individuals in HC group, 8 individuals in MDD group, and 13 in AD group were included. Some individuals included in this research were used to workout (walk on treadmill), while others were sedentary. The sample size was calculated using GPower® software version 3.1, and the estimated sample was about 30 individuals.

Experimental procedure

The experimental procedure was performed in three visits. The first visit took about 2 hours. In this visit, written informed consent, anamnesis (age, education, medication, comorbidities), short-form International Physical Activity Questionnaire (IPAQ) (rating 1–5: sedentary, insufficiently active A and B, active, and very active) involving physical activity over the past 7 days²², Global cognitive state assessed by Mini-Mental State Examination (MMSE)²³, and depressive symptoms by Geriatric Depression Scale (GDS)²⁴ were assessed.

In the second visit, 1 week after the first visit, individuals were submitted to a cardiopulmonary effort test in a treadmill ergometer (InbraMed Pro®) using a ramp protocol to estimate the maximal oxygen consumption (VO_{2max})²⁵. The speed/slope increases every 30 seconds and was defined based on the difference between the initial and final speed. The test was configured to be finished in 10 min and, based on its results, the VO_{2max} was estimated. The electrocardiographic Digital MICROMED® 12-lead was used to monitor and record blood pressure and electrocardiogram traceability to assure no cardiological disorders. Also, weight and height were recorded to determine the body mass index (BMI).

In the third visit, during the mornings, about 1 month after the first visit, the participants carried out a single bout of acute PE on the treadmill. Individuals underwent a 30-minutes walk on a treadmill, including 5 min of warm-up, 20 minutes of moderate intensity ($70\%VO_{2max}$), and 5 min of cool down. Blood pressure was recorded in preintervention and postintervention. The subjective rating perceived exertion (RPE) was measured by Borg's scale²⁶, with rating ranging from 6 (no exertion at all) to 20 (maximal exertion). HR was obtained by a monitor, recording prestressor, post-stressor, and every 5 min during the acute PE.

Cortisol assay and collection

All participants were instructed to avoid eating and drinking 1 h before the saliva collection. Salivary cortisol samples were collected in two moments, namely, preexercise and immediately postexercise, which were

performed between 11 a.m. and 1 p.m. Before collection, participants were asked about sleep hours in the last night and were instructed about how to collect stimulated saliva. The secretion is promoted by mechanical movements in jaw after rinsing some water in the mouth. After collection, falcon tubes were stored and kept frozen ($-20^{\circ}C$) until the cortisol assay.

After defrosted and centrifuged tubes at 3000 RPM for 10 min, the ELISA test (Enzyme Linked Immunosorbent Assay), using a previously validated and commercially available kit (IBL®) was performed. The cortisol limit of detection was $20.0 \mu L$, and the intra- and inter-assay variability were considered 2.1 and 5.2%, respectively (within a 20.0–800.0 ng/mL dosage range).

Statistical analysis

Shapiro-Wilk and Levene's tests were used to evaluate normality and homoscedasticity, respectively, for all data. One-way analysis of variance (ANOVA) (F) was performed to compare groups in terms of age, education, BMI, VO_{2max} , MET_{max} , sleep hours, HR pre, HR 10 min, HR 15 min, HR 20 min, delta HR (postexercise – preexercise), delta cortisol (postexercise – preexercise), delta RPE (postexercise – preexercise), speed, and slope during the acute physical stressor. Kruskal-Wallis (χ^2) was calculated for MMSE, GDS, IPAQ classification, IPAQ (MET/week), RPE pre, RPE 10 min, RPE 15 min, RPE 20 min, and RPE post.

A χ^2 test was used to compare gender among groups. Tukey post hoc test was also performed to find differences between them. Furthermore, a repeated-measure ANOVA (F) was used to analyze cortisol levels among groups (HC \times MDD \times AD) and within moments (preexercise and postexercise). The degree of freedom considered was Greenhouse–Geisser correction. Spearman correlation was performed to investigate correlation between delta cortisol and RPE pre, RPE post, HR pre, HR post, and IPAQ (MET/week). Linear regression was used to investigate the association among variables that showed difference in baseline condition (e.g., gender and hours of sleep) with delta cortisol.

To determine the magnitude of the difference in cortisol levels between pre- and post-values in HC, MDD, and AD groups, the effect size (ES) analyses were used. The results were interpreted according to Cohen's²⁷ (trivial: $d \leq 0.2$; small: $d = 0.2-0.49$; moderate $d = 0.5-0.79$; and large: $d \geq 0.8$). Analyses were performed using SPSS® software version 26.0 (IBM Corp., New York, USA), and figure was performed using GraphPad Prism® software version 5.01. The p-value < 0.05 was the threshold for statistical significance.

RESULTS

Sample characteristics in baseline are presented in Table 1, showing that the three groups did not differ in age ($F=2.208$; $p=0.129$), years of education ($F=2.311$; $p=0.118$), VO_{2max} ($F=2.435$; $p=0.106$), MET_{max} ($F=2.435$; $p=0.106$), BMI ($F=1.168$; $p=0.326$), IPAQ ($\chi^2=0.870$; $p=0.647$), and IPAQ (MET/week) ($\chi^2=1.275$; $p=0.528$), while a significant difference was observed in gender ($\chi^2=13.861$; $p\leq 0.001$; $MDD=HC<AD$) and hours of sleep in the day before acute exercise ($F=7.266$; $p=0.003$; $AD=MDD<HC$). As expected, patients with AD showed a reduced global cognitive status compared to MDD and HC groups ($\chi^2=18.392$; $p\leq 0.001$; $MDD=HC>AD$). Moreover, MDD group presented higher depression symptoms than AD and HC groups ($\chi^2=9.208$; $p=0.010$; $MDD=HC<AD$).

Table 2 demonstrates values of RPE and HR pre-, during, and postexercise speed and slope of the treadmill in acute stressor test. However, some data were missing in RPE (five in HC and three in MDD groups) and HR (five in HC and two in MDD groups). There was statistical difference in RPE pre ($\chi^2=6.266$; $p=0.044$; $MDD=HC<AD$). There were nonsignificant difference observed for the other variables: RPE 10 min ($\chi^2=5.358$; $p=0.069$), RPE post ($\chi^2=5.539$; $p=0.063$), RPE 15 min ($\chi^2=4.299$; $p=0.117$), RPE 20 min ($\chi^2=4.065$; $p=0.131$), delta RPE ($\chi^2=1.860$; $p=0.395$), speed of treadmill ($F=1.920$, $p=0.169$), HR pre ($F=0.273$; $p=0.764$), HR 10 min ($F=0.203$; $p=0.818$), HR 15 min ($F=0.122$;

$p=0.886$), HR 20 min ($F=0.196$; $p=0.823$), HR post ($F=1.580$; $p=0.229$), and delta HR ($F=1.225$; $p=0.313$). One-way ANOVA showed significant difference in treadmill slope during exercise ($F=4.941$; $p=0.016$; $AD=HC<MDD$), with significant difference between AD and HC groups ($p=0.012$) reaching the same exercise intensity stipulated in 70% of VO_{2max} during stressor test.

The repeated-measure ANOVA revealed no interaction for cortisol on the moment \times group [$F(2.000, 28.000)=1.285$; $p=0.293$] and no effect for group ($F=0.323$; $p=0.727$). However, there was a significant effect for moment [$F(1.000, 28.000)=4.930$; $p=0.035$], with a decreased cortisol levels in postexercise for all groups (Figure 1). Gender as a covariate confirmed our outcomes and showed a trend to reduction in these levels ($F=3.949$; $p=0.057$). The comparison of delta cortisol among groups also showed nonsignificant difference ($F=1.285$; $p=0.293$). However, a reduction on cortisol levels of 6.5% for HC group, 8.8% for AD group, and 28.76% for MDD group was observed.

ES analysis revealed a small ES for patients with MDD ($d=0.402$) and trivial for patients with AD ($d=0.166$) and HC group ($d=0.090$). As expected, there was a positive correlation between HR pre and RPE pre ($r=0.478$; $p=0.013$) and between HR post and RPE post ($r=0.478$; $p=0.016$). Besides, in linear regression, nonsignificant results were observed for delta cortisol and gender ($R^2=0.088$; $p=0.106$) and for delta cortisol and hours of sleep ($R^2=0.012$; $p=0.550$).

Table 1. Descriptive characteristics of the sample in baseline.

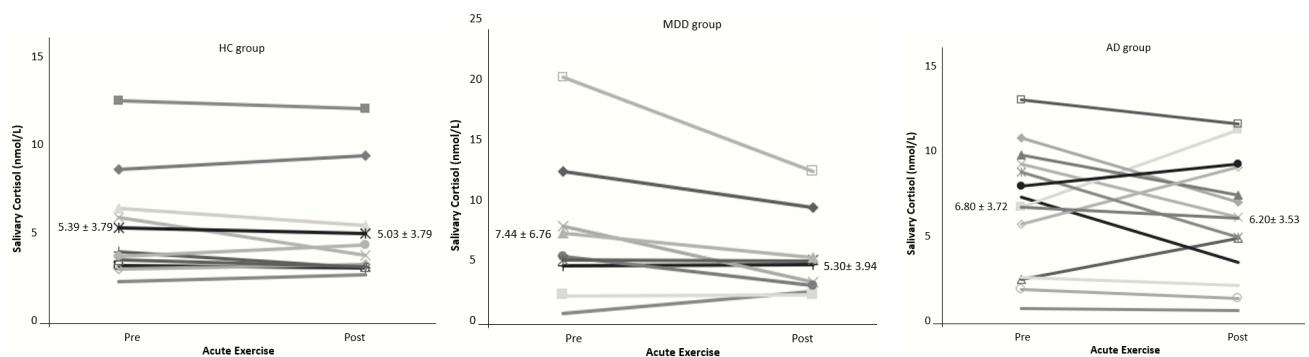
	HC (n=10)	MDD (n=8)	AD (n=13)	p-value	Post hoc
Female*	10 (100.0)	7 (87.5)	4 (30.77)	$\leq 0.001^*$	$MDD=HC<AD$
Age (years)	72.30 \pm 9.24	73.37 \pm 9.45	79.77 \pm 9.03	0.129	
Education (years)	16.30 \pm 7.53	11.87 \pm 4.19	11.23 \pm 5.28	0.118	
MMSE (score)*	29.00 (2.00)	29.00 (3.25)	20.00 (7.00)	$\leq 0.001^*$	$MDD=HC>AD$
GDS (score)*	1.00 (2.25)	5.50 (10.25)	1.00 (4.50)	0.010*	$MDD=HC<AD$
BMI (kg/m ²)	25.10 \pm 1.97	27.39 \pm 4.07	24.90 \pm 4.66	0.326	
VO_{2max} (mL/kg/min)	23.94 \pm 5.92	23.94 \pm 5.16	18.78 \pm 7.38	0.106	
IPAQ classification	4.00 (2.00)	2.00 (2.00)	3.00 (1.25)	0.647	
IPAQ (MET/week)	876.00 (4138.00)	495.00 (557.00)	871.50 (852.63)	0.528	
MET (mL/kg/min)	6.84 \pm 1.69	6.84 \pm 1.47	5.36 \pm 2.11	0.106	
Sleep (hours)*	7.00 \pm 1.05	6.50 \pm 1.19	8.54 \pm 1.50	0.003*	$AD=MDD<HC$

MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale; HR: heart rate; BMI: body mass index; SD: standard deviation; MET: metabolic equivalent; VO_{2max} : maximal oxygen consumption; IPAQ: International Physical Activity Questionnaire; HC: healthy control; MDD: major depressive disorder; AD: Alzheimer's disease. *Significant difference among groups. Data expressed in mean \pm SD or median (interquartile range) or n (%).

Table 2. Characteristics of the sample during acute exercise and changes (post–pre) with physical stressor.

	HC (n=10)	MDD (n=8)	AD (n=13)	p-value	Post hoc
RPE pre (score)	11.40±0.55	8.75±2.19	9.31±2.29	0.044*	MDD=HC<AD
RPE 10 min	12.80±0.45	6.87±5.79	12.00±1.96	0.069	
RPE 15 min	12.80±0.45	7.37±6.14	13.08±1.55	0.117	
RPE 20 min	13.20±0.45	7.62±6.32	13.61±2.02	0.131	
RPE post (score)	13.40±1.14	10.87±2.10	12.77±2.31	0.063	
ΔRPE (score)	2.00±1.00	2.12±2.69	3.46±2.93	0.395	
HR pre (score)	78.60±13.72	78.50±9.41	75.38±10.62	0.764	
HR 10 min	106.00±7.61	75.50±47.61	104.08±16.85	0.818	
HR 15 min	110.80±8.64	79.37±50.03	108.61±20.23	0.886	
HR 20 min	112.20±10.69	79.37±50.06	110.00±20.88	0.823	
HR post (score)	109.00±4.47	82.25±34.49	97.92±18.54	0.229	
ΔHR (score)	30.40±15.42	15.00±14.19	22.54±14.43	0.313	
Speed (km/h)	4.68±0.49	4.84±0.71	4.08±1.11	0.169	
Slope (%)*	7.70±4.79	4.25±1.83	2.85±1.62	0.016*	AD=HC<MDD

Δ: post (after exercise) – pre (before exercise); HR: heart rate; HC: healthy control; MDD: major depressive disorder; AD: Alzheimer's disease; RPE: rating perceived exertion; *Significant difference; SD: standard deviation. Data are expressed in mean±SD.



HC: healthy control; MDD: major depressive disorder; AD: Alzheimer's disease.

Figure 1. Effect of acute stressor (physical exercise) in cortisol levels in older individuals: healthy control group (A), major depressive disorder group (B), and Alzheimer's disease group (C). Data are presented in mean±standard deviation.

DISCUSSION

The main objective of this study was to investigate the cortisol reactivity to a single session of PE in MDD, AD, and HC elderly individuals. We hypothesized that cortisol levels would increase after acute PE in all groups, with results more pronounced for patients with MDD and AD. Notwithstanding, a significant cortisol reduction for all groups was observed.

The association between HPA axis dysfunction and MDD has been investigated over the six decades²⁸; since then, both hypocortisolism and hypercortisolism at rest were found, which can impact the acute reactivity to a stressor agent. A previous meta-analysis¹⁵, with 43 articles in which 39 used pharmacological stressors and 6 used psychological tasks, concluded that aging increased the cortisol response to challenge. It was

speculated that the lack of negative feedback resulting in higher cortisol levels was due to an impairment in brain structures, such as the hippocampus and prefrontal cortex generally observed in MDD²⁹ and AD³⁰. However, this explanation does not take into account some specific characteristics of these diseases in older individuals. For example, MDD older individuals are less likely to endorse affective symptoms and more likely to present cognitive changes, somatic symptoms, and loss of interest than are depressed young adults³¹.

MDD individuals seem to be more influenced by lifelong stress, which may be related to the exhaustion phase of stress-causing significant changes in the HPA axis³². A previous study demonstrated that lower evening cortisol levels may predict poorer course in elderly with MDD³³. It is important to take into consideration the medication used by this population, because psychoactive medication was generally associated with lower cortisol levels³⁴. Other study found a diminished ability to respond to the stress of awakening among depressed older persons³⁵. In a longitudinal study, it was observed that a low mean salivary cortisol concentration and a small difference between morning and evening cortisol concentration may be risk factors of depression³⁶. Moreover, apathy, fatigue, and exhaustion³⁷ are very common symptoms in MDD and AD older individuals and are associated with hyporeactivity of HPA axis and consequent decrease in cortisol levels.

There are also other mechanisms related to aging. MDD and AD older individuals present more enhanced susceptibility to inflammaging⁸, which can affect the function of the glucocorticoid receptor (GR) and lead to hypercortisolism³⁸ and consequently a worse memory³⁹. Although a previous meta-analysis has observed hypercortisolism in AD in the mornings¹², it is possible to hypothesize that individuals with more inflammaging and GR resistance can show reduced cortisol reactivity. It is also expected that AD individuals may encounter difficulties or even be incapable of evaluating the potential threat of a given stress event⁴⁰. In contrast, a recent study showed that higher salivary cortisol reactivity to acute psychosocial stress test in healthy individuals aged 50 years or above was a hallmark of developing cognitive impairment 5 years later¹⁷, probably because senescence was turned to senility when occur inflammation and disorders come.

In addition to these speculations regarding MDD and AD characteristics, it is important to consider the type of stressor chosen. Physical stressor was less explored and previous studies have investigated adult populations with MDD and found nonsignificant blood cortisol changes after bicycle ergometer till exhaustion⁴¹ and a small increase of blood cortisol after bicycle ergometer

till exhaustion⁴². A previous study with salivary sample observed cortisol reduction after bicycle ergometer with moderate intensity, which corroborates our results⁴³.

In this study, cortisol reduction showed a small ES for all groups, with the highest effect for MDD compared to the other groups. Perhaps, these individuals had been more influenced by lifelong stress, which could be related to the exhaustion phase of stress-causing significant changes in the HPA axis⁴⁴. Besides, other variables that could influence in results were not evaluated in this study, such as early life experience, chronic fatigue, social support, personality factors, chronic stress, and burnout⁴⁵⁻⁴⁷. We also have to point out the effect of acute stress using a rolling treadmill, because some individuals were extremely adapted to this type of stressor and others may experience some anxiety or afraid to be evaluated and anticipatory cortisol response must be considered. Meantime, this type of exercise is safe and adequate to use in this population.

Strengths and limitations of the study and clinical relevance

This study has some limitations. First, we cannot generalize for all patients with AD and MDD because of the heterogeneity and individual characteristics (gender, hours of sleep, physical performance, and BMI) of the small sample. Another limitation was that we only took two moments to observe this reactivity, and we know that it is necessary and important to observe the curve of this reactivity with more moments before and especially 15, 30, 45, and 60 min after exercise.

Notwithstanding, it is important to highlight that this is the first study, to the best of our knowledge, to evaluate cortisol reactivity of a physical stressor in MDD and AD individuals. However, there is much to investigate. It is desirable to study the elderly population with neuropsychiatric disorders to better understand how these individuals may cope with stressor agent and also contribute to elucidate the physiopathology of such disorders regarding to the stress, while it is unavoidable to observe the heterogeneity of the subjects considering that it is inherent in this type of study.

Thus, the relationship between acute stress, healthy elderly, and, even more, those with neuropsychiatric disorders is still under debate and more research is required in future. This type of study has a pivotal relevance to clinical practice because their findings could provide adequate support assistance, care, and information to multidisciplinary professionals who follow up patients with AD and MDD. These professionals can offer treatment to prevent or minimize consequence and deterioration on memory and mood in these patients, improving quality of life.

A future study with a larger and more balanced sample needs to be investigated, managing the influence of these variables in the outcome and considering that there is a cortisol variability within individuals of the same group.

Older individuals, regardless of the presence of mental disorder, show a decrease in salivary cortisol after a physical stressor. Nevertheless, this response seems to be more evident in MDD, which can be associated with

chronic stress, HPA dysregulation, and a consequent inability to cope with stressor agents.

Authors' contributions. AB, HM: conceptualization, investigation, methodology, project administration, visualization, writing – original draft, and writing – review & editing. BO, EP, PD: review. JL, AD: funding acquisition, project administration, supervision, and review.

REFERENCES

- Arthur A, Sava GM, Barnes LE, Borjian-Borojany A, Dening T, Jagger C, et al. Cognitive Function and Ageing Studies Collaboration. Changing prevalence and treatment of depression among older people over two decades. *Br J Psychiatry*. 2020;216(1):49-54. <https://doi.org/10.1192/bjp.2019.193>
- Trevisan K, Cristina-Pereira R, Silva-Amaral D, Aversi-Ferreira TA. Theories of aging and the prevalence of Alzheimer's disease. *Biomed Res Int*. 2019;2019:9171424. <https://doi.org/10.1155/2019/9171424>
- Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2015;86(12):1299-306. <https://doi.org/10.1136/jnnp-2015-310548>
- Kim D, Wang R, Kiss A, Bronskill SE, Lancot KL, Herrmann N, et al. Depression and Increased Risk of Alzheimer's Dementia: Longitudinal Analyses of Modifiable Risk and Sex-Related Factors. *Am J Geriatr Psychiatry*. 2021;29(9):917-26. <https://doi.org/10.1016/j.jagp.2020.12.031>
- Sotiropoulos I, Silva JM, Gomes P, Sousa N, Almeida OF. Stress and the etiopathogenesis of Alzheimer's disease and depression. *Adv Exp Med Biol*. 2019;1184:241-57. https://doi.org/10.1007/978-981-32-9358-8_20
- Lee AL, Ogle WO, Sapolsky RM. Stress and depression: possible links to neuron death in the hippocampus. *Bipolar Disord*. 2002;4(2):117-28. <https://doi.org/10.1034/j.1399-5618.2002.01144.x>
- den Heijer T, van der Lijn F, Koudstaal PJ, Hofman A, van der Lugt A, Krestin GP, et al. A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain*. 2010;133(Pt 4):1163-72. <https://doi.org/10.1093/brain/awq048>
- Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14(10):576-90. <https://doi.org/10.1038/s41574-018-0059-4>
- McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci*. 1998;840:33-44. <https://doi.org/10.1111/j.1749-6632.1998.tb09546.x>
- Moraes H, Deslandes A, Maciel-Pinheiro PT, Corrêa H, Laks J. Cortisol, DHEA, and depression in the elderly: the influence of physical capacity. *Arq Neuropsiquiatr*. 2016;74(6):456-61. <https://doi.org/10.1590/0004-282x20160059>
- Bremner MA, Deeg DJ, Beekman AT, Penninx BW, Lips P, Hoogendijk WJ. Major depression in late life is associated with both hypo- and hypercortisolemia. *Biol Psychiatry*. 2007;62(5):479-86. <https://doi.org/10.1016/j.biopsych.2006.11.033>
- Zheng B, Tai R, Yang Z, Middleton L, Udeh-Momoh C. Cortisol hypersecretion and the risk of Alzheimer's disease: a systematic review and meta-analysis. *Ageing Res Rev*. 2020; 64:101171. <https://doi.org/10.1016/j.arr.2020.101171>
- McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 2007;87(3):873-904. <https://doi.org/10.1152/physrev.00041.2006>
- Zorn JV, Schür RR, Boks MP, Kahn RS, Joëls M, Vinkers CH. Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*. 2017;77:25-36. <https://doi.org/10.1016/j.psyneuen.2016.11.036>
- Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology*. 2005;30(1):80-91. <https://doi.org/10.1016/j.psyneuen.2004.06.002>
- Notarianni E. Hypercortisolemia and glucocorticoid receptor-signaling insufficiency in Alzheimer's disease initiation and development. *Curr Alzheimer Res*. 2013;10(7):714-31. <https://doi.org/10.2174/15672050113109990137>
- Souza-Talarico JN, Alves AR, Brucki SM, Nitirini R, Lupien SJ, Suchecki D. Cortisol reactivity to a psychosocial stressor significantly increases the risk of developing Cognitive Impairment no Dementia five years later. *Psychoneuroendocrinology*. 2020;115:104601. <https://doi.org/10.1016/j.psyneuen.2020.104601>
- Bjørkløf GH, Engedal K, Selbæk G, Kouwenhoven SE, Helvik AS. Coping and depression in old age: a literature review. *Dement Geriatr Cogn Disord*. 2013;35(3-4):121-54. <https://doi.org/10.1159/000346633>
- de Souza-Talarico JN, Chaves EC, Nitirini R, Caramelli P. Stress and coping in older people with Alzheimer's disease. *J Clin Nurs*. 2009;18(3):457-65. <https://doi.org/10.1111/j.1365-2702.2008.02508.x>
- Stranahan AM, Lee K, Mattson MP. Central mechanisms of HPA axis regulation by voluntary exercise. *Neuromolecular Med*. 2008;10(2):118-27. <https://doi.org/10.1007/s12017-008-8027-0>
- Moraes HS, Deslandes AC, Cevada T, Souza AC, Laks J. The effect of physical exercise on cortisol levels in older adults: a systematic review. *Rev Bras Ativ Fis Saúde*. 2012;17(4):314-20.
- Booth ML. Assessment of physical activity: an international perspective. *Res Q Exerc Sport*. 2000;71 Suppl 2:114-20. <https://doi.org/10.1080/02701367.2000.11082794>
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-98. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982-1983;17(1):37-49. [https://doi.org/10.1016/0022-3956\(82\)90033-4](https://doi.org/10.1016/0022-3956(82)90033-4)
- American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 7th ed. Baltimore: Lippincott Williams & Wilkins; 2006.
- Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14(5):377-81. PMID: 7154893.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*, New York, NY: Routledge Academic; 1988.
- Gibbons J, Mchugh P. Plasma cortisol in depressive illness. *J Psychiatr Res*. 1962;2:162-71. [https://doi.org/10.1016/0022-3956\(62\)90006-7](https://doi.org/10.1016/0022-3956(62)90006-7)
- Herman JP, McKlveen JM, Solomon MB, Carvalho-Netto E, Myers B. Neural regulation of the stress response: glucocorticoid feedback mechanisms. *Braz J Med Biol Res*. 2012;45(4):292-8. <https://doi.org/10.1590/s0100-879x2012007500041>
- Elgh E, Lindqvist Astot A, Fagerlund M, Eriksson S, Olsson T, Näsman B. Cognitive dysfunction, hippocampal atrophy and glucocorticoid feedback in Alzheimer's disease. *Biol Psychiatry*. 2006;59(2):155-61. <https://doi.org/10.1016/j.biopsych.2005.06.017>
- Fiske A, Wetherell JL, Gatz M. Depression in older adults. *Annu Rev Clin Psychol*. 2009;5:363-89. <https://doi.org/10.1146/annurev.clinpsy.032408.153621>
- Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol*. 2016;6(2):603-21. <https://doi.org/10.1002/cphy.c150015>
- Kabia FM, Rhebergen D, van Exel E, Stek ML, Comijs HC. The predictive value of cortisol levels on 2-year course of depression in older persons. *Psychoneuroendocrinology*. 2016;63:320-6. <https://doi.org/10.1016/j.psyneuen.2015.10.006>
- Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry*. 2009;66(6):617-26. <https://doi.org/10.1001/archgenpsychiatry.2009.50>

35. Rhebergen D, Korten NC, Penninx BW, Stek ML, van der Mast RC, Oude Voshaar R, et al. Hypothalamic-pituitary-adrenal axis activity in older persons with and without a depressive disorder. *Psychoneuroendocrinology*. 2015;51:341-50. <https://doi.org/10.1016/j.psyneuen.2014.10.005>
36. Grynderup MB, Kolstad HA, Mikkelsen S, Andersen JH, Bonde JP, Buttenschøn HN, et al. A two-year follow-up study of salivary cortisol concentration and the risk of depression. *Psychoneuroendocrinology*. 2013;38(10):2042-50. <https://doi.org/10.1016/j.psyneuen.2013.03.013>
37. Strahler J, Fischer S. Diurnal cortisol and alpha-amylase in the daily lives of older adults with vital exhaustion. *Physiol Behav*. 2018;185:39-45. <https://doi.org/10.1016/j.physbeh.2017.12.023>
38. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci*. 2012;1261:55-63. <https://doi.org/10.1111/j.1749-6632.2012.06633.x>
39. Almela M, Hidalgo V, van der Meij L, Pulpulos MM, Villada C, Salvador A. A low cortisol response to acute stress is related to worse basal memory performance in older people. *Front Aging Neurosci*. 2014;6:157. <https://doi.org/10.3389/fnagi.2014.00157>
40. Souza-Talarico JN, Caramelli P, Nitrini R, Chaves EC. Effect of cortisol levels on working memory performance in elderly subjects with Alzheimer's disease. *Arq Neuro-Psiquiatr*. 2008;66(3B):619-624. <https://doi.org/10.1590/s0004-282x2008000500003>
41. Kiive E, Maarros J, Shlik J, Tõru I, Harro J. Growth hormone, cortisol and prolactin responses to physical exercise: higher prolactin response in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(6):1007-13. <https://doi.org/10.1016/j.pnpb.2004.05.035>
42. Krogh J, Nordentoft M, Mohammad-Nezhad M, Westrin A. Growth hormone, prolactin and cortisol response to exercise in patients with depression. *J Affect Disord*. 2010;125(1-3):189-97. <https://doi.org/10.1016/j.jad.2010.01.009>
43. Ida M, Ida I, Wada N, Sohmiya M, Tazawa M, Shirakura K. A clinical study of the efficacy of a single session of individual exercise for depressive patients, assessed by the change in saliva free cortisol level. *Biopsychosoc Med*. 2013;7(1):18. <https://doi.org/10.1186/1751-0759-7-18>
44. Herman JP, McKivern JM, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol*. 2016;6(2):603-21. <https://doi.org/10.1002/cphy.c150015>
45. Kudielka BM, Federenko IS, Hellhammer DH, Wüst S. Morningness and eveningness: the free cortisol rise after awakening in "early birds" and "night owls". *Biol Psychol*. 2006;72(2):141-6. <https://doi.org/10.1016/j.biopsycho.2005.08.003>
46. Zänker S, Bellingrath S, Wüst S, Kudielka BM. HPA axis responses to psychological challenge linking stress and disease: What do we know on sources of intra- and interindividual variability? *Psychoneuroendocrinology*. 2019;105:86-97. <https://doi.org/10.1016/j.psyneuen.2018.10.027>
47. Kudielka BM, Hellhammer DH, Wüst S. Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology*. 2009; 34(1):2-18. <https://doi.org/10.1016/j.psyneuen.2008.10.004>