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Research

Subjective and Physiological Stress Measurement in a Multiple Sclerosis Sample and the relation with Executive Functions Performance

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Abstract

In Multiple Sclerosis (MS), the Hypothalamic-Pituitary-Adrenal (HPA) axis functioning may be dysregulated, due to the high cortisol levels involved in the disease activity. HPA axis dysregulation can affect cognitive performance, including executive functions. This study aimed to evaluate capillary cortisol and perceived stress, and to verify the association with the performance of EFs in individuals diagnosed with MS and control individuals. Capillary cortisol and perceived stress were evaluated and the association with the performance of healthy individuals (n = 35) and MS (n = 69), most of them with Remitting-Relapsing Multiple Sclerosis (RRMS), with Expanded Disability Status Scale (EDSS) between 0 and 6 were evaluated. Instruments: BADS; WCST; Stroop Test and Perceived Stress Scale. No significant statistical difference was found in the comparison of means among the groups, however, an association was found when using statistical correlation tests between cortisol and cognitive performance in the clinical group ($r = 0.31$, $p = 0.10$), and absence of correlations with perceived stress measure. It was possible to observe interaction between group factors and low level of cortisol and problem solving/cognitive flexibility in the MS group. The results indicated that stress measures used in the present study seem to influence the performance of inhibitory control and problem solving/cognitive flexibility, the latter with low levels of cortisol in individuals with MS. We suggest studies that examine different measures of physiological stress and characteristics of the disease.

Keywords: Executive Functioning; Cortisol; Perceived Stress; Autoimmune Disease.

Introduction

Life events that are perceived as stressors may result in the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis [1]. The repercussions of stress are identified through changes in neuroendocrine and mental functioning, when the individual perceives stimuli as stressors [2, 3]. Multiple Sclerosis (MS) is considered an autoimmune disease that causes destruction of the myelin sheath and axons. Studies have shown that individuals diagnosed with MS fail to suppress cortisol release [4-6].

Stressful events result in the hypothalamic corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) production. CRH stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH). CRH effect as an ACTH secretor is stimulated by AVP. ACTH stimulates the adrenal cortex in the cortisol production resulting in an inhibitory effect on the CRH hypothalamic production. Thus, the HPA axis is self-regulating, in part, through cortisol's inhibitory effects. However, in chronic stress, this feedback mechanism becomes deregulated. In turn, this deregulation results in increased cortisol levels [7], despite reports of hypocortisolism in the presence of chronic stress [8].

Capillary cortisol concentration analysis is considered a valid biomarker and one of the most recent for the long-term measurement of exposure to this hormone [9, 10]. Cortisol measured through hair may be associated with medical conditions indicating chronic HPA axis activation or even high stress levels [11]. Studies have shown an association between cortisol and cognitive performance, such as memory and executive functions (EFs), which depend on the integrity of brain structures, such as the hippocampus and the prefrontal cortex, in healthy individuals [12,13].

Perceived stress in individuals suffering from chronic stress, especially related to work, was associated with impairment in EF tasks such as verbal fluency and prospective memory [14]. The latter was related to the executive control and the functioning of frontal circuits through strategies and planning of a future action [15-17].

Despite the aforementioned data, studies on the influence of stress, evaluated through physiological measures in individuals with autoimmune diseases in cognitive performance, especially in the different subcomponents of EFs, are scarce in the literature. Moreover, existing studies present inconsistent data. This study aimed to evaluate capillary cortisol and perceived stress, and to verify the association with the performance of EFs such as problem solving, cognitive flexibility, planning and inhibition in individuals diagnosed with MS and control individuals.

Material and Methods

Sample

Our sample was composed by 64 individuals from the Neuroimmunology Outpatient Clinic of the Sao Lucas Hospital - PUCRS diagnosed with MS [18] revised and adapted McDonalds criteria (2010) and EDSS ≤6.0 and 33 normal control subjects. The participants were selected by convenience and were literate, fluent in Portuguese and with a minimum age of 18 years old. The groups were matched by age, years of study and gender. Exclusion criteria for either groups were past or current neurological disease and/or affecting the Central Nervous System (CNS); chronic or acute virus infections; use of corticosteroids in the last month; diagnosed dementia; cognitive, motor, visual and/or auditory impairments that impede the application of research instruments; IQ rated as "extremely low" and "borderline"; psychiatric disorders, with the

exception of depression; past or current history of drug addiction and/or alcoholism; pregnant women, in pre or per-menstrual period; presence of menopausal symptoms; and individuals with less than one centimeter hair length. For the MS groups, the exclusion criteria remained the same, including neurological disease affecting the CNS other than MS; being in a relapse; and participating in or having participated in neuropsychological rehabilitation programs after diagnosis of MS.

EFs Evaluation

- Behavioral Assessment of the Dysexecutive Syndrome (BADS) [19], a translated version, currently in Brazilian adaptation process [20]. It is an ecological measure that consists of six subtests that evaluate: cognitive flexibility; troubleshooting; planning; and judgment. The subtests are as follows: Rule Shift Cards Test (cognitive flexibility); Action Programme (problem solving); Key Search (planning); Zoo Map (planning); Temporal Judgment; Modified Six Elements (planning). Total classification is allowed as: damaged, borderline, low average, medium high, superior and much higher.
- Wisconsin Card Classification Test (WCST) [21]: Computer test consisting of 64 letters with stimuli in three categories: color; shape and number. Assesses Executive Functions demanding the ability to develop and stay with appropriate problem-solving strategies.
- Stroop Test [22]; Brazilian standards [23].
- Symbol Digit Modalities Test [24].
- Perceived Stress Scale (PSS-10) [25] adaptation for the Brazilian population [26].

Control and Trace

- Sociodemographic and Health Aspects Questionnaire;
- Functional evaluation will be performed by the Expanded Disability Status Scale (EDSS) [27]
- Patient Health Questionnaire-9 (PHQ-9) (developed by Robert L. et al., Brazilian adaptation [28]
- Modified Fatigue Impact Scale (MFIS) (Brazilian adaptation and validation [29]
- The Mini International Neuropsychiatric Interview (M.I.N.I Plus) [30], translated and adapted to the Brazilian population [31]
- Wechsler Abbreviated Scale of Intelligence – WASI – reduced version [32]

Biochemical Analysis

Hair strands of approximately 3 mm in diameter (~20 mg of hair strand) and of 1 cm in length were cut from the posterior vertex position of subjects' heads with surgical scissors. The cortisol concentrations were determined from the 1 cm hair segment most proximal to the scalp. Based on an average hair growth rate of 1 cm/month [33], the hair segment should reflect cumulative cortisol secretion for one months prior to collection. After collection, the scalp end of the sample was identified, and hair samples were stored at room temperature.

Hair cortisol extraction from the hair was performed using a previously described protocol [34], which was adapted by our laboratory. For the study, we performed a slight alteration of the extraction procedure: 20 mg of whole and non-pulverised hair were prepared in 1.5 mL methanol and incubated in water bath for 24 h at 50 ºC. After incubation, ~ 1.0 mL of supernatant methanol (containing cortisol extract) was removed to a clean microtube and evaporated under a constant stream of nitrogen at 50 ºC for 20 min using TurboVap® Classic LV (Biotage, Sweden). The residues were reconstituted with 0.2 mL of phosphate buffered saline (pH 8.0) and vortexed for 1 min. Samples were frozen at -20° C until assayed according to the manufacturer's instructions (Enzo Life Sciences Inc.). For a double-blinded measurement of cortisol in the extracts, we used a commercially available high-sensitivity salivary cortisol enzyme-linked immunosorbent assay (ELISA) (Salimetrics LLC, State College, PA, USA) according to the manufacturer's instructions.

Ethical Procedures

This study respected the established norms for research with human being's accomplishment by the Federal Council of Psychology - Resolution number 016/2000 and by the Regional Health Council (2012) - Resolution number 466/2012.

Collection procedures

Clinical group participants were contacted at first, in a routine consultation at the Neuroimmunology Outpatient Clinic of the São Lucas Hospital of PUCRS. The contact was performed in person, at a time when the criteria for study inclusion were verified. In this first contact, patients were invited to participate in the study and its objectives were explained. In case of acceptance, the EDSS was verified with the participating neurologist and the Informed Consent Form (ICF) was signed. The first 69 participants from each group who met the criteria and who agreed to participate in the study were selected. For the control group, the first contact was via phone through the explanatory text and the second contact was, especially, for the signature of the ICF, for the hair collection that was performed by the researcher just before the application of the tests, scales and inventories. In case of acceptance of the clinical group participants, there were given guidelines for hair collection that occurred in the same way as the control group. Afterwards, data collection was performed. The evaluation took place in a meeting of approximately 100 minutes. The instruments were not necessarily applied in the same order for all participants, except for the Perceived Stress Scale and the Modified Fatigue Impact Scale that were applied at the beginning of the evaluation to avoid bias related to fatigue and stress resulting from the tests' application.

Data Analysis and Statistical Procedures

Data were tabulated and analyzed by SPSS (Statistical Package for Social Sciences) software, version 18.0. First, data were submitted to descriptive statistics procedures to evaluate the variables studied in terms of frequency distribution, scores, averages, standard deviations and confidence intervals. Variables with asymmetry and kurtosis patterns below the reference point were analyzed with non-parametric statistics (e.g. days of last menstruation). Student's t-test was used to compare averages between and among groups. ANOVA Two-away 2x2 was used to verify possible main effects or interaction of cortisol and group variable factors on the performance of EFs for parametric data. Pearson's correlation was used to verify relationships between the level of cortisol and perceived stress and the performance of EFs. Spearman's correlation was used to verify the association between cortisol level and Stroop Test performance, number of card 3 errors, due to the non-normal distribution of the variable.

Outcomes

Table 1 shows the data related to the characteristics of the disease for the clinical group, Sociodemographic characteristics, cortisol and perceived stress for the control group and clinical group. It was not statistically balanced between the control group and the quadruple in the average as studies of age and years of studies t (1.103) = 1.228; p = 0.224; IC 95% [-1.81182, 7.60478], and t (1.103) = 0.533; p = 0.596; IC 95% [-1.35533, 2.34373]. The same occurred with the statistically significant control in the comparison between control group and group with respect to cortisol t (1.96) = 1.392; p = 0.168; 95% CI [-7.52304, 42.46915] and for the perceived performance t (1.103) = 1.311; p = 0.194; IC 95% [-1.08609, 5.25917]. However, as a means of communication, it was possible to verify the group of patients that presented greater intensity, both in relation to cortisol, as in relation to the perceived stress. There was no significant statistical difference in the comparison between groups in relation to the last menstrual period (U = 183.000, z = -1.036, p = 0.300). Regarding the use of psychoactive drugs, in the clinical group 46.4% used antidepressants; 10.1% used benzodiazepines; 4.3% used antipsychotics; and 2.9% used hypnotics. In the control group, 8.6% used antidepressants.

Variables	Control Group	Clinical Group
Age M(DP)	40.85 (11.48)	43.75 (11.11)
Years of Study M (DP)	12.10 (4.46)	12.59 (4.47)
IQ M (DP)	97.80 (6.98)	92.44 (13.52)
Last Menstruation Dates***	9.50 (4.0-24.25)	13.00 (7.0-20.0)
Cortisol M (DP)	30.36 (23.11)	47.83 (95.10)
Perceived Stress M (DP)	13.97 (7.52)	16.05 (7.94)
Perceived Stress n (%)**	31 (88.5)	60 (87.0)
EDSS Score M (DP)	-	3.26 (2.06)
Diagnostic Time M (DP)*	-	74.52 (55.31)
Symptom Time M (DP)*	-	112.69 (82.96)
RRMS n (%)	-	61 (88.4)
Was treated for MS n (%)	-	65 (94.2)

Legend. M: mean; DP: standard deviation; *** median(tercis); **stress perceived as low or normal; *in months; RRMS: multiple sclerosis relapsing-remitting

Table 1: Descriptive Data Regarding the Characteristics of the Disease for the Clinical Group and Sociodemographic Characteristics, Cortisol and Stress Perceived for Both Groups.

Variables	Control Group	Clinical Group
	n (%)	n (%)
Women	30 (85.7)	52 (75.4)
Menopause*	8 (26.7)	17 (32.7)
Contraceptive Method*	14 (46.7)	21 (40.4)
Working	23 (65.7)	19 (27.5)
Extra-curricular Activity	10 (28.6)	20 (29.0)
Physical Activity	14 (42.4)	34 (50.0)
Smoker	2 (5.7)	10 (14.5)
Current/past psychotherapy	1 (2.9)	20 (29.0)
Depression**	1 (2.9)	11 (15.9)
Fatigue**	9 (25.7)	41 (59.4)

*Legend. *women only; **presence*

Table 2: Descriptive Sociodemographic and Health Data in Frequency for Both Groups

Table 2 s Sao Francisco, hows data related to socio-demographic and health aspects for both groups in terms of frequency. It is possible to notice that the great majority of the sample for both groups was female. Less than half of the women used contraceptive methods for both groups. In a qualitative way, it is possible to perceive a higher number of individuals who performed some work activity in the group of healthy individuals, in comparison to the clinical group. In the latter group, as expected, the number was higher in individuals who underwent or were going through psychological treatment at the time, and presented depression and fatigue compared to healthy individuals.

From the analysis performed considering as a dependent variable the WCST's CLR and the high cortisol level ≥ 21 and low ≤ 20 and the variable group as factors, it was possible to observe interaction between the group and cortisol level ($p = 0.047$), being that the pairwise comparison indicated that the difference was between the low cortisol level in which the control group presented better performance in CLR in WCST $F (1.96) = 6.168$; $p = 0.015$; [-18.137, -2.016]; $\eta 2 = 0.04$, with $M = 31.18$ and $DP = (13.17)$ and $M = 21.11$ and $DP = (11.27)$ for the control group and clinical group, respectively. The same result was found for the completed WCST categories ($p = 0.048$), and the pairwise comparison showed better performance for the control group $F (1.96) = 6.496$; $p = 0.013$; IC [-1.841, -0.228]; $\eta 2 = 0.04$, where $M = 2.56$ and $DP = (1.36)$; 95% IC [1.891, 3.234] and $M = 1.52$ and $DP = (1.15)$ for the control group and clinical group, respectively.

It was possible to observe a statistically significant difference in the comparison between moderate magnitude fatigue averages in individuals with high and low cortisol in the control group, considering individuals with low cortisol (≤ 20) presented greater fatigue compared to individuals with high cortisol ≥ 21 $t (1.96) = 2.142$; $p = 0.040$; 95% IC [0.56964, 23.80536] $d = 0.75$. Results were not statistically significant when considering depressive symptoms and high and low cortisol in both groups.

Regarding the correlation analysis between cortisol and performance in EFs evaluation tests, it was possible to observe a significant weak positive correlation between cortisol and Stroop Test numbers of errors in card 3 in the clinical group and a significant positive correlation between cortisol and the failure to maintain the WCST context in the control group. It was not possible to observe a statistically significant correlation between the perceived stress and the performance in EFs evaluation tests (data not shown). Table 3 shows data related to correlations for both groups.

Tests EFs/Cortisol	Control Group (N = 33)	Clinical Group (N = 64)
	r/p	r/p
STROOP		
Errors Card 3**	0.11/0.541	0.31/0.010*
Interference	-0.08/0.654	0.05/0.672
WCST		
PR	0.10/0.553	-0.01/0.903
PE	0.17/0.331	-0.05/0.668
NPE	0.07/0.699	-0.18/0.153
CLR	-0.15/0.399	0.21/0.091
Complet. Cat.	-0.21/0.242	0.16/0.185
Fail. M Cont.	0.57/0.000*	0.01/0.890
BADS (GS)		
R. Shift. Cards (errors)	-0.28/0.057	-0.032/0.402
Action Prog.	0.08/0.624	0.06/0.629
Key Search	-0.12/0.501	-0.04/0.734
Temporal J.	-0.11/0.513	-0.11/0.371
Zoo Map	0.04/0.807	-0.24/0.057
Six Mod. E.	-0.06/0.739	0.03/0.757
BADS (WS)		
R. Shift. Cards	0.30/0.085	-0.07/0.581
Action Prog.	0.08/0.624	0.05/0.685
Key Search	-0.14/0.422	-0.02/0.871
Temporal J.	-0.11/0.513	-0.11/0.356
Zoo Map	0.09/0.614	-0.08/0.529
Six Mod. E.	-0.04/0.809	0.00/0.994

Legend. ** Spearman Correlation Test. Errors Card 3= Errors Card 3; PR = Perseverative Responses; PE = Perseverative Errors; NPE = Non-Perseverative Errors; CLR = Conceptual Level Response; Complet. Cat. = Completed Categories; Fail. M. Cont. = Failure to Maintain Context; GS = Gross Score; R. Shift. Cards = Rule Shift Cards; Action Prog. = Action Program; Temporal J.= Temporal Judgement; Six Mod. E. = Six Modified Elements; WS = Weighted Score; *Meaningful result ($p \leq 0.05$)

Table 3: Correlations between Cortisol and EFs Evaluation Tests for Both Group

Discussion

The present study found no statistically significant difference in cortisol and perceived stress in the comparison between the group of individuals diagnosed with MS and the group of healthy individuals. However, observing the data, most individuals (over 80%) for both groups did not perceive stress. The Lazarus and Folkman [35] considers that stress is a transaction between the individual and the environment, being this model, frequently used in studies of coping with stress in chronic diseases. Thus, the model indicates that both the environmental stimuli and the reactions of individuals to these stimuli should be considered in the understanding of stress. The stress process is triggered when the resources of the individuals' assessment to face the stressor is extrapolated by the measured external demands (environmental stimuli) and this is considered a harmful environmental stimulus to the individual [36].

Coping with chronic diseases associated stress can be different at different times of disease development [37]. The absence of significant cortisol results between the groups may suggest that stress through biological factors in the present sample may not be related to the course of the disease but rather the exacerbation of the disease, related to the sudden presence of symptoms that may or may not remit within a period of weeks or months [38]. Also, through the variables frequency data related to health aspects, it was possible to observe that half of the clinical group sample practiced exercises, which may have influenced stress perception management, as well as cortisol due to the beneficial effects of physical exercise on stress [36].

Recent studies have shown the effects of stress on the performance of EFs [39]. The present study showed a weak positive association between cortisol and performance in an inhibitory control task in the group of individuals diagnosed with MS. That is, the higher the level of cortisol, the greater the errors committed in the task. Study defines as cognitive inhibition the ability to selectively attenuate a stimulus or ignore information and defines response inhibition as the suppression of a proponent response [39]. This type of inhibition is usually associated with the detrimental effects of stress [40,41]. The result described above agrees with the theory of stress and cognitive function proposed by Gagnon and Wager and Vogel et al. [42, 43]. This theory argues that stress alters more the cognition of top-down processes than of bottom-up processes, and EFs are considered top-down processes, including inhibitory control.

Stress seems to predominantly influence EFs through the positive regulation of cortisol, considering that high cortisol impairs cerebral pre-frontal cortical function [44, 43]. In the present study, cortisol was positively correlated with failure to maintain the WCST context, a measure of problem resolution and cognitive flexibility in healthy individuals [45]. That is, the results suggest that the higher the level of cortisol, the worse the performance of the ability to identify correct strategic responses, which suggests insight into the correct principles for problem solving. Despite the scarcity of studies on the effects of stress on cognitive flexibility, the data corroborate the results of the present study regarding the association of cortisol with performance in certain subcomponents of EFs, showing cognitive impairment followed by induced stress [46-48].

In the present study, the results showed few correlations between cortisol and EFs performance. Such a shortage of significant results may occur since stress has multiple effects on different biological processes, besides cortisol, such as increased sex hormones and altered immune system functioning [49-52], which has effect over cognition [49, 53].

Concerning perceived stress and cognitive performance, the present study showed no correlation. This result is corroborated by a study that showed no correlation between perceived stress and measures of cognition evaluation, including EFs [54]. The sample was similar to the present studies, with subtype of RRMS and EDSS ≤6.5.

The present study showed that being in the MS group and having a low cortisol level impaired performance to the extent of solving problems involving cognitive flexibility, such as CLR and completed WCST categories. The latter result was found in the comparison of performance with healthy individuals. Cognitive flexibility is characterized by the individual's ability to change the direction of actions and thoughts in accordance with the demands of the environment and change them when necessary. It understands the ability as changes of perspective or flexible adjustments due to new circumstances-rules, thus helping in solving problems [45,55]. A study found that the response to cortisol correlated with worse performance in assessing cognitive flexibility in a sample of healthy individuals [56]. Changes in cortisol levels were associated with cognitive flexibility, with a reduction in time-dependent performance of response to HPA axis stimulation [48].

In the comparison of the effect of acute stress through the administration of cortisol on the performance of different subcomponents of EFs, stress is indicated to act from distinct mechanisms besides cortisol [39]. Dehydroepiandrosterone (DHEA), an endogenous hormone secreted by the adrenal cortex in response to ACTH and its derivative DHEA-S, is considered a neuro-steroid involved in response to stress, through behavioral benefits and neurotrophic actions [57]. A study showed a positive relationship between DHEA-S assessed through saliva and executive skills, such as the decision-making during stress of military soldiers suggesting that DHEA-S acts as an anti-stress effect on cognition in humans [58].

Corroborating results of the present research, studies investigated the effect of hydrocortisone administration directly prior to neuropsychological testing, including measures of cognitive flexibility assessment [59,60]. The results did not show effects of high cortisol level on cognition. Furthermore, there are studies that investigated cognitive performance when on cortisol suppression and found deleterious effects on cortisol suppression [61,62].

Conclusions

In the present sample, the individuals diagnosed with MS did not differ from the healthy control subjects regarding stress, measured through cortisol and subjective measure, through perceived stress. It was possible to verify that the great majority of the sample perceived the level of stress as low and normal. These results suggest that the present sample consisted of non-stressed individuals. Moreover, the correlation observed was especially between the evaluation of the inhibitory control with cortisol in the MS group, and the latter variable was high when the cortisol level was low in the group of healthy individuals. In addition, it was possible to observe interaction only with low cortisol level and performance in the measurement of problem solving-cognitive flexibility in the MS group. The results make it clear that measure of stress assessment, such as perceived stress and cortisol (the latter, at least by itself) do not seem to be responsible for producing stress effects in EFs, except for the association with performance in inhibitory control, although it is a weak one. High levels of stress did not interact with the EFs performance in both groups.

The present study has limitations. Possible coping strategies used by individuals to deal with the disease, as well as minimizing the effects of stress, were not evaluated. The sample consisted of patients with a minimum and moderate level of disability. The subtype of the disease was, for the most part, RRMS, and the sample calculation was not performed for stress measures. Thus, it is not possible to generalize the results, being these related to this sample and its particularities. Finally, another important limiting factor of the study is the fact that the instrument used in the evaluation of perceived stress is a scale not adapted to MS. We suggest future studies that consider heterogeneous samples in terms of disease subtypes and levels of inability to better understand different MS profiles and the effects of stress through instruments adapted to the clinical population.

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