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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

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), 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 hair cortisol concentration and perceived stress as well as verify the association with the performance of executive function in both individuals diagnosed with MS and control individuals. Hair cortisol concentration and perceived stress were evaluated and their association with the performance of healthy individuals ($n=33$) and those with MS ($n=64$), most of them with remitting-relapsing multiple sclerosis (RRMS) assessed using the Expanded Disability Status Scale (EDSS). Instruments that were employed to measure perceived stress and health aspects included the Behavioral Assessment Dysexecutive Syndrome, Wisconsin Card Sorting Test, 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 ($r=0.31$, $p=0.10$). Further, an absence of correlations with perceived stress measure was noted. 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 such as more time of stress.

Keywords Executive functioning · Cortisol · Perceived stress · Autoimmune disease

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Introduction

Life events that are perceived as stressors may result in the activation of the hypothalamic–pituitary–adrenal (HPA) axis (Belda et al. 2015). The repercussions of stress are identified through changes in neuroendocrine and mental functioning when the individual perceives stimuli as stressors (Goldstein and Kopin 2007; Roos et al. 2018). Multiple sclerosis (MS) is an autoimmune disease that causes destruction of the myelin sheath and axons, characterized by relapses and insidious progressions with clinical characteristics, symptomatology, and heterogeneous severity (Krieger et al. 2016; Spanò et al. 2018). Studies have shown that individuals diagnosed with MS fail to suppress cortisol release (Fassbender et al. 1998; Karussis 2014; Najafi and Moghadasi 2017; Pereira et al. 2018).

Stressful events result in the production of the hypothalamic corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH stimulates the pituitary gland to produce the adrenocorticotropic hormone (ACTH), and the effect of CRH as an ACTH secretor is stimulated by AVP. ACTH stimulates the adrenal cortex during cortisol production, resulting in an inhibitory effect on CRH hypothalamic production. Thus, the HPA axis is self-regulating, in part, through the inhibitory effects of cortisol. However, in chronic stress, this feedback mechanism becomes deregulated. In turn, this deregulation results in increased cortisol levels (Furtado and Katzman 2015); despite reports of hypocortisolism in the presence of chronic stress (Heim et al. 2000).

Hair cortisol concentration is a valid matrix for retrospective measures of systemic cortisol exposure (measurement of chronic stress) (Russell et al. 2011; Staufenbiel et al. 2015). Cortisol measured through hair may be associated with medical conditions indicating chronic HPA axis activation or even high stress levels (Wosu et al. 2013).

Studies have shown an association between cortisol and cognitive performance, such as memory and executive function (EF), which depend on the integrity of brain structures, such as the hippocampus and the prefrontal cortex, in healthy individuals (Evans et al. 2011; Hansson et al. 2015). 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 (Öhman et al. 2007). Prospective memory has been related to the executive control and functioning of frontal circuits through strategies and planning of a future action (Lezak 1995; Henry et al. 2004; Kliegel et al. 2004).

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

Materials and methods

Sample

A total of 69 patients diagnosed with MS were recruited from the Neuroimmunology Outpatient Clinic of the São Lucas Hospital from Porto Alegre, Brazil. In addition, 35 healthy control participants were recruited from Porto Alegre using a community-based convenience sampling strategy. The period for collecting samples lasted approximately 17 months, from May 2016 to October 2017. The patients had the diagnosis of definite MS disease in accordance with revised McDonald's criteria (Polman et al. 2011). The Expanded Disability Status Scale (EDSS) score was used for propensity score matching (mean ± SD 3.39 ± 2.07; median 3.75; tercis 1.6–5.4; total $n = 64$). All participants provided written informed consent for participation in accordance with the study protocol. The participants were selected by convenience and were literate, fluent in Portuguese, and at least 18 years of age. The groups were matched by age, years of study, and gender. The exclusion criteria for either group were as follows: (a) past or current neurological diseases (with exception of MS), (b) acute or chronic virus infections, (c) use of corticosteroids in last month, (d) diagnosis of dementia, (e) the presence of cognitive, motor, visual, and/or auditory impairments that impact the application of measurements, (f) IQ rated as "extremely low" or "borderline", (g) diagnosis of psychiatric disorders, with the exception of depression (participants who presented wake-sleep cycle disorder, according to criteria of the DSM-5 Diagnostic and Statistical Manual of Mental Disorders (Cordioli et al. 2014) were excluded, for a specific study on sleep-related disorder and MS-related, please see Veauthier et al. 2016), (h) past or current history of drug addiction, (i) women who are pregnant or pre- or perimenstrual, (j) the presence of menopausal symptoms, (k) participating in or having participated in neuropsychological rehabilitation programs (for the MS group), and (l) individuals with less than 1-cm hair length (for hair cortisol analysis of 1-cm hair segment).

EF evaluation

Four instruments were employed to measure EF.

- The Behavioral Assessment of the Dysexecutive Syndrome (BADS) (Wilson et al. 1996), with a translated version currently in Brazilian adaptation process (Macuglia et al. 2016), 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; and Modified Six Elements (planning). Total classification is summarized as damaged, borderline, low average, medium high, superior, and much higher.
- The Wisconsin Card Classification Test (WCST) (Heaton and Thompson 1992) is a computer-assisted test consisting of 64 letters with stimuli in three categories: colors, shapes, and numbers. The test assesses EF that demands the ability to develop and implement appropriate problem-solving strategies. The Stroop Test (Strauss et al. 2006; Brazilian standards; Duncan 2006) evaluates the ability to inhibit interferences, impulsive responses to competitive stimuli, and automatic behaviors as a function of a specific instruction.
- The Symbol Digit Modalities Test (Smith 1982) evaluates information processing speed by associating nine different geometric shapes with numbers from 1 to 9, within 90 s.
- The Perceived Stress Scale (PSS-10) (Cohen et al. 1983; adaptation for the Brazilian population; Luft et al. 2007) consists of ten items, supported on a Likert frequency scale, ranging from never (0) to always (4).

Control and trace

- The Sociodemographic and Health Aspects Questionnaire consists of identification data, schooling, health aspects, such as gestation, medication use, psychiatric disorders, smoking, alcohol use, drug use, and mental health treatments. The instrument was constructed by the authors of the study.
- Functional evaluation was performed using the EDSS (Kurtzke 1983). The instrument consists of an ordinal scale used in the evaluation of MS patients based on eight functional systems. The score ranges from 0 to 1, where 0 corresponds to absence of disability and 10 to death by MS.
- The Patient Health Questionnaire-9 (PHQ-9) (Brazilian adaptation, Santos et al. 2013) was used for the evaluation of depressive symptoms. The following criteria indicated the presence of depression: five or more symptoms, one or more of which included depressed or anecdotal mood and that each symptom corresponded to a response of 2 or 3 (“1 week or more” and “almost every day”, respectively), with the exception of the “suicidal thoughts” symptom, for which any value from 1 to 3 (“less than 1 week”, “1 week or more”, and “almost every day”, respectively) was accepted.
- The Modified Fatigue Impact Scale (MFIS) (Brazilian adaptation and validation, Pavan et al. 2007) contains 21 questions distributed across three domains (physical, cognitive, and psychosocial). A score of 38 or more characterizes the presence of fatigue.
- The Mini-International Neuropsychiatric Interview (M.I.N.I Plus) (Sheehan et al. 1998; translated and adapted to the Brazilian population; Amorin 2000) is a brief diagnostic interview based on the diagnostic criteria of DSM-IV and the International Classification of Diseases (ICD-10). The instrument was used to verify, in particular, the existence of posttraumatic stress disorders (PTSD).
- The Wechsler Abbreviated Scale of Intelligence—WASI—reduced version (Trentini et al. 2014) consists of two subscales that provide an estimated IQ.

Biochemical analysis

Hair strands of approximately 3 mm in diameter (mean ± SEM 22.91 mg ± 8.91 of hair strands) and of 1-cm in length were cut from the posterior vertex position of subjects’ heads with surgical scissors. Subsequently, 1-cm hair sections (representing $1-m$th periods) were cut and minced with clean and fine-tipped surgical scissors into 1 mm pieces. Based on an average hair growth rate of 1-cm per month (Silva and Enumo 2014), the 1-cm hair segment should reflect cumulative cortisol secretion for the 1 month prior to collection. After collection, the scalp end of the sample was identified, and hair samples were stored at room temperature for up to 12 months.

Hair cortisol extraction from the hair was performed using a previously described protocol (Kirschbaum et al. 2009), which was adapted by our laboratory. For the study, we implemented a slight alteration of the extraction procedure due to absence of a mixer mill for hair pulverization. At least 10 mg of hair per 1-cm section was weighed and manually milled with surgical scissors into different clean centrifuge tubes. Powdered hair were prepared in 1.5 mL methanol and incubated in water bath for 24 h at 50 °C. After incubation, approximately 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 °C 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 for at least 15 days until assayed. For a double-blinded measurement of cortisol in the extracts, we used a commercially available high-sensitivity salivary cortisol enzyme-linked immunosorbent assay (ELISA) (Cortisol ELISA Kit, Enzo Life Sciences, Inc., Farmingdale, USA) according to the manufacturer's instructions. All samples were run in duplicates. Of the 104 participants, ~6.7% ($n=7$) were excluded from the current analyses due to a failure in hair cortisol extraction and analysis (missing data). The final analyses for 1-cm hair cortisol included 97 participants (controls: $n=33$; cases: $n=64$).

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 first contacted during a routine consultation at the Neuroimmunology Outpatient Clinic of the São Lucas Hospital of PUCRS. The contact was performed in person after the criteria for study inclusion were verified. During 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 MS 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 following the explanatory text and the second contact was in person to obtain a signature on the ICF and to complete the hair collection, which was performed by the researcher before the application of the tests, scales, and inventories. Hair collection occurred in the same way for the clinical participants as those in the control group. Afterwards, data collection was performed. The evaluation took place in a meeting of approximately 100 min. The instruments were not necessarily applied in the same order for all participants, except for the Perceived Stress Scale (PSS-10) and the MFIS that were applied at the beginning of the evaluation to avoid bias related to fatigue and stress resulting from the application of the tests.

Data analysis and statistical procedures

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. In this concern, data were tested for normality of distribution using the Kolmogorov–Smirnov or Shapiro–Wilk tests. 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. Two-way analysis of variance (ANOVA) was used to verify possible main effects or interaction of hair cortisol concentration and group variable factors on the performance of EF for parametric data. Pearson's correlation was used to verify relationships between hair cortisol concentration for the 1-cm hair segment and perceived stress and the performance of EF. In addition, Spearman's correlation was used to verify the association between hair cortisol concentration for the 1-cm hair segment and Stroop Test performance (number of card 3 errors) due to the non-normal distribution of the variable. All statistical analyses of cortisol and instrument scores were performed using SPSS software 18th version (SPSS, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

Results

Characteristics of the disease, sociodemographics, and measures of stress evaluation

The results from this study is shown in Table 1, which details the characteristics of the disease for the clinical group, sociodemographic characteristics, hair cortisol concentration, and perceived stress for both control and clinical groups. No statistically significant differences were found between the control and clinical group in the average of age ($t(1.103)=1.228$; $p=0.224$; IC 95% [-1.81, 7.60]), and years of education ($t(1.103)=0.533$; $p=0.596$; IC 95% [-1.35, 2.34]). In addition, we found no significant differences regarding hair cortisol concentration ($t(1.96)=1.392$; $p=0.168$; 95% CI [-7.52, 42.46]), and perceived performance ($t(1.103)=1.311$; $p=0.194$; IC 95% [-1.08, 5.25]), when we compared control and clinical groups. However, it was possible to verify that the group of patients with MS presented greater intensity, both in relation to hair cortisol and in relation to perceived stress. In contrast, we did not find significant differences regarding last menstrual period between groups ($U=183.000$, $z=-1.036$, $p=0.300$).

Sociodemographic and health data in terms of frequency

Data related to sociodemographic and health aspects for both groups in terms of frequency are detailed in Table 2. Notably, the great majority of the sample for both groups was female (85.7% and 75.4%, control and clinical group, respectively) and a greater number of individuals in the control

Table 1 Descriptive data regarding the characteristics of the disease for the clinical group and sociodemographic characteristics, hair cortisol concentration and stress perceived for clinical and healthy control groups

Variables	Control group ($n=33$)	Clinical group ($n=64$)
Age (mean ± SD)	40.85 (11.48)	43.75 (11.11)
Years of education (mean ± SD)	12.10 (4.46)	12.59 (4.47)
IQ (mean ± SD)	97.80 (6.98)	92.44 (13.52)
Last menstruation dates[a]	9.50 (4.0–24.25)	13 (7.0–20.0)
Cortisol (mean ± SD)	30.36 (23.11)	47.83 (95.10)
Perceived stress (mean ± SD)	13.97 (7.52)	16.05 (7.94)
Perceived stress *n* (%)[b]	31 (88.5)	60 (87.0)
EDSS score (mean ± SD)	–	3.39 (2.07)
EDSS score[a]	–	3.75 (1.6–5.4)
Diagnostic time (mean ± SD)[c]	–	74.52 (55.31)
Symptom time (mean ± SD)[c]	–	112.69 (82.96)
RRMS *n* (%)	–	61 (88.4)
Was treated for MS *n* (%)	–	65 (94.2)

DP standard deviation, *RRMS* multiple sclerosis relapsing-remitting

[a]Median (tercis)

[b]Stress perceived as low or normal

[c]In months

Table 2 Descriptive sociodemographic and health data for clinical and healthy control groups

Variables	Control group *n* (%)	Clinical group *n* (%)
Women	30 (85.7)	52 (75.4)
Menopause[a]	8 (26.7)	17 (32.7)
Contraceptive method[a]	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[b]	1 (2.9)	11 (15.9)
Fatigue[b]	9 (25.7)	41 (59.4)

[a]Women only

[b]Presence

group (65.7%) had participated in some level of employment at the time of collection.

In the clinical group, as expected, the number of individuals who had undergone or were going through psychological treatment at the time was higher and they presented more depression and fatigue compared to healthy individuals.

Association between measures of stress evaluation and performance of executive functions

From the two-way ANOVA, we modeled the conceptual level responses (CLR) of the WCST as the dependent variable using the variables group and degrees of the hair cortisol concentration (low cortisol concentration group: hair cortisol concentration ≤ 20 mg/pg; high cortisol concentration group: hair cortisol concentration ≥ 21 mg/pg) as factors. We revealed a significant interaction effect between group and hair cortisol concentration on CLR ($p=0.047$). The pairwise multiple-comparison analysis indicated that the difference was between the low hair cortisol concentration in which the control group presented better performance in WCST (CLR) in comparison with clinical group ($F(1.96)=6.168$; $p=0.015$; [− 18.13, − 2.01]; $\eta^2=0.04$) (mean ± SD: control group = 31.18 ± 21.11; clinical group = 21.11 ± 11.27). The same result was found for the completed categories (WCST) ($p=0.048$). The pairwise multiple-comparison analysis showed better performance for the control group in comparison with the clinical group ($F(1.96)=6.496$; $p=0.013$; IC [− 1.841, − 0.228]; $\eta^2=0.04$) (mean ± SD: control group = 2.56 ± 1.36; clinical group = 1.52 ± 1.15).

Regarding the correlation analysis between hair cortisol and performance in EF evaluation tests, it was possible to observe a significant positive correlation between cortisol and Stroop Test numbers of errors in card 3 in the clinical group as well as 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 perceived stress and performance in EF evaluation tests (data not shown). Table 3 shows data related to correlations for both groups.

Table 3 Correlations between hair cortisol and evaluation of executive functions (EF) for clinical and healthy control group

Tests EFs/cortisol	Control group ($n=33$) r (p value)	Clinical group ($n=64$) r (p value)
STROOP		
Errors card 3[a]	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)

[a]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 value ≤ 0.05)

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. Further, the data indicates that most individuals (over 80%) for both groups did not perceive stress. Lazarus and Folkman (1987) described that stress is a transaction between the individual and the environment, and this model is 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 individual's assessment of resources to face the stressor is extrapolated by the measured external demands (environmental stimuli) to the point that it is considered a harmful environmental stimulus to the individual (Beneton et al. 2017).

Coping with chronic disease-associated stress can vary throughout disease development (Topciu 2013). 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 related to the exacerbation of the disease and the sudden presence of symptoms that may or may not remit within a period of weeks or months (Artemiadis et al. 2011). Moreover, the frequency data related to health aspects indicated 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 (Beneton et al. 2017; for a specific study on physical exercise and stress, please see; Scheffer et al. 2018).

Recent studies have shown the effects of stress on EF performance (Shields et al. 2016). 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. In this study, cognitive inhibition refers to the ability to selectively attenuate a stimulus or ignore information and defines response inhibition as the suppression of a proponent response (Shields et al. 2016). This type of inhibition is usually associated with the detrimental effects of stress (Vinski and Watter 2013; Sänger et al. 2014). The result described above agrees with the theory of stress and cognitive function proposed by Gagnon and Wagner (2016) and Vogel et al. (2016). This theory argues that stress alters the cognition of top-down processes to a greater degree than bottom–up processes, and EF is considered a top-down process, including inhibitory control.

Stress seems to influence EF predominantly through the positive regulation of cortisol, considering that high cortisol impairs cerebral prefrontal cortical function (Vogel et al. 2016; Luettgau et al. 2018). 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 (Cunha et al. 2005). 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 EF, showing cognitive impairment followed by induced stress (Plessow et al. 2011; Laredo et al. 2015; Shields et al. 2017).

In the present study, the results showed few correlations between cortisol and EF 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 (Segerstrom and Miller 2004; Lennartsson et al. 2012; Allen et al. 2014; Kuebler et al. 2015), which has an effect over cognition (Segerstrom and Miller 2004; Mehta and Josephs 2010; Lennartsson et al. 2012; Allen et al. 2014; Kuebler et al. 2015). There is clinical evidence showing differences between genders in the incidence and prevalence of CNS inflammatory disorders, including MS (Gold et al. 2018). Differences in chromosomal composition, reproductive organs, and sex hormones influence immune responses to foreign and self-antigens result in adaptive immune responses in females that are more vigorous, including T cell activity and higher antibody production (Klein and Flanagan 2016). Taken together, the data suggest that the pathobiology of these disorders may not be the same in men and women. A potential implication of this is that male and female patients may also differ in their response to treatment of the disease, necessitating specific therapeutic approaches. It was demonstrated that women's responses to immune changes are stronger when compared to men (Libert et al. 2010).

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 EF (López-Alava et al. 2017). The sample was similar to the present studies with the subtype of RRMS and EDSS $\leq$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. Further, it understands the ability as changes of perspective or flexible adjustments due to new circumstances rules, thus helping in solving problems (Cunha et al. 2005; Diamond 2013). In particular, one study found that the response to cortisol correlated with worse performance in assessing cognitive flexibility in a sample of healthy individuals (Goldfarb et al. 2017). Changes in cortisol levels were associated with cognitive flexibility and with a reduction in time-dependent performance of response to HPA axis stimulation (Shields et al. 2017).

In the comparison of the effect of acute stress through the administration of cortisol on the performance of different subcomponents of EF, stress is indicated to act from distinct mechanisms besides cortisol (Shields et al. 2016). Dehydroepiandrosterone (DHEA), an endogenous hormone secreted by the adrenal cortex in response to ACTH and its derivative DHEA-S, is a neurosteroid involved in response to stress through behavioral benefits and neurotrophic actions (Krause et al. 2014). 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 has an anti-stress effect on cognition in humans (Morgan et al. 2004).

Corroborating results of the present research, studies investigated the effect of hydrocortisone administration directly prior to neuropsychological testing, including measures of cognitive flexibility assessment (Otte et al. 2007; Wingenfeld et al. 2011). The results did not show effects of high cortisol level on cognition. Furthermore, other studies have investigated cognitive performance when on cortisol suppression and found deleterious effects on cortisol suppression (Rimmele et al. 2010, 2015).

Conclusions

In the present sample, the individuals diagnosed with MS did not differ from the healthy control subjects regarding stress, as measured through hair cortisol and subjective measure through perceived stress. It was possible to verify that the great majority of the sample perceived their level of stress as low and normal. These findings 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 levels and performance in the measurement of problem-solving-cognitive flexibility in the MS group. The results make it clear that measures of stress assessment, such as perceived stress and hair cortisol (the latter, at least by itself), do not seem to be responsible for producing stress effects in EF, except for the association with performance in inhibitory control, although it is a weak one. High levels of stress did not interact with EF performance in either group.

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. Future longitudinal studies coupled with novelty approaches could bring us a step closer to getting a clearer picture on the role of MS subtypes as well as the levels of inability caused by exposure to different forms of stress across the life span. For this, the use of a chronic measure of stress evaluation by measuring larger centimeters of hair (> 1 cm) could allow to find more consistent differences in cortisol levels between individuals diagnosed with MS and healthy individuals.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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