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Negative affect, perceived health, and endocrine and immunological levels in caregivers of offspring with schizophrenia

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Abstract

Background: Negative affect (NA) and chronic stress are separately associated with health imbalances, and the interaction between the two aspects remains unclear. Care of relatives with long-term pathologies could be a likely model in the study of this issue, as caregivers frequently report chronic stress and health complaints. The aim of this study is examine the role of NA on psychophysiological stress-induced response and health in schizophrenia caregivers. **Method:** Forty-one caregivers were distributed into two groups accordingly to their scores in NA. Thirteen non-caregivers were included as a control group. Participants were exposed to a repeated acute psychosocial stress while salivary cortisol, immunoglobulin A (IgA), and skin conductance level (SCL) were measured before, during, and after stress. Mood, state-anxiety, care conditions and perceived general health were also assessed. **Results:** Caregivers with higher NA reported negative perceptions, worse health, and greater decreases in cortisol and IgA response than caregivers with low NA and than non-caregivers. **Conclusions:** NA could reduce the capability to develop adaptive psychophysiological stress responses. From a preventive view, the evaluation of NA could be useful to detect and assist high-risk individuals in potentially chronically stressed populations.

Keywords: caregivers, cortisol, immunoglobulin A, skin conductance level, negative affect.

Resumen

Afecto negativo, salud percibida y niveles endocrinos e inmunológicos en cuidadores de hijos con esquizofrenia. **Antecedentes:** afecto negativo (AN) y estrés crónico se asocian con desequilibrios de salud, y la interacción entre ambos permanece desconocida. El cuidado de familiares a largo plazo es un modelo de estudio, ya que informan de estrés crónico y problemas de salud. El objetivo es examinar el papel del AN sobre la respuesta de estrés y la salud en cuidadores de esquizofrenia. **Método:** cuarenta-y-un cuidadores fueron distribuidos en dos grupos de acuerdo con su AN y trece no cuidadores formaron el grupo control. Los participantes fueron expuestos a un estresor psicosocial agudo repetido, midiéndose el cortisol, la inmunoglobulina A (IgA) y el nivel de conductancia cutánea (SCL) antes, durante y después del estrés. También se evaluó el estado de ánimo, el estado de ansiedad, las condiciones de cuidado y la salud percibida. **Resultados:** los cuidadores con mayor AN muestran peor salud, y mayores disminuciones de cortisol y de respuesta de IgA que los cuidadores con menor AN y los no cuidadores. **Conclusiones:** el AN podría reducir la capacidad para desarrollar respuestas psicofisiológicas adaptativas al estrés. Desde un punto de vista preventivo, la evaluación de AN podría ser útil para la detección precoz en poblaciones de alto riesgo.

Palabras clave: cuidadores, cortisol, inmunoglobulina A, nivel de conductancia de la piel, afecto negativo.

Negative affect (NA) is considered a tendency to experience negative emotions (Denollet & Pedersen, 2009). High-NA individuals report dysphoria, anxiety, irritability, perceived threats and punishments, and have a high predisposition to a broad spectrum of pathologies (Steptoe, Wardle, & Marmot, 2005) and disrupted capabilities of adaptive responses in the immune and endocrine systems (Aguilera, 2011).

Studies have focused on the activities of the endocrine, immunological and autonomous systems at rest and in acutely stressful conditions in healthy individuals. In response to stress, NA has been positively related to cortisol levels (Quirin, Kazén, Rohrmann, & Kuhl, 2009) and negatively associated with natural killer and antibody responses (Marsland, Cohen, Rabin, & Manuck, 2001). In the autonomous systems, NA has been positively related to skin conductance level (SCL) (Levenson, 1992), although the results are not homogeneous.

Data provided from acute stimulation is extremely useful for understanding the underlying mechanisms involved in stress response and health. Additionally, NA is a relatively stable predisposition that modulates cognition, and this could vary how the world is perceived, specially, in a chronically stressed status. It is possible that NA and chronic stress reciprocally facilitate each other in a loop of negative cognition. In any case, the study of chronically stressed populations could be useful to examine the impact on health of the interaction between acute and chronic stress and affectivity.

Caregiving can be considered as a valuable model of chronic stress in a non-clinical population. Taking care of a relative for a long period implies overburden, especially in the case of offspring with chronic psychiatric disorders, and could lead to general health complaints (Chang, Chiou, & Chen, 2010).

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Studies focused on the effect of care on stress-induced physiological responses in caregivers are scarce and report no differences in cortisol response (Epel et al., 2010), elevated adrenocorticotropic hormone (ACTH) with lower inflammatory levels and higher scores for NA (Lovell & Wetherell, 2011). Although no studies exist regarding SCL in caregivers, lower SCL responses have been reported in other potentially stressed samples (Nesic & Duka, 2006). Additionally, several modulating factors involved in the care context such as social support (Benson & Karlof, 2009) and coping strategies (González-Bono, De Andrés-García, & Moya-Albiol, 2011) are not usually included in caregiving studies.

To our knowledge, no studies have examined the relationship between the autonomic nervous system, hypothalamic-pituitary-adrenal (HPA) and immunological response to acute stress and NA in caregivers. Although it is accepted that personality factors can modulate health outcomes in caregivers, these factors have received little attention (Möller-Leimkühler & Mädger, 2011). Previous data revealed a significant worsening in health and disrupted immune and hormonal responses to stress, together with higher trait-anxiety and expression of anger in parents of offspring with autistic spectrum disorder (ASD) in comparison with controls (De Andrés-García, Moya-Albiol, & González-Bono, 2012). These results lead us to suspect that NA could be modulating, at least in part, the stress response.

The aim of the present study was to examine whether NA is associated with a worsening in health and its role on endocrinal, immunological and physiological responses to acute stress in caregivers of patients with schizophrenia. We hypothesised that caregivers with a predisposition to exhibit higher NA will also show a worsening in health complaints, higher cortisol and SCL responses, and buffered antibody activity in comparison with caregivers with lower NA and controls.

Method

Participants

The sample was composed of 41 caregivers (M_{age}= 63.35, *SEM*= 1.12), mothers (*n*= 33) and fathers (*n*= 8) of offspring diagnosed with schizophrenia, and an initial sample of 14 controls (four men and 10 women) who care for healthy children. Criteria for inclusion as a caregiver was being a first-degree relative who is mainly responsible for offspring with schizophrenia and living with the patient in the same home. For the control group, inclusion criteria were to have healthy offspring and not to have been a caregiver to any relative with any pathology during the last two years. Other characteristics of this groups such as age, gender, etc., were similar to the group of caregivers. Caregivers were classified into two groups on the basis of the NA scores: HIGH-NA (14 caregivers) and LOW-NA (27 caregivers). Characteristics of the patients for both groups are shown in Table 1. In the control group, only one participant (a man) showed HIGH-NA and was eliminated. Thus, all the participants of the control group had LOW-NA scores.

Instruments

Psychosocial stressor. Caregivers usually cope with repeated episodes of stress in a short period of time. Thus, participants were exposed to two similar periods of psychosocial stress in a single session lasting 15 minutes. Both periods consisted in a public speech task and mental arithmetic calculations in front of a committee of three members, with a simulation of a video-recording (Kirschbaum, Pirke, & Hellhammer, 1993).

Criteria variables. NA included the scores of trait-anxiety, trait-anger and depression. Trait-anxiety was evaluated by the Spanish adaptation of the State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) (reliability coefficients from .82 to .92). Anger-temperament was evaluated using the Spanish version of the State-Trait Anger Expression Inventory-2 (Spielberger, Jacobs, Russell, & Crane, 1983) (reliability coefficients from .65 to .86). Depression was evaluated by means of severe depression on Goldberg's General Health Questionnaire (GHQ-28) (Goldberg & Hillier, 1979) (Cronbach's alpha higher than .92).

Psychological variables. Coping styles were assessed by the COPE inventory (Carver, Scheier, & Weintraub, 1989) (reliability coefficients from .62 to .92.). This scale provides five second-order factors: behavioural coping, cognitive coping, coping with emotions, behavioural disengagement, and cognitive disengagement. Social support was evaluated using the Medical Outcomes Study Social Support Survey (MOS) (Sherbourne & Stewart, 1991), which assesses emotional, instrumental and affectionate support, and positive social interaction (Cronbach's alpha higher than .91). State-anxiety was evaluated using the Spanish adaptation of the State-Trait Anxiety Inventory (Spielberger et al., 1970). Mood was evaluated using the abbreviated version of Profile of Mood States (McNair, Lorr, & Droppleman, 1992) (Cronbach's alpha higher than .80).

Burden of caregivers and status of the patients. Care-giving burden (CBI) was evaluated using the Care Burden Inventory (Zarit, Reever, & Bach-Peterson, 1980) (reliability coefficient = .92). Severity and symptoms of schizophrenic relatives were evaluated by clinical staff. The EEAG (Bobes, Portilla, Bascarán, Sáiz, & Bousoño, 2002) evaluates the global functioning of psychiatric patients (reliability coefficient ranging from .69 to .91). The Spanish version of the PANSS (Peralta & Cuesta 1994) has three scales: positive, negative and general psychopathology (reliability coefficient greater than .80).

Perceived health complaints. Health status was evaluated by the revised Scale of Somatic Symptoms (RSSS) (Sandín & Chorot, 1995), referring to physical complaints (reliability coefficients from .79 to .84). The GHQ-28 was also used to evaluate psychiatric symptoms.

Table 1
Characteristics of the care recipients for HIGH-NA and LOW-NA groups. Mean ± SEM and count (%)

	HIGH-NA	**LOW-NA**
Age	35.37 ± 1.07	34.45 ± 1.58
Gender		
Male	15 (78.9%)	17 (77.3%)
Female	4 (21.1%)	5 (22.7%)
Illness duration	14.68 ± 1.24	15.32 ± 1.89
Schizophrenia subtype		
Paranoid	14 (73.7%)	13 (59.1%)
Disorganized	2 (10.5%)	4 (18.2%)
Residual	3 (15.8%)	1 (4.5%)
Undifferentiated	2 (10.5%)	4 (18.2%)
Number of hospitalizations	3.05 ± 0.87	1.45 ± 0.49

Endocrine and immunological measurements

Cortisol analysis. Cortisol levels were determined by RIA using an appropriate reactive (Spectria, Orion Diagnostica, Finland) with 1.0-nmol/l sensitivity. All samples were analysed in duplicate, including the samples of the same subject in the same assay. Saliva samples were collected within a period of two months and frozen at -20 ºC until analysis. The maximum intra- and inter-assay variation coefficient was below 7.1%.

Immunoglobulin A (IgA) analysis. Salivary collection for IgA was controlled for a 2-min period. IgA levels were determined by nephelometry using an appropriate reactive (Dade Behring, Germany) with a sensitivity of 0.08-0.14 mg/dL. The intra- and inter-assay variation coefficient below 5.1%.

Electrophysiological recording. BIOPAC System (Santa Barbara, CA) was used to measure SCL. This system was connected to a UIM100 (universal interface module) signal pre-amplifier that was connected to a computer for data acquisition (MP100) and storage (AcqKnowledge 4.2). A skin conductance module (GSR100C) amplified the electrical signal with a constant voltage circuit below 0.5 volts. Two Ag/AgCl electrodes (TSD203) were put on the middle phalanxes of the fore and ring fingers of the non-dominant hand.

Procedure

The study was conducted between 4 pm and 8 pm. After five minutes of habituation at a constant temperature (23 ºC), participants and rehabilitation staff completed a battery of questionnaires. Measurements at rest were collected by means of saliva samples for measuring cortisol (Csal 1) and immunoglobulin A (IgA 1), and the psychological states were evaluated. The first psychosocial stress period then started. Five minutes after the stress, saliva samples were collected (Csal 2 and IgA 2) and state questionnaires were completed. Saliva samples for cortisol determinations were collected 15, 30 and 45 minutes after the stress finished (Csal 3, Csal 4 and Csal 5, respectively). The second psychosocial stress period then started. Five minutes later, saliva samples were collected (Csal 6), and state questionnaires were completed. Further saliva samples for cortisol were collected 15 and 30 minutes after the stress finished (Csal 7 and Csal 8, respectively).

SCL was continuously registered five minutes before (baseline 1), during (task 1), and five minutes after the first stressor (post-task 1), and the second stressor (baseline 2, task 2, and post-task 2, respectively).

This study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

Data analysis

The sample was distributed into HIGH-NA and LOW-NA groups using Clusters analysis and forced into two clusters.

For variables measured only once, one way ANOVAs with 'group' as between subject factors and t-tests for independent samples were performed for between group comparisons, according to Levene's tests for equality of variance.

After checking for normality of data by means of Kolmogorov-Smirnov tests, cortisol levels were transformed to logarithmic data. Repeated multivariate ANOVA measurements for mood, cortisol, IgA and SCL were then carried out with 'group' as between subject factors, and 'moment' and 'stressor' (first and second stressor) as within subject factors. When initial differences between groups were found, repeated ANCOVAs measurements were performed. Contrasts were carried out *a posteriori* with repeated measurements and univariate ANOVAs, and with Bonferroni adjustments where appropriate.

All statistical procedures were performed using the SPSS 15.0 and considering $p<.05$ as significant.

Results

Checking the criterion variable

The cluster analysis resulted in two groups at the second iteration: HIGH-NA group (14 caregivers) and LOW-NA group (40 participants, including caregivers and the control group). After iterations, the centres of the final clusters were 31.79 for trait-anxiety, 8.29 for STAXI temperament, and 3.5 for depression for the HIGH-NA group; and for the LOW-NA group and the centres of trait-anxiety were 15.28, 4.78 for STAXI temperament and 0.80 for depression. The ANOVA revealed significant differences among centres of both clusters for all the variables (for all, $p<.002$).

As expected, significant differences between the three groups were found for the criteria variables (for all, $p<.0001$). In all cases, HIGH-NA group showed higher scores than the others groups (for all, $p<.0001$). No gender differences were found.

Characteristics of the sample

No significant differences among groups were found for age, BMI and distribution by gender.

Regarding palliative strategies, a significant effect of 'group' was found on cognitive coping style, $F(2, 53) = 4.17$, $p = .02$. LOW-NA caregivers was the group with highest scores in cognitive coping, significantly different from HIGH-NA caregivers and CONTROL (for both, $p<.03$), but there were no differences between HIGH-NA and CONTROL. Referring to social support, an effect of 'group' was found on instrumental, emotional, affectionate support and positive social interactions, $F(2, 53) = 3.76$, $p = .03$, $F(2, 53) = 3.56$, $p = .04$, $F(2, 53) = 3.11$, $p = .05$ and $F(2, 53) = 3.9$, $p = .03$, respectively. No significant differences between the two groups of caregivers were found, although the HIGH-NA and LOW-NA groups showed lower scores than the CONTROL group (for all, $p<.01$). No other significant differences were found.

With regards to care conditions in caregivers, no significant differences between groups were found for the years caring, time weekly caring, caregiver burden, and the severity of the symptoms and global autonomy of the patients. HIGH-NA reported a higher degree of worry about the future of the patient and suffering for the disease than LOW-NA caregivers, $t(39) = -2.45$, $p = .02$ and $t(39) = -2.15$, $p = .04$, respectively.

Perceived health

Significant effects of 'group' were obtained for anxiety and insomnia, immunological, gastrointestinal, muscular-skeletal and genitor-urinary symptoms, $F(2,53) = 7.62$, $p<.001$, $F(2, 53) = 8.52$, $p<.001$, $F(2, 53) = 7.13$, $p =. 002$, $F(2, 53) = 5.75$, $p = .006$ and $F(2, 53) = 5.16$, $p = .009$, respectively. The HIGH-NA group reported

more symptoms than the other groups in these variables (for all, $p<.05$). LOW-NA caregivers also reported more symptoms than the CONTROL group in anxiety/insomnia, immunological and gastrointestinal (for all, $p<.05$), but not in other symptoms.

Stress responses modulated by NA

Initial differences between groups were found on states of anxiety, fatigue, depression and tension, $F(2,53) = 7.97$, $p<.001$, $F(2,53) = 8.37$, $p<.001$, $F(2,53) = 4.03$, $p = .02$ and $F(2,53) = 5.83$, $p = .005$, respectively. HIGH-NA caregivers presented higher scores than CONTROLs in all scales (for all, $p<.03$), but also higher scores than LOW-NA caregivers in anxiety and fatigue (for both, $p<.05$). No other significant differences were found for pre-stress levels of cortisol, IgA and SCL.

In response to stress, no significant effects of the 'group' were obtained for levels of mood.

For cortisol levels (Figure 1), significant effects for 'stressor' and Stressor × Group interaction were found, $F(1, 51) = 15.58$, $p<.0001$, and $F(2, 51) = 4.08$, $p = .02$, respectively. In the total sample, cortisol levels were significantly higher in the first than in the second stressor ($p<.001$). Interestingly, the three groups differed significantly on Csal-7, $F(2, 53) = 4.13$, $p = .02$, levels of cortisol for HIGH-NA being significantly lower than for LOW-NA and CONTROL groups (for both, $p<.04$).

Significant effects of 'moment' and nearly significant for the Moment × Group interaction (Figure 2) were found for IgA, $F(1, 51) = 16.62$, $p<.0001$, and $F(2, 51) = 2.81$, $p = .07$, respectively, although decreases in the IgA levels were greater in the HIGH-NA than in LOW-NA group. The 'moment' factor was significant in both groups, $F(1, 13) = 12.49$, $p = .004$, and $F(1, 26) = 7.7$, $p<.01$, respectively. However, these decreases in caregivers contrast with the lack of differences found in the CONTROL group.

For SCL (Figure 3), significant effects of 'stressor', 'moment', Moment × Stressor and Moment × Group interactions were obtained, $F(1, 51) = 7.16$, $p<.01$, $F(1.39, 70.81) = 72.81$, $p<.0001$, $F(1.62, 82.81) = 13.81$, $p<.0001$, and $F(2.78, 70.81) = 3.12$, $p = .04$, respectively. The stressor was efficient in eliciting a significant response, as SCL increased significantly from the baselines to tasks and from baselines to post-task levels in both stressors in the total sample (for both, $p<.0001$), but not from task to post-task levels. Moreover, SCL was higher for the first than for the second stressor ($p<.001$). When the Moment × Group interaction was examined, no significant effect of the 'group' was found in each moment.

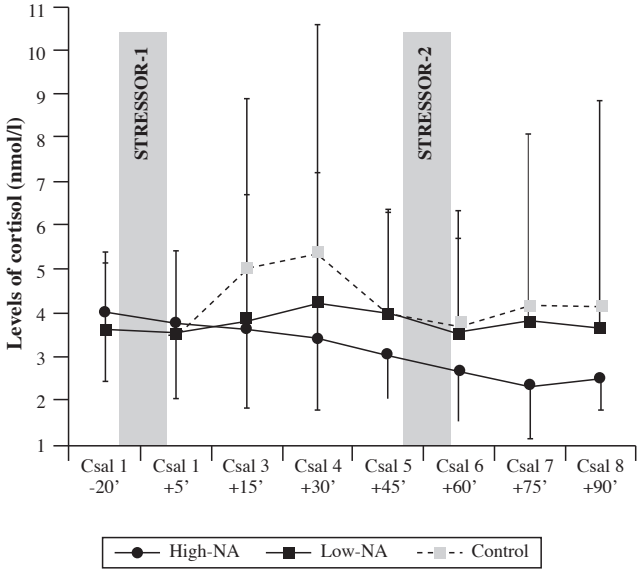

Figure 1. *Cortisol levels (mean and SEM) in both groups*

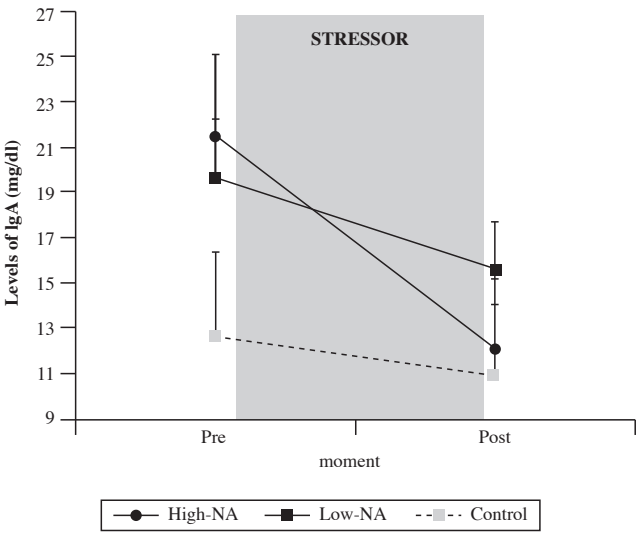

Figure 2. *IgA levels before and after the stressor in both groups*

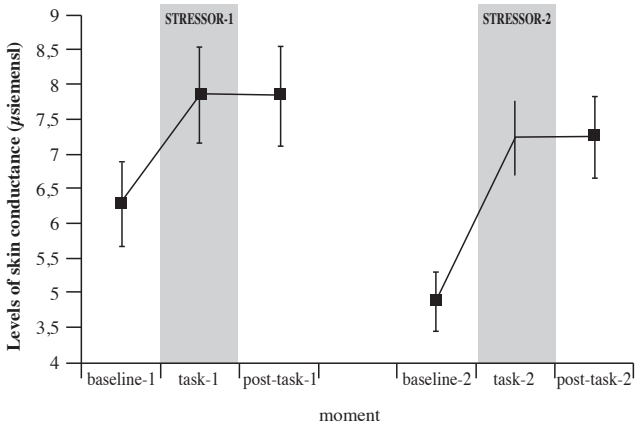

Figure 3. *SCL before, during, and after both stress episodes in the total sample*

Discussion

The results of the present study suggest that NA should be taken into account to explain individual differences in physiological responses to stress and health status in chronically stressed populations such as caregivers of schizophrenic patients. Caregivers with higher NA show worse perceived health, more worry about the care recipient, and they have lower immunological and endocrine response to stress than caregivers with low NA and the general population. Taken together, these results suggest that NA could be a potential risk factor in the interactions between chronic stress and health.

In the present study, NA is associated with a predisposition to process information from a negative point of view. HIGH-NA caregivers were more worried about the future of the patient and felt a higher degree of suffering for the disease of their relative than LOW-NA caregivers. However, they had been caring a similar number of years as the other caregivers and their care recipients were not more severe. Thus, the actual setting of care is not enough to justify these negative perceptions. Additionally, unlike the LOW-NA caregivers, they were unable to develop cognitive coping and presented similar scores to controls. In agreement with the cognitive pattern of HIGH-NA caregivers, previous studies evidence that emotion-focused coping strategies are a protective factor for higher anxiety levels in caregivers one year later (Cooper, Katona, Orrell, & Livingston, 2008). Accordingly, HIGH-NA caregivers cope with the acute stressors with worse mood than other groups, as they report greater state-anxiety and fatigue before the stress, but there are no differences after the stress. Moreover, the HIGH-NA group presents a similar reduction of social support as other caregivers, suggesting that social support is a construct more related to the caregiver role than to the NA itself.

Although it is difficult to clarify whether NA found in some caregivers is a result – or another consequence – of the caregiving process, it could be a risk factor to consider in a caregiver population, as NA has been proposed as an important predictor in disease etiology and progression via neurobiological changes that occur with emotion experiences (DeSteno, Gross, & Kubzansky, 2013). In fact, HIGH-NA caregivers reported more complaints than the other groups. Similar results have been found in parents of children with ASD (De Andrés-García et al., 2012; Lovell, Moss, & Wetherell, 2012a), although the role of NA was obviated in these studies.

In accordance with results obtained in this study, negative emotionality reduces the capability to develop adaptive physiological responses to repeated acute stress. In fact, HIGH-NA caregivers showed progressive decreases of cortisol levels that contrast with the stability shown by LOW-NA caregivers, suggesting that NA is associated with a suppression of the adaptive response of the HPA axis to repeated stressful events. These differences cannot be attributed to burden or social support, aspects associated with disturbances on the HPA axis in caregivers (Lovell, Moss, & Wetherell, 2012b), as no differences between the two groups of caregivers were found in these dimensions.

Data from healthy samples lead us to expect higher responses in higher NA individuals (Quirin et al., 2009). Contrary to the hypothesis, NA buffers cortisol response to repeated acute stress in a caregiver sample. Thus, the effect of the interactions between chronic and acute stress could be on the basis of these discrepancies. In fact, the cortisol levels displayed by HIGH-NA caregivers in this study failed to show the well-described stress-induced cortisol response (Kirschbaum et al., 1993); but they are in the range described in younger caregivers of patients with ASD after stress (De Andrés-García et al., 2012). Participants of this study were caring during a mean of 15 years and this buffered response could reflect the exposure of a prolonged period of stress, as imbalances in the adaptive response could be expected (McEwen & Stellar, 1993). Nevertheless, cortisol levels were significantly higher in the first stressor than in the second stressor, suggesting a certain degree of habituation.

Although marginally significant, caregivers with high NA also showed a greater decrease in IgA levels after acute stress than the other groups, in accordance with previous studies with caregivers (De Andrés-García et al., 2012; Lovell & Wetherell, 2011), but NA was not considered. A high NA is associated with a low antibody response after stress response in a healthy population (Marsland et al., 2001). As expected, this datum suggests that NA favours greater decreases in IgA levels after stress. However, the consideration of these results as a stress-induced immunosuppression is venturous. More measurements after stress are needed and the possible influence of salivary flow on IgA concentration must be considered. Additionally, the marginally significant result could reach statistical significance with larger samples.

Groups did not differ in SCL after acute psychosocial stress. However, stress periods were efficient for eliciting SCL responses, although results suggest some considerations. Firstly, a novelty effect is possible because SCL baseline level in the first stressor was higher than in the second stressor, indicating a certain degree of habituation pre-stress, but not during the task and afterwards – where levels are similar. Secondly, the total sample showed a lack of recovery, as levels did not return to the baseline after the stressful situation. Finally, NA does not seem to modulate SCL response in caregivers, which is not in accordance with results found in a healthy young population of non-caregivers (Hajcak, McDonald, & Simons, 2004).

This study has limitations. Firstly, the sample is biased in terms of gender, although this is an ecologically valid point because women are more involved in the care of relatives than men (Laidlaw, Coverdale, Falloon, & Kydd, 2002). Secondly, no group of controls with high NA has been used, but this fact could be considered a result itself, as only one control individual presented high NA in the initial sample. Finally, NA is a complex construct that has been differently evaluated in studies, making it difficult to establish comparisons between studies.

Despite the limitations, the present study contributes to emphasize the need to consider NA in the relationship between chronic-acute stress interaction and health from an integrative approach in future research. These results are relevant in the context of therapeutic and preventive programs to detect high risk individuals in a population that could be chronically stressed.

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