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Concise Report

Neuroendocrine–immune relationships between emotion regulation and health in patients with rheumatoid arthritis

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***Objectives*. Emotion regulation is hypothesized to be related to health through neuroendocrine–immune changes. This study examined the role of the neuroendocrine variables 24-h urinary cortisol and noradrenaline, and the immune variable serum interleukin 6 as mediators between emotion regulation styles and health (perceived health and disease activity: erythrocyte sedimentation rate (ESR) and Thompson joint score).**

***Methods*. Sixty patients with rheumatoid arthritis (mean age 59.0 ± 11.2 yr; 38 female) participated.**

***Results*. Emotion regulation was not associated with immune functioning or disease activity, but it was somewhat related to neuroendocrine functioning: one of the emotion regulation styles, ambiguity, was related to noradrenaline in women ($r = 0.39$) but not in men. The indicators of neuroendocrine functioning (cortisol and noradrenaline) were correlated ($r = 0.40$), as were indicators of immune functioning (interleukin 6) and inflammatory activity (ESR; $r = 0.53$), but analyses did not indicate a role of these physiological variables in mediating between emotion regulation and health: neuroendocrine variables were not related to interleukin 6 or ESR, and none of the physiological parameters was correlated with joint score or perceived health.**

***Conclusions*. To examine whether the proposed mediational processes apply to individual patients, a longitudinal within-subjects design is needed. In our cross-sectional study, emotion regulation was somewhat related to neuroendocrine functioning, but our study did not uncover a potential mediational role of cortisol, noradrenaline or interleukin 6 in the relationship between emotion regulation and health in rheumatoid arthritis.**

KEY WORDS: Emotions, Psychological adaptation, Alexithymia, Stress, Erythrocyte sedimentation rate, Interleukin-6, Noradrenaline, Cortisol, Psychoneuroimmunology, Rheumatoid arthritis.

Activity of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) system, which are critically involved in both psychological and inflammatory processes, may mediate bidirectional relationships between emotion regulation and the immune response and health in rheumatoid arthritis (RA) [1–3] (Fig. 1).

Emotion regulation refers to the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions [3]. Examples of emotion regulation strategies are the ability to recognize one's emotions, the intensity of emotions, and the expression or suppression of emotions. Experiencing emotions intensely and suppressing emotional experiences are suggested to be physiologically arousing [3, 4]. The resulting chronically elevated sympathetic nervous system activity may affect health, especially in a physiologically compromised system such as RA. Emotion regulation styles that are physiologically relaxing or neutral may counteract adverse health consequences [5]. A few studies suggested that emotion regulation affects neuroendocrine and immune functioning [3, 6].

Our group demonstrated relationships between emotion regulation and health in patients with RA [7]. The purpose of the present cross-sectional study was to examine the role of the physiological variables 24-h urinary cortisol, and noradrenaline and serum interleukin 6 (IL-6) as mediators between emotion regulation styles on the one hand and inflammatory activity (erythrocyte sedimentation rate, ESR), joint score and perceived health on the other.

Methods

Participants and procedure

Participants were recruited by rheumatologists and rheumatology nurses of the rheumatology divisions of seven hospitals in the Utrecht area, The Netherlands, participating in the Utrecht Rheumatoid Arthritis Cohort study group. A letter with information on the study and a questionnaire booklet were handed out to patients during their regular check-ups. Emotion regulation questionnaires were filled in by 345 patients. On average, 13

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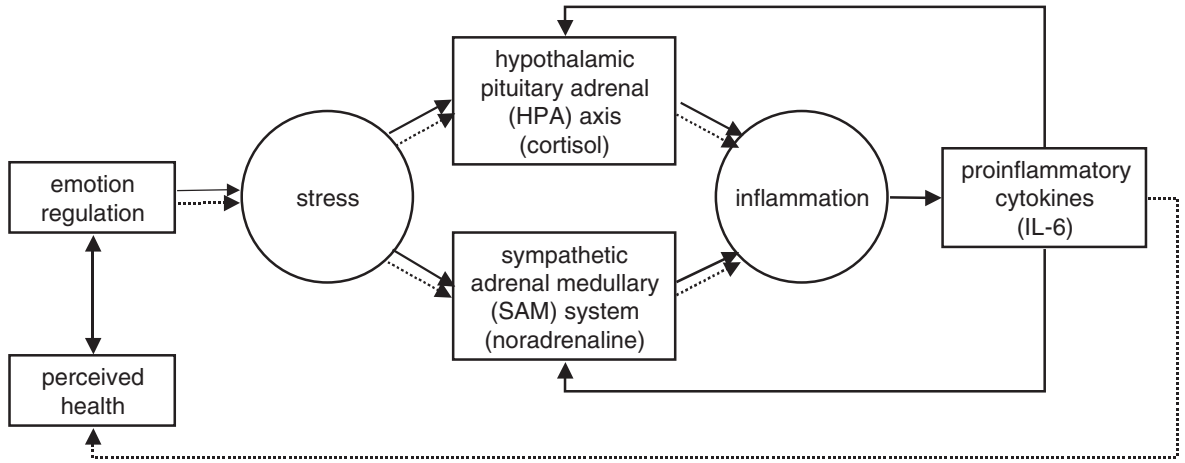

FIG. 1. Model of potential physiological mediators between emotion regulation and health. Solid lines represent positive relationships, dotted lines represent negative relationships. The hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) system are critically involved in the inflammatory process, but can also be activated by stress reactions or be down-regulated after persistent stress. Cortisol and catecholamines, including noradrenaline, are end-products of the HPA and SAM systems, respectively. Cortisol and catecholamines have shown both immunosuppressive and immunostimulating effects, depending on their concentration and receptor-binding capacity. During inflammation, proinflammatory cytokines such as IL-6 activate the neuroendocrine stress system. Proinflammatory cytokines that signal the brain may also be involved in changing how individuals perceive their health, by reducing psychological, social and physical well-being and functioning (so-called sickness behaviour).

(S.D. = 5) months later, physiological variables, inflammatory activity, joint score and perceived health were measured in 72 volunteers from among these patients at the baseline assessment before the start of a randomized controlled trial. This trial compared the effects of home-based emotional disclosure (experimental intervention) and discussion of time management (control condition). The effects of this trial will be reported in a separate paper. Patients had indicated which medication they used in the 4 weeks preceding the assessments. Twelve patients who used glucocorticoids were excluded. Data on the remaining 60 participants are analysed in the present study. The characteristics of the participants are reported in Table 1. Compared with the remainder of the 345 patients, they were characterized by less frequent use of analgesics, more frequent use of non-steroidal anti-inflammatory drugs (NSAIDs), lower scores on negative affect, and higher scores on positive affect and physical functioning. Written consent was obtained from all participants and both studies were approved by the ethical committee of the University Medical Center Utrecht.

Patients collected a 24-h urine sample, from the second void of the first day up to and including the first void of the second day, and filled in questionnaires on perceived health. On the second day in the afternoon (between 13:30 and 15:30 h), patients came to the University Medical Center Utrecht for a joint examination and to have blood drawn for cytokine and ESR assessment.

Assessments

Emotion regulation. Four psychometrically sound questionnaires were administered to assess how individuals typically respond to emotional situations: the Toronto Alexithymia Scale 20 [8], the Ambivalence over Emotional Expressiveness Questionnaire [9], the Self-Assessment Questionnaire Nijmegen [10] and the Five Expressivity Facet Scales [11]. Principal component analysis was used to summarize the 14 scales of these questionnaires into four aspects of emotion regulation [7]. 'Ambiguity' is a combination of alexithymia (difficulty identifying and describing emotions) and ambivalence on expressing

TABLE 1. Patient characteristics of 60 patients with rheumatoid arthritis

Gender (female/male)	38/22
Age: mean ± S.D. (range), yr	58.99 ± 11.2 (33–80)
Educational level (primary/secondary/tertiary)	8%/75%/17%
Disease duration: mean ± S.D.(range), yr	12.91 ± 12.0 (0.60–53)
Medication used for RA	
Analgesics	37%
Non-steroidal anti-inflammatory drugs (NSAIDs)	83%
Disease-modifying anti-rheumatic drugs (DMARDs)[a]	95%
Medication use for conditions other than RA	23%
Comorbidity	
Lung disease	3%
Cardiovascular disease	20%
Diabetes	8%
Cancer	2%
Other comorbidity	3%
Physiological parameters	
Cortisol: mean ± S.D. (range), nmol/24 h (reference data, 50–250)	108.68 ± 50.11 (4–247)
Mean noradrenaline ± S.D. (range), nmol/24 h (reference data, 90–470)	282.22 ± 108.64 (96–525)
Interleukin 6 (IL-6): mean ± S.D. (range), pg/ml	4.56 ± 2.86 (0.06–11.82)
Disease activity	
Erythrocyte sedimentation rate: mean ± S.D. (range), mm 1st h (possible range 1–140)	15.98 ± 12.36 (2–55)
Thompson joint score: mean ± S.D. (range) (possible range 0–534)	20.67 ± 30.43 (0–107)

[a]Of patients using DMARDs, 77% ($n = 44$) used MTX, 21% ($n = 12$) hydroxychloroquine, 11% ($n = 6$) sulphasalazine, 9% ($n = 5$) TNF-α blockers, 5% ($n = 3$) leflunomide, 2% ($n = 1$) intramuscular gold and 2% ($n = 1$) cyclosporine.

emotions. 'Control' reflects keeping feelings inside and trying to restrain feelings and be rational. 'Orientation' encompasses attending to and valuing emotions, and experiencing emotions intensely. 'Expression' is the expression of both negative and positive emotions towards others. The internal consistency of the styles of emotion regulation varied between $\alpha = 0.63$ for orientation and $\alpha = 0.79$ for ambiguity [7].

Neuroendocrine variables. Urine samples were processed and stored according to guidelines, with HCl added after 24-h collection for noradrenaline analyses [12]. Cortisol concentration was measured after dichloromethane extraction using an immunometric technique on an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Noradrenaline excretion was measured by standard high-performance liquid chromatography with electrochemical detection (HPLC-ECD). Output (in nmol/24 h) was corrected for urinary volume.

Immune variable. Serum levels of IL-6 were determined using a high-sensitivity enzyme-linked immunoabsorbent sandwich assay (R & D Systems, Minneapolis, MN, USA). One value of IL-6 was lower than the detection limit (0.06 pg/ml). This missing value was set to the detection limit value.

Disease activity. ESR was assessed by the method of Westergren. The Thompson joint score [13] was calculated from tender and swollen joint counts.

Perceived health. Four psychometrically sound self-report questionnaires were administered: the shortened Profile of Mood States [14], the Impact of Rheumatic diseases on General health and Lifestyle [15], the Health Assessment Questionnaire [16] and the Rheumatoid Arthritis Disease Activity Index [17]. Principal component analysis on the 16 scales of these instruments indicated five aspects of perceived health [7]: 'negative affect' (depressed and tense mood), 'positive affect' (energetic and cheerful mood), 'social functioning' (actual and perceived social support), 'physical functioning' [self-care, disability (reversed sign) and mobility] and 'disease activity' (pain and self-assessed disease activity). The internal consistency of these components varied from $\alpha = 0.59$ for social functioning to $\alpha = 0.91$ for negative affect and disease activity [7].

Statistical analysis

One instance of incomplete urine collection was treated as a missing value. A single extreme outlier on cortisol output and one on joint score were replaced by the value 2.5 S.D. above the mean. All variables showed normal to nearly normal distributions (highest skewness value for Thompson joint score, 1.63). Parametric analyses were performed. Transforming the variables logarithmically or using non-parametric statistics did not significantly change the results.

Pearson correlation coefficients between the variables of emotion regulation, physiology and health were calculated. For significant associations between emotion regulation and health (disease activity and perceived health), we used common methods to test whether these associations were mediated by physiological variables. To take account of multiple testing, the Bonferroni criterion was used: the standard α level of 0.05 was divided by the number of correlations per research question.

Independent sample *t*-tests (for dichotomous variables) or correlations were used to find which demographic or disease-related variables (sex, age, disease duration, comorbidity and medication use) were related to emotion regulation, physiology and health. In *post hoc* covariance analysis, partial correlations adjusted for potentially confounding covariates were computed. SPSS 11.5 was used.

Results

Relationships of emotion regulation with physiology

Ambiguity ($r = 0.40$, $P = 0.002$), orientation ($r = -0.44$, $P < 0.001$) and expression ($r = -0.30$, $P = 0.023$) were correlated with noradrenaline output. After Bonferroni correction, the association between expression and noradrenaline was no longer significant. Emotion regulation was not significantly correlated with cortisol or IL-6.

Mutual relationships between physiological variables. The two neuroendocrine measures cortisol and noradrenaline were significantly correlated ($r = 0.40$, $P = 0.002$), but did not correlate with IL-6 ($r = -0.01$ and $r = -0.05$, respectively).

Relationships of physiology with health. Cortisol and noradrenaline were not significantly correlated with ESR ($r = -0.04$ and $r = -0.19$, respectively), but IL-6 was ($r = 0.53$, $P < 0.001$). None of the physiological parameters was related to the joint score ($r = -0.02$, -0.08 and 0.02, respectively). A significant correlation between noradrenaline and social functioning ($r = -0.32$, $P = 0.014$) became non-significant after Bonferroni correction. All other correlations were not significant.

Physiological mediation. Because emotion regulation was not correlated with ESR and joint score, and the physiological parameters were not related to perceived health, it was not applicable to examine potential physiological mediators between emotion regulation and health.

Post hoc covariance analyses. After adjusting for the covariates sex, age and use of NSAIDs, correlations between emotion regulation and physiology remained in the same direction but became lower. The correlation between ambiguity and noradrenaline became $r = 0.26$ ($P = 0.057$) and that between orientation and noradrenaline became $r = -0.21$ ($P = 0.119$). Sex was predominantly responsible for this weakening effect. Men were higher on ambiguity, lower on orientation and higher on noradrenaline than women. Ambiguity was correlated with noradrenaline in women ($r = 0.39$) but not in men ($r = 0.03$), while men and women did not differ in correlations of orientation and noradrenaline ($r = -0.21$ and -0.19, respectively).

Discussion

Although the joint regulatory activation of the HPA and SAM systems by corticotrophin releasing hormone was reflected by a mutual association of noradrenaline and cortisol output, emotion regulation showed a moderate association with noradrenaline only. The association between ambiguity and noradrenaline is in agreement with inhibition theories stating that keeping emotions inside requires physiological work [4], and with empirical findings showing associations of the related constructs suppression and alexithymia with higher basal neuroendocrine levels and blood pressure [18, 19]. Ambiguity and noradrenaline were only related in women. Prospective research should examine the suggestion that frequent use of ambiguity as the emotion regulation style could be unhealthy in the long run in women with RA.

The moderate association of orientation with lower noradrenaline does not support the hypothesis that experiencing emotions intensely is associated with physiological hyperarousal [4]. The association largely reflects the higher noradrenaline and lower orientation scores in men than in women. Although not significant after Bonferroni adjustment, the association of expression with lower noradrenaline output is in agreement with physiological relaxation theories proposing that expressing feelings has a physiological effect through resolution of inhibition or through stress reduction [4, 5].

The proinflammatory cytokine IL-6 and the inflammation indicator ESR were highly correlated. IL-6 is a potent activator of the HPA axis [20], but in our study cortisol and noradrenaline

output levels were not related to serum IL-6 or ESR, perhaps because we used 24-h measures of neuroendocrine functioning while IL-6 was tested at a single time point. Although neuroendocrine–immune correlations have been reported in RA [e.g. 21], our results agree with studies finding no relation between neuroendocrine functioning and IL-6 [22] or ESR [23]. Perhaps in established RA, the SAM system loses control of the immune system and inflammation [2] and HPA system activity is too low for the degree of inflammation [24]. Acknowledging the methodological limitations of our study, deficient neuroendocrine–immune communication might explain our observation of limited association between emotion regulation and the disease process in RA.

Proinflammatory cytokines such as IL-6 are suggested to trigger a reduction in psychological, social and physical well-being [25], but our study did not find a correlation between IL-6 and perceived health. Because of individual differences in adaptation to the disease, perceived health may have become independent from physiological changes associated with repeated inflammation.

Styles of emotion regulation were related to perceived health but not to disease activity. Since cortisol, noradrenaline and IL-6 were not related to perceived health, the examination of a mediational model made no sense. Our study did not provide a single indication for physiological mediation of the relationship between emotion regulation and health.

A limitation of our study is the relatively small sample size. Consequently, we were unable to test a full model at once, controlling for the other variables and directions of relationships. Although emotion regulation styles are considered and proven stable characteristics of individuals [11], we cannot fully rule out the possibility that the long time interval between the self-report and physiological measures hampered our test of the mediational hypothesis. Another restriction is that our cross-sectional study examined individual differences. Beside the present condition and medication, past inflammatory and psychosocial stress will have determined whether specific physiological, and perhaps psychological, response systems have become up-regulated or down-regulated. We cannot generalize beyond our cross-sectional design to processes in individual patients. For this, our results need confirmation in a longitudinal within-subjects design. A final restriction is that our conclusion relates to patients with RA who receive common medication that might affect physiological responding.

To conclude, our cross-sectional study did not uncover a potential mediational role of cortisol, noradrenaline or IL-6 in the relationship between emotion regulation and health in RA. We found a moderate association between emotion regulation and neuroendocrine functioning, as well as an association between immune activation and inflammatory activity, but the psychological–neuroendocrine and the immune–inflammatory systems were not related, and were mostly unrelated to health.

Rheumatology	Key messages
	• Although emotion regulation is suggested to be somewhat related to neuroendocrine functioning and immune functioning is associated with inflammatory activity, no neuroendocrine–immune mediation between emotion regulation and health was indicated.

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