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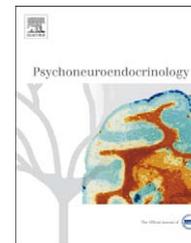
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# Rejection sensitivity relates to hypocortisolism and depressed mood state in young women

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## KEYWORDS

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Cortisol awakening  
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Hypocortisolism;  
Rejection sensitivity;  
Fear of social  
evaluation;  
Atypical depression

## Summary

Rejection sensitivity and the associated fear of negative social evaluation (FNSE) trait are characteristics of hypocortisolemic syndromes such as atypical depression. However, a meta-analysis showed that acute FNSE evokes strong cortisol responses in humans. This is consistent with suggestions that hypocortisolism reflects a protective adaptation to a history of high cortisol responses. This leads us to hypothesize that measures of trait FNSE relate to hypocortisolism. Moreover, because FNSE relates positively to depressed mood state, but negatively to cortisol, we expect that the positive relationship between depressed mood state and cortisol will show up most clearly when controlling for the confounding effect of FNSE on this relationship. In the present study we measured salivary cortisol awakening response and psychological variables in 194 community women aged 18–30 years. The results confirmed our hypotheses. We propose that dispositional FNSE is associated with a history of frequent high cortisol responses, leading to long-term protective inhibition of further cortisol and energy mobilization. The present results have special relevance for mental health problems that have high prevalence among young women.

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## 1. Introduction

The hormone cortisol has a wide range of physiological functions, including the mobilization of resources and

stress-protective down-regulation of other physiological systems (Sapolsky et al., 2000). Both chronically high and low cortisol levels may relate to mental and physiological health. Low cortisol levels or hypothalamus–pituitary–adrenal (HPA) hypoactivity have been found in syndromes like atypical depression, post-traumatic stress disorder (PTSD), fibromyalgia, burnout, chronic fatigue syndrome (CFS), psychosomatic disease, low back pain, irritable bowel syndrome, and alexithymia (Gold and Chrousos, 1998; Heim et al., 2000; Fries et al., 2005). These findings seem puzzling in light of the common occurrence of elevated cortisol levels during stress and melancholic depression (Gold and Chrousos, 1998). The hypocortisolemic disorders are usually defined by accentuating one of the symptoms of high stress sensitivity, fatigue, and pain (Wessely et al., 1999; Fries et al., 2005). Although much is unknown about the meaning and nature of HPA axis alterations in these syndromes, the high comorbidity and overlap between these syndromes that has been found in large community samples, reviews and meta-analyses, have led to the hypothesis that they share a common physiological pathway (Wessely et al., 1999; Aaron and Buchwald, 2003; Henningsen et al., 2003; Fries et al., 2005; Aggarwal et al., 2006; Arguelles et al., 2006; Kato et al., 2006; Schur et al., 2007). For the present purposes, we will refer to these disorders as “hypocortisolemic syndromes”.

Atypical depression and other hypocortisolemic syndromes that are accompanied by fatigue, pain, and anxiety have a higher prevalence in premenopausal women compared to men (Wilhelm and Parker, 1994; Antonijevic, 2006; Halbreich and Kahn, 2007). In a recent study of 1718 adolescent boys and 1749 adolescent girls from a healthy population, severe fatigue lasting for  $\geq 1$  month was observed in 16.4% of the total sample of girls and in 4.0% of the boys (ter Wolbeek et al., 2006). In both girls and boys, the duration of fatigue was positively related to severity of comorbid depression and anxiety symptoms, and the number of hypocortisolemic syndrome-related symptoms. In their work, ter Wolbeek et al. (2006) suggest that in girls a “higher sensitivity in stimulus processing” develops during adolescence. In the current paper, which describes a study of young adult women from a healthy population, we will argue that this higher sensitivity is, in fact, higher rejection sensitivity. This higher rejection sensitivity is often found in individuals with hypocortisolemic syndromes such as atypical depression.

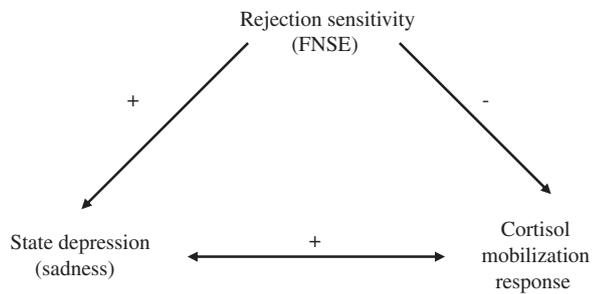
Atypical depression is characterized by fatigue, leaden paralysis, hypocortisolemia, increased appetite, and increased sleep drive (Gold and Chrousos, 1998; Antonijevic, 2006), as well as by rejection sensitivity (Parker et al., 2002; Parker and Crawford, 2007). A recent reappraisal of atypical depression features stressed the importance of rejection sensitivity and lifetime panic disorder and social phobia (Parker et al., 2002). Recent studies suggest that among premenopausal women with major depression, atypical features may be quite typical (Antonijevic, 2006). Similarly, a short-term longitudinal study of adolescents found that rejection sensitivity accounted fully for the sex difference in depression (Rudolph and Conley, 2005). Moreover, it has been suggested that patients with atypical depression-like syndromes could represent the tip of an iceberg, and many patients who complain of fatigue and many aches and pains

could have an underlying problem similar to that in atypical depression without meeting standard diagnostic criteria for this disorder (Gold and Chrousos, 1998).

Rejection sensitivity and the associated fear of negative social evaluation (FNSE) trait are characteristics of hypocortisolemic syndromes such as alexithymia (Suslow et al., 2000), PTSD (Posternak and Zimmerman, 2002), and are even central to social phobia and atypical depression (Posternak and Zimmerman, 2002; Harb et al., 2002; Parker et al., 2002). However, according to a meta-analysis (Dickerson and Kemeny, 2004), acute FNSE evokes strong and consistent cortisol responses in humans. Assuming that trait FNSE is associated with a history of high cortisol responses, these findings can be reconciled by the proposal that hypocortisolemia reflects a protective response following on a history of repeated high cortisol responses (Fries et al., 2005). Indeed, one of the most robust findings of a meta-analysis of relationships between chronic stress and cortisol levels in humans was that time since stress onset was negatively associated with HPA activity (Miller et al., 2007). Compatible with this, in a prospective study the initial hypercortisolemia of sexually abused children relative to controls changed to hypocortisolemia starting at around the age of 15, and reaching significance at about 18–20 years (Putnam, 2007).<sup>2</sup> Indeed, in healthy university students, the number of adverse life events predicted low cortisol responses to a psychosocial stress task (Elzinga et al., 2008). Also, in a large community sample self-reported chronic stress was associated with the atypical depression symptoms fatigue, hypersomnia, increased appetite, but less so with sadness (Keller et al., 2007). This leads us to hypothesize that measures relating to trait FNSE, due to a history of chronic stress, relate to hypocortisolemia; this despite positive relations between such measures and depressed mood state, and between depressed mood state and cortisol levels (see Figure 1).

In the present study, we measured the cortisol awakening response, which is the increase in cortisol concentration that typically takes place in the 20–45 min after waking up in the morning, and is usually assessed with saliva samples. The magnitude of awakening response is positively associated with levels of general chronic stress, work stress, and depression. For instance, an increased awakening response was found in unmedicated acutely depressed patients (Bhagwagar et al., 2005). However, attenuated awakening responses have been described in people suffering from non-melancholic (probably atypical) depression (Huber et al., 2006), CFS (Roberts et al., 2004), and PTSD (Wessa et al., 2006), and in relation to momentary symptom severity in clinical burnout (Sonnenschein et al., 2007). The cortisol awakening response has been positively associated with prior-day feelings of loneliness, sadness, threat, and lack of control, and negatively with same-day levels of fatigue, somatic symptoms (Adam et al., 2006), and positively with same-day number of positive social contacts (Stetler and Miller, 2005). It has been hypothesized that the awakening

<sup>2</sup>Interestingly, childhood physical, and especially sexual abuse, appears to be more common among hypocortisolemic syndrome patients (Wessely et al., 1999), and rejection sensitivity mediated the relationship between childhood sexual abuse and later depressive symptoms (Luterek et al., 2004).



**Figure 1** Visualization of how we hypothesize that variables are related to each other. We hypothesize that trait FNSE relates to low cortisol mobilization (= awakening) responses and to high depressed mood state (sadness). We expect a positive relationship between depressed mood state and cortisol. Because trait FNSE relates positively to depressed mood state, but negatively to cortisol, we expect the positive relationship between depressed mood state and cortisol will show up most clearly when controlling for the confounding effect of FNSE on this relationship. The figure displays directional arrows because we assume that trait measures (e.g. FNSE) are more likely to influence state measures (depressed mood state and, partly, cortisol mobilization response) than the other way around. FNSE, fear of negative social evaluation.

response reflects a mobilization of energy resources and enhancement of arousal, to meet the anticipated demands of the upcoming day (Schulz et al., 1998; Buijs et al., 2003; Adam et al., 2006). Indeed, it is larger on working days than weekend days (Kunz-Ebrecht et al., 2004). Even though inconsistent results regarding the cortisol awakening response exist (e.g. Mommersteeg et al., 2006) and its physiological mechanism is still unknown, indications that it reflects mobilization of energy resources and enhancement of arousal to meet upcoming demands, suggest that this measure of HPA axis regulation may be sensitive to complaints such as fatigue and low arousal that characterize atypical depression. To stress this interpretation of the cortisol awakening response, we will refer to it as a “cortisol mobilization” response.

In contrast of the association of complaints of fatigue and low arousal with low cortisol mobilization, acute depressed mood state (i.e. sadness) may relate to increased cortisol mobilization (Bhagwagar et al., 2005; Adam et al., 2006). This converges on our hypotheses that characteristics of atypical depression may relate to low cortisol mobilization, whereas depressed mood state may relate to high cortisol mobilization. Atypical depression, although also associated with depressed mood state, is associated relatively strongly with fatigue and low arousal, whereas melancholic depression is more strongly associated with increased arousal and depressed mood state (Gold and Crousos, 1998). Moreover, both in a large community sample and when analyses were restricted to those meeting DSM-III-R diagnostic criteria for major depression, fatigue and low arousal related to chronic stress, while sadness and increased arousal related to other, more acute adverse life events (Keller et al., 2007). These differences between atypical depression and melancholic depression may be involved in

associations with hypocortisolism and hypercortisolism, respectively (Gold and Crousos, 1998).

We derived our hypotheses partly from results from studies of healthy populations (e.g. Adam et al., 2006) in which complaints and underlying problems similar to atypical depression may be prevalent (Gold and Crousos, 1998; ter Wolbeek et al., 2006), and will test our hypotheses in a healthy population. However, we explained that the mechanisms under study might be relevant to clinical depression, too. Studying associations between traits, symptoms and cortisol in a community sample may increase our knowledge of possible pathophysiological processes involved in depressive disorders and sub-clinical symptoms of depressive disorders.

To summarize, we hypothesize that trait FNSE questionnaire scores relate to low cortisol mobilization responses and to high depressed mood state. We expect a positive relationship between depressed mood state and cortisol mobilization. Moreover, because trait FNSE relates positively to depressed mood state, but negatively to cortisol mobilization, we expect that the positive relationship between depressed mood state and cortisol will show up most clearly when controlling for the confounding effect of FNSE on this relationship (see Figure 1).

## 2. Methods and materials

### 2.1. Subjects

This study is part of a larger project named Twin Interdisciplinary Neuroticism Study (TWINS) in which the genetic and environmental origins of neuroticism and related endophenotypes are explored. The sample for the TWINS study was selected from the recently established Groningen Twin Register. In total 125 female twin pairs aged 18–30 years participated in the study. See Table 1. The Ethics Committee of the University Medical Center Groningen approved the study, and all subjects gave written consent prior to participation. Additional information about participants and procedures has been presented elsewhere (Riese et al., 2006).

**Table 1** Descriptives of the participants ( $n = 194$ ).

	Mean	(SD)
Fear of negative social evaluation (FNSE)	8.3	(2.3)
Depressed mood state	0.9	(1.9)
Age (years)	23.5	(3.5)
Body mass index ( $\text{kg}/\text{m}^2$ )	23.0	(3.9)
Current smokers (%)	22.6%	
Saliva cortisol at	Mean	Mean
	sampling	cortisol (SD)
	time (SD)	in nmol/l
Awakening	640 h (35)	9.3 (5.3)
Awakening+30 min	711 h (34)	17.7 (7.8)
Awakening+45 min	726 h (35)	20.0 (8.7)
Awakening+60 min	741 h (35)	20.4 (8.5)

## 2.2. Procedure

Subjects were contacted by phone to set an appointment for a visit to our laboratory for psychophysiological testing (3–3.5 h) for the TWINS. During this phone call, among other instructions, verbal instructions were given for cortisol sampling. Subjects were requested to refrain from intense physical exercise on the day preceding the laboratory visit until arrival in our lab. In addition, subjects refrained from eating, drinking and smoking after 22:00 h the day preceding the laboratory visit until arrival in our laboratory. Salivettes for saliva collection were sent to the subject's home address accompanied with a written instruction. Subjects recorded the actual times saliva collection took place, and indicated any deviations from the instructions. Breakfast was served upon arrival in our laboratory.

## 2.3. Saliva sampling

The subjects collected four morning saliva samples at home using the Sarstedt Salivette sampling device (Sarstedt, Rommelsdorfer Str, D-51588 Nümbrecht, Germany). The first morning sample was collected immediately after waking up (still lying in bed), and subsequently 30, 45, and 60 min post-awakening. Since participants arrived approximately at 830 h at our laboratory, the sampling-time variation of the morning samples was limited. On average the first sample was taken at 639 h, the second at 709 h, the third at 725 h, and the fourth at 739 h.

Subjects were instructed to brush their teeth after they had collected the last saliva sample. Saliva samples were transported to our laboratory by the subjects. Immediately, saliva was extracted from the salivettes and stored at  $-20^{\circ}\text{C}$  until analysis. Cortisol concentration was determined in one batch at the Department of Bindingsanalyse, University Medical Center Groningen. Cortisol concentration was determined by an in-house developed radio immuno assay. The intra-assay coefficient of variation was between 4.1% and 8.2%, and the corresponding inter-assay coefficient of variation was between 5.6% and 12.6%.

## 2.4. Questionnaires

**FNSE:** We used the total score of four items with clear FNSE content from the Interpersonal Sensitivity Measure, a questionnaire that has been constructed to discriminate and predict atypical from typical depression (Boyce and Parker, 1989), as our measure of trait FNSE (range: 4–16). The four items that we judged to be related to sensitivity to negative social evaluation (see also Harb et al., 2002): "If someone is critical of something I do, I feel bad", "I always expect criticism", "My value as a person depends enormously on what others think of me", and "I care about what people feel about me". The items were completed on a 4-point Likert-type scale with the following anchors: "1 = very unlike me", "2 = moderately unlike me", "3 = moderately like me", "4 = very like me". The Cronbach's alpha measure of internal consistency was 0.77.

**Depressed mood state:** The Profile of Mood States (POMS) 32-item short version (Wald and Mellenberg, 1990) was filled out by the participants after a short acclimatization period

upon arrival in the laboratory. Subjects indicated on a Likert-type scale (0–4) to which extent an adjective described their mood at that moment. The POMS consists of five sub-scales: fatigue, vigor, depression, anger, and tension, and has been translated and validated for a Dutch population. For the present study the depression sub-scale (range: 0–32) was used to assess depressed mood state. Since the raw depression scores did not follow a normal distribution, the scores were ln-transformed twice, to better approximate a normal distribution. Repeating all analyses with the raw depression scores gave highly comparable findings, which would have led to the same conclusions as currently formulated. Cronbach's alpha of POMS depressed mood state was 0.79.

## 2.5. Cortisol data cleaning

In total 250 subjects were asked to collect the saliva samples. However, three subjects did not return their salivettes, and 10.9% of the salivettes did not contain enough saliva for cortisol determination, leading to the loss of 39 additional subjects. The quality of the data set was assured by exclusion of (1) six subjects using corticosteroid-containing medication; (2) excluding cortisol values (three subjects) that were 3SD above the mean for each time point to reduce the impact of outliers; (3) non-compliance to the protocol was defined as failing to take a saliva sample within 30 min of the requested sampling time, and resulted in removing one sample and thus one subject. All other saliva samples were reported to be taken within 15 min of the requested sampling time, except for one sample that was taken 17 min past the requested sampling time of 60 min after awakening. After these procedures, data of 198 subjects were left for inclusion in the analyses.

Of the 198 subjects, for 178 (89.9%) subjects the cortisol mobilization response was positive (increased after awakening), for 20 (10.1%) it was negative (decreased after awakening). In our study, the percentage subjects with a positive cortisol mobilization response is comparable to percentages reported by others (76.8% (Wüst et al., 2000) and 89% (Kupper et al., 2005)). All analyses were performed twice, once using the total data set and once after excluding subjects with a negative cortisol mobilization response. Because the present results were similar and significant with both selection procedures, we present the results using the total data set.

We calculated the "area under the curve with respect to increase" (AUC<sub>i</sub>, a measure of time-dependent change, in this case the cortisol awakening/mobilization response) (Pruessner et al., 2003). The reported sample times of individual subjects were used in the calculations. After removing values that deviated more than 3SD from the mean 195 AUC<sub>i</sub> values were available for analyses and followed a normal distribution.

## 2.6. Statistical analysis

One subject was excluded from all analyses because she failed to correctly fill out the FNSE. This means that 194 subjects were included in the final analyses. Age, body composition, smoking habits, phase of reproductive cycle,

oral contraceptive use, and sleep quality potentially influence cortisol measures (Kupper et al., 2005). In our data set, AUCi was affected by oral contraceptive use, smoking status (yes/no), and body mass index (BMI) and were regressed out in SPSS (Version 12.0.2). Data were analyzed with a series of multivariate linear regression analyses using the software package STATA (version 8.2). To control for the dependency of the data from two individuals of one twin pair, twins were clustered in STATA such that observations within a twin pair were treated as non-independent, and the twin pair themselves as independent (Froot, 1989). The cortisol AUCi was predicted in a linear regression model with FNSE and depressed mood state entered simultaneously as predictors. To test assumptions of linear regression analysis, scatter plots of AUCi and depressed mood state or FNSE against each other did not suggest that there were non-linear relationships between the variables. Checking the residuals of the regression analysis showed that they were close enough to normality to presume the assumptions were not violated; skewness = 0.30, kurtosis = 3.13. To test if FNSE was a confounder of the prediction of cortisol AUCi by depressed mood state, we employed an intervening variable test (Freedman and Schatzkin, 1992).

### 3. Results

Table 1 displays descriptives of the 194 subjects. Scores on FNSE correlated positively with depressed mood state ( $r = 0.43, p < 0.001$ ). The correlations between questionnaire scores and cortisol AUCi, and partial correlations after partialling out either FNSE or depressed mood state, are shown in Table 2. Table 3 shows the results of the regression analysis predicting AUCi, with FNSE and depressed mood state simultaneously entered as predictors ( $F(2, 111) = 8.09, p < 0.001, R^2 = 0.09$ ). As hypothesized, FNSE scores related to low cortisol mobilization responses (AUCi). Depressed mood state related positively to AUCi, but only with FNSE included in the model. This last effect is consistent with

FNSE being a negative confounder of the association between depressed mood state and cortisol mobilization (Figure 1). A negative confounder is a variable that has opposite sign correlations with a dependent and independent variable, and when included in the regression, increases the predictive validity of the independent variable (Figure 1; MacKinnon et al., 2000). We propose that the trait measure FNSE is a negative confounder of the depressed mood state and cortisol AUCi relationship (Figure 1).

To test the significance of this confounding effect, i.e. to test if FNSE significantly decreased or abolished the prediction of cortisol AUCi by depressed mood state scores, we employed a confounding variable test (Freedman and Schatzkin, 1992; MacKinnon et al., 2000). FNSE proved to be a significant negative confounder of the prediction of AUCi

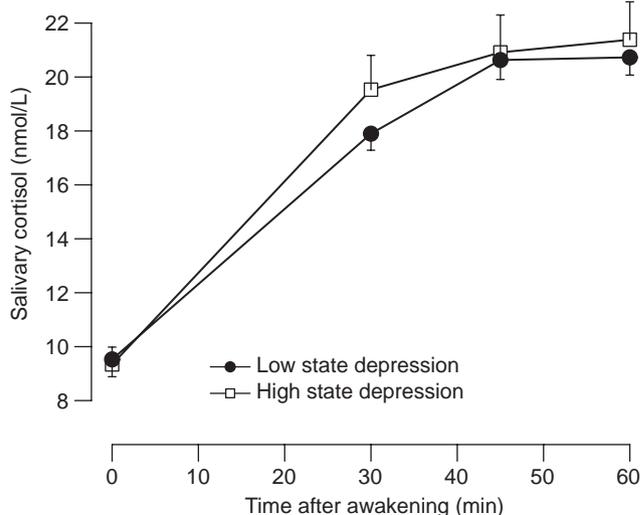


Figure 2 Patterns of early morning saliva cortisol levels of subjects scoring high vs. low on depressed mood state. For illustrative purposes only, low- and high-scoring groups were created based on median split on the psychological variable. Error bars represent standard errors.

Table 2 Partial correlations between questionnaire scores and cortisol AUCi.

	AUCi	AUCi controlled for FNSE	AUCi controlled for depressed mood state
FNSE	-0.22*		-0.26*
Depressed mood state	0.08	0.17*	

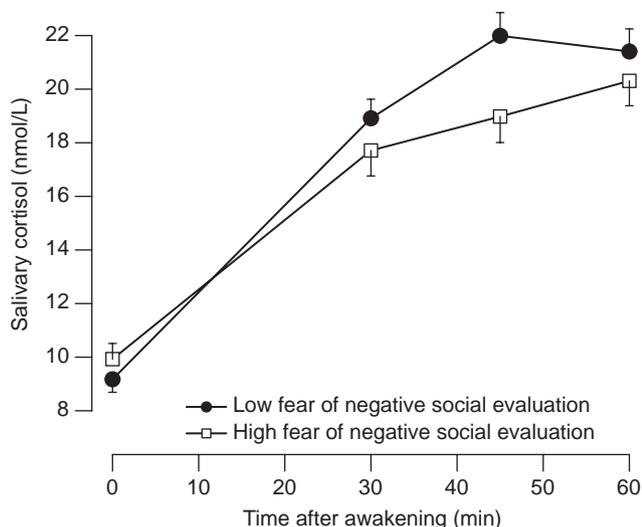
Oral contraceptive use, smoking, and body mass index were regressed out of the cortisol AUCi;  $n = 194$ .

\* $p < 0.05$ .

Table 3 Regression analysis predicting cortisol AUCi.

	Depressed mood state				FNSE			
	B	Robust SE	t-Value	p-Value	B	Robust SE	t-Value	p-Value
AUCi	33.76	15.31	2.21	0.03	-42.15	10.76	-3.92	0.000

Oral contraceptive use, smoking, and body mass index were regressed out of the cortisol AUCi;  $n = 194$ .



**Figure 3** Patterns of early morning saliva cortisol levels of subjects scoring high vs. low on fear of negative social evaluation. For illustrative purposes only, low- and high-scoring groups were created based on median split on the psychological variable. Error bars represent standard errors.

by depressed mood state scores ( $t(193) = 3.24, p < 0.01$ ). Figures 2 and 3 show the pattern of early morning saliva cortisol levels of subjects scoring high vs. low on FNSE, respectively, of subjects scoring high vs. low on depressed mood state.

To test for possible relationships between the psychometric variables FNSE and depressed mood state, and the sample times (and intervals between samples) their correlations were calculated. Correlations were between  $-0.09$  and  $0.11$  and not significant ( $0.13 < p < 0.99$ ). Including the sample time variables as predictors in the reported regression analyses did not change results.

#### 4. Discussion

As hypothesized (Figure 1), FNSE scores related to high depressed mood state and low cortisol mobilization response. Depressed mood state related positively to cortisol mobilization response, but only with FNSE included in the model. FNSE proved to be a significant negative confounder of the prediction of cortisol mobilization response by depressed mood state scores: because FNSE is associated with higher depressed mood state and lower cortisol mobilization response, the positive association between depressed mood state and cortisol mobilization response only showed up after controlling for the variance associated with FNSE. Although the proportion of variance in cortisol explained by FNSE and depressed mood state was small, the relationships may be informative about underlying physiological mechanisms. Moreover, since repeated measurements would have increased the trait proportion of the cortisol mobilization response (Hellhammer et al., 2007), the present study which employed single-day assessments is likely to underestimate the association between the trait FNSE measure and the trait-related proportion of the

cortisol mobilization response. Even though based on subjects from a healthy population, the results support our proposal that FNSE may mediate relationships between atypical depression and hypocortisolism.

It has been suggested that people with hypocortisolemic syndrome-related symptoms could have an underlying problem similar to that in atypical depression without meeting diagnostic criteria for this disorder (Gold and Chrousos, 1998), and such symptoms are prevalent among young women in a population cohort (ter Wolbeek et al., 2006). Starting from this premise, the present results from a population cohort may be relevant for atypical depression and its relationship to social anxiety. In women specifically, social anxiety, atypical depression, and other hypocortisolemic syndromes mentioned in Introduction, are highly comorbid (Aaron and Buchwald, 2003; Halbreich and Kahn, 2007). In a factor analysis by Harb et al. (2002), the factor accounting for the largest portion of variance of increased Interpersonal Sensitivity Measure scores in social phobics was an 11-item factor they called interpersonal worry and dependency. Three of our four FNSE items are among the four top-loading items of this factor. This is consistent with the high comorbidity between atypical depression and social phobia, and the importance of rejection sensitivity in both; in fact, the boundaries between social phobia and atypical depression are not clear (Katschnig, 1996; Parker et al., 2002; Posternak and Zimmerman, 2002). The two related syndromes may share a mechanism that relates rejection sensitivity to cortisol regulation.

The interrelationship between atypical depression and social anxiety may be an example of the dynamics we addressed in the present study. As we discussed, low cortisol mobilization in syndromes characterized by rejection sensitivity (e.g. atypical depression) may reflect a protective adaptation to a history of repeated high cortisol responses to social evaluative threat (i.e. social anxiety). This means that atypical depression and social anxiety may be two sides of the same coin. Symptoms of atypical depression and social anxiety may be in a constant flux reflecting context-dependent dynamics between social arousability and stimulus processing sensitivity (i.e. rejection sensitivity) on the one hand, and contingent changes in threshold of protective inhibitory responses on the other hand. Indeed, anxiety disorders often precede the onset of major depression, specifically atypical depression in women at younger ages (Halbreich and Kahn, 2007). Similarly, both in a large community sample and when the sample was restricted to those meeting DSM-III-R diagnostic criteria for major depression, chronic stress was related to the atypical depression symptoms fatigue, hypersomnia, and increased appetite (Keller et al., 2007). Although at this point our proposal is speculative, it is in line with proposals based on animal research (Porges, 2001; McEwen and Wingfield, 2003).

McEwen and Wingfield (2003) offer a somewhat similar explanation of hypocortisolism in their theory of allostatic overload. According to this theory, when a negative energy balance and cortisol increases pass a threshold, they trigger an emergency survival mode such that a positive energy balance is regained, and cortisol secretion is reduced to avoid deleterious effects of chronic hypercortisolism and arousal. The cortisol mobilization response may be

a sensitive measure of dynamics between social anxious arousability and atypical depressive inhibition of arousal and energy mobilization, as it appears to reflect both the accumulation of arousal and allostatic load, and the subsequent protective inhibitory response of low cortisol and energy mobilization: the cortisol mobilization response has been positively associated with prior-day feelings of loneliness, sadness, threat, and lack of control, and negatively with same-day levels of fatigue and somatic symptoms (Adam et al., 2006).

Similarly, Porges (2001) explains the low levels of cortisol in some social and affective disorders within the context of his polyvagal theory. According to the theory, when mobilization strategies (fight-flight behaviors) are ineffective in removing the individual from the stressor and modulating stress, then the nervous system may degrade to a phylogenetically earlier level of organization. Thus, low cortisol or a hyporesponsive HPA axis may reflect a neural strategy associated with disengagement (e.g. dissociative states) and conservation of metabolic resources (Porges, 2001).

#### 4.1. Limitations and future research

Only young women were included in this study. Using such a homogenous population has its benefits since the results cannot be confounded by gender and/or a wide age range. However, it will be necessary to find out if the same relationships are present in older female, and in male subjects, because sex differences are likely in the variables we have studied. Although our data suggest mechanisms that may be operative both at sub-clinical and clinical levels, we studied only healthy subjects from a community sample. Future studies need to determine if the present findings generalize to clinical populations. Future studies may also study the developmental patterns in the relationships observed, as FNSE, hypocortisolism, and hypocortisolemic syndrome-related symptoms in girls, all seem to develop or increase during adolescence (Westenberg et al., 2004; ter Wolbeek et al., 2006; Putnam, 2007). The proportion of variance in cortisol explained by FNSE and depressed mood state was small. Still, the relationships we found may be informative about underlying physiological mechanisms. The trait FNSE measure consisted of four items of a questionnaire designed to discriminate atypical from melancholic depression. This suggests cautious interpretation of the results. Future studies should compare this measure of FNSE with alternative measures regarding their power to predict cortisol mobilization responses. As subjects who differ in FNSE may also differ in compliance with the saliva collection instructions, the observed relationships should be replicated in a study in which compliance is independently verified.

The associations we found between FNSE and cortisol mobilization may be sensitive to context. Similar to our present proposal, Mason et al. (2001) argued that low cortisol levels in some PTSD patients reflect protective disengagement coping strategies, which represent secondary compensatory adaptations to counteract primary arousal symptoms. The general pattern is below-normal cortisol levels when conditions involve little acutely superimposed

psychosocial stress and a supportive setting in which disengagement coping mechanisms can be readily used. On the other hand, above-normal cortisol levels may be observed when greater psychosocial stress is superimposed and situations make it more difficult to effectively use disengagement defences (Mason et al., 2001; Tops et al., 2006). In the present study, subjects woke up in the safe environment of, in most cases, their own homes, in anticipation of the unfamiliar challenge imposed by the psychophysiological testing in our laboratory, later that morning. This is different from most other studies measuring cortisol mobilization responses, and may have been an important aspect of our study, as it may have increased chances of finding individual differences in displaying either a cortisol mobilization response to the challenge, or, perhaps facilitated by the safe environment of their own home and bedroom, a protective inhibitory/disengagement response preventing such mobilization. Hence, context is a variable that needs attention in future studies.

#### 5. Conclusion

We hypothesized and found that trait FNSE relates to low cortisol mobilization responses. Moreover, because trait FNSE relates positively to depressed mood state, but negatively to cortisol mobilization, we found that the positive relationship between depressed mood state and cortisol showed up most clearly when controlling for the confounding effect of FNSE on this relationship. We proposed that trait FNSE is associated with a history of frequent high cortisol responses, leading to long-term protective inhibition of further cortisol and energy mobilization. We suggest that cortisol mobilization is involved in mobilization of metabolic resources (e.g. in the context of depressed mood state, anxiety, or other challenges), and when negative energy balance and cortisol increases pass a threshold (due to social anxiety, i.e. FNSE), individuals are redirected to a survival mode (atypical depression) such that a positive energy balance is regained, and cortisol mobilization is limited to avoid deleterious effects of chronic hypercortisolism and arousal (McEwen and Wingfield, 2003). The present results have special relevance for mental health problems that have a high prevalence among young women.

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## Conflict of interest

The authors reported no biomedical financial interests or potential conflicts of interest.

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