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The assocation between levels of cortisol secretion and fear perception in patients with remitted depression predicts recurrence

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ABSTRACT

Aim

This study examines the association between cortisol secretion and fear perception in remitted patients, in order to identify mechanisms underlying risk for recurrence of depression. We hypothesized that the stronger the association between cortisol secretion and fear perception in persons with remitted depression, the more recurrence will be experienced. We also investigated whether high levels of cortisol and fear perception per se predict more recurrence. These effects were assumed to be stronger in women than in men.

Methods

In a prospective design we investigated 77 outpatients with remitted depression and related the association between their 24-h urinary free cortisol secretion and fear perception (from ambiguous faces and from vocal expressions) to recurrence of depression within 2 years. We applied Cox regression models, partial correlations, and Fisher's z tests.

Results

In 21 patients depression recurred. Irrespective the channel of perception (eye or ear), the interaction between fear perception and cortisol secretion was significantly related to recurrence of depression. Patients high or low on both variables were more at risk. This increased risk was also reflected by a significant association between cortisol secretion and facial fear perception, but only among subjects who experienced recurrence. A trend in the same direction was found for vocal fear perception. Fear perception and cortisol secretion per se did not predict recurrence. No gender differences were found.

Conclusion

The association between cortisol secretion and fear perception (probably indicative for altered fear circuits in the brain) constitutes a mechanism underlying risk for recurrence of depression.

INTRODUCTION

Recurrence rates of depression after recovery are high, incurring considerable social and financial costs (Angst, 1999; Pincus and Pettit, 2001; Crown et al., 2002). Therefore, identification of risk factors for recurrence is important.

Differential regulation of the hypothalamic-pituitary-adrenal (HPA) axis has been presumed to constitute risk for depression (Holsboer, 2000). During the depressed state, cortisol secretion is increased in most of the patients with severe depression. The likelihood that HPA-axis hyperactivity becomes permanent is higher when patients suffered several episodes (Gurguis et al., 2004; Bos et al., 2005). Such persistent HPA-axis hyperactivity may in turn set persons at risk for recurrence (Ribeiro et al., 1993; Zobel et al., 1999; Zobel et al., 2001).

Vulnerability to depression in some individuals may be a consequence of a diathesis–stress process in which maladaptive interpersonal skills and cognitive representations of the self and others in relationships are diatheses (Joiner and Coyne, 1999). Individuals having a negative bias in the perception of their social environment may experience more stress. This increases the likelihood that stressful interpersonal events occur, resulting in more recurrence of depression (Hammen, 1992; Segal et al., 1996). The perception of (schematic) facial expressions of emotions seems to be a good model to assess a negative bias. Such bias has been frequently demonstrated in depressed patients (see for instance Mandal and Bhattacharya, 1985; Gur et al., 1992; Rubinow and Post, 1992; George et al., 1998; Hale et al., 1998; Gotlib et al., 2004), and has been found to be linked to unfavorable outcome of depression (Bouhuys et al., 1999a) and to relapse (Bouhuys et al., 1999b).

Empirical evidence from studies of animals and healthy persons has linked cortisol secretion to the processing of threatening stimuli and to amygdalar activity in the brain (Adolphs, 2002; LeDoux, 2003; Shinnick-Gallagher et al., 2003). Together with the above described differential neuroendocrine and cognitive function in depression, this linkage between fear perception and cortisol secretion prompted us to hypothesize that depressed and control subjects may differ in this respect (Bouhuys et al., 2005). Indeed, we found that cortisol secretion was specifically related to facial fear perception in depressed women, whereas overall levels of cortisol and perception of fear did not differ between depressed and control subjects. We interpreted these findings in terms of depressed women having developed sensitive fear circuits

in which cortisol and fear perception have become directly linked. We supposed that this association constitutes a gender-specific mechanism underlying risk for depression. To test this presumption more soundly, we investigated this association *prospectively*, and studied perception of fear from both visual and auditory stimuli.

We hypothesized that the stronger the association between 24-h cortisol secretion and perception of fear in patients with remitted depression will be, the more recurrence will be suffered within 2 years, and that this is more true for women than for men. We also investigated whether higher levels of cortisol and fear perception per se predict more recurrence. In addition, we explored whether putative risk of recurrence connected to the one type of fear perception can be explained by the other type.

METHODS

Participants

We investigated 77 outpatients with remitted depression. These patients form a subgroup of 104 patients who participated in a larger longitudinal study on predictors of recurrence of depression. After patients had given informed consent, their attendants' diagnosis was independently confirmed (Composite International Diagnostic Interview (CIDI, lifetime version). Patients between 18 and 65 years with major depressive disorder (MDD) or dysthymia were included (DSM-IV; American Psychiatric Association, 1994), if their index episode was less than 6 months ago and they had no missing data on the neuroendocrine and cognitive measures (see further). Persons with psychotic symptoms, a dysfunction of the CNS, substance dependence, an organic cause of the disorder, or severe communication problems were excluded.

Seventy-five participants were remitted from MDD, 2 participants were remitted from dysthymia. Fourteen participants suffered from "double depression" and 26 participants experienced comorbid anxiety. Forty-two of the participants with MDD had a history of recurrent depression, 33 had had a single episode. The group consisted of 51 women and 26 men. Their mean age at baseline (T0) was 44.0 years ± 10.8 (SD), range 24–65 years.

After inclusion, participants' severity of depression was assessed 4-weekly with the Beck Depression Inventory (BDI, Beck et al., 1961). We considered patients remitted who scored 8 or less for two consecutive times (Frank et al.,

1991). Once remission was established, baseline assessments were performed (T0), consisting among other things of a Hamilton Rating Scale for Depression interview (HRSD; Hamilton, 1967), two cognitive tasks, and a cortisol measurement.

After the baseline assessments the participants completed the BDI on a 4-weeks basis during a 2-year follow-up. If BDI scores exceeded 14 for 2 consecutive times (see Frank et al., 1991), the CIDI (12-months version) was conducted to establish recurrence of depression. In case of recurrence, further assessments were cancelled; in the other case the follow-up was continued. At 6, 12, 18, and 24 months after T0, medication use in the preceding 6 months was assessed by means of a questionnaire.

Cortisol

Participants collected their urine over a 24-h interval starting from 5:00 p.m., within 14 days after T0. The volume ranged from 460 to 5900 ml (M = 2075 ml; SD = 977). Urine samples were kept frozen at 20°C until assays were done. Cortisol was measured by radio-immunoassay (RIA) with locally prepared rabbit antiserum. It was purified on Sep-pack columns and isolated on Sephadex LH-20 columns. Cortisol scores were log-transformed.

Cognitive tasks

Participants performed two cognitive decoding tasks, one concerning the interpretation of facial expressions and the other of vocal expressions. In this study we focused on *bias* in fear perception rather than the ability to perceive fear correctly.

Task 1: perception of facial expressions

The perception of schematic facial expressions was assessed (see Fig. 1). The participants judged the 12 faces with respect to: elation, invitation, rejection, fear, anger, sadness, and disgust. Each of the emotions was rated on a 5-point scale as to their applicability to each of the 12 faces. The scale ranged from 0%–100%. The faces were presented in random order on a monitor. We distinguished 3 ambiguous faces (face 3, 4, and 5). Normal persons perceive equal amounts of positive and negative emotions from these faces (Bouhuys et al., 1995). Guided by our previous studies (see introduction), in the present study we only investigated fear perception from these ambiguous faces.

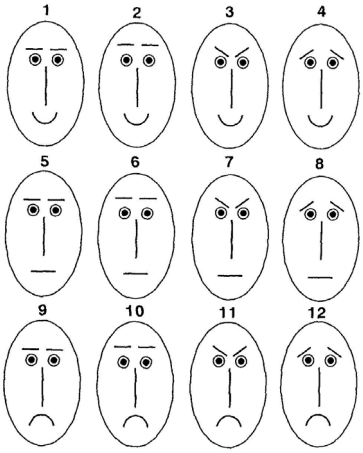

Figure 1 Faces judged by remitted subjects.

Task 2: perception of vocal expressions

The second task concerned vocal expressions and consisted of 2 subtasks, an emotion task and a control task. The control task was added to determine whether general cognitive deficits can explain results in the emotion task. This control task consisted of 18 sentences, expressed in a neutral, inquiring, or affirming tone of voice. The emotion task consisted of 36 sentences that expressed fear, sadness, anger, surprise, happiness, or were spoken in a neutral tone of voice. Speakers were 2 actors: 1 male and 1 female. Three linguistically neutral sentences were used ("the old car drives through the streets of the capital", "the large plane flies over the trees of the rainforest", and "baba baba baba"). The sentences were recorded, digitized, and implemented in a computer program. Stimuli were presented in random order via the speakers of a computer. Participants were asked to decide which of the 6 emotions was expressed in the sentences.

To assess possible perceptual bias, we counted the number of times the emotion fear was indicated when an expression was identified incorrectly. This number was adjusted for the overall number of incorrect responses (% fear perception can range from 0–100%).

Statistical analyses

Several variables can be considered as potential confounders. Age has been found to be positively associated with cortisol secretion during depression (Deuschle et al., 1998) and with emotion perception (Gunning-Dixon et al., 2003). Perception and education are assumed to be related as well. Therefore, we adjusted all analyses for gender, age, and education.

We applied Cox proportional hazards regression analyses: cortisol secretion, fear perception, and the interaction between these variables were examined with respect to the prediction of recurrence of depressive episodes. This analysis accounts for the variation in time to recurrence (i.e. the interval in weeks after T0). Observations of participants who did not experience a recurrence within the 2-year follow-up were considered censored. To explore the putative significant relation between interaction terms and recurrence of depression, partial correlations between cortisol secretion and fear perception were calculated among subjects differing in recurrence status. For between-group comparisons Fisher's z tests were applied.

In the Cox regression model two-way (gender x cortisol or gender x fear) and three-way gender interactions (gender x cortisol x fear) were tested, adjusting for lower-order terms. No significant gender interactions were found (all $p > .10$).

The variables were standardized to reduce collinearity between main effects and cross-product terms. We tested two-sidedly and alpha was set at 5%.

RESULTS

Sample characteristics and rate of recurrence

The mean BDI score at T0 was 3.6 (SD = 2.4, range 0–8). The mean HRSD score was 4.3 (SD = 3.4, range 0–15). Fifty-four (70.1%) participants used psychoactive medication at T0 (modern antidepressants, n = 42; tricyclic antidepressants, n = 11; sedatives, n = 12; mood stabilizers, n = 4). Of the 53 participants using antidepressants, 14 stopped using them in the course of the follow-up. Two participants started antidepressant medication in the course of the follow-up.

Twenty-one of the 77 participants (27.3%) experienced a new depressive episode within 2 years after T0. Of these, 12 (57.1%) were female and 9

(42.9%) were male. The majority (81.0%) of the recurrent episodes occurred within 1 year after T0.

We performed some control analyses using Cox regression. None of the demographic (gender, age, education) and clinical variables (HRSD, BDI, recurrent depression vs. single episode) nor medication use at T0 was significantly related to time to recurrence. We tested whether changes in use of antidepressant medication in the course of the follow-up were related to recurrence, by comparing participants who used antidepressants continuously (n = 39) with participants who stopped antidepressant medication (n = 14) and participants who remained free of antidepressants at all (n = 24). Time to recurrence was not significantly different for these 3 groups.

In addition, the scores on the vocal control task were not related to time to recurrence, indicating that putative deviations of vocal fear perception in participants differing in recurrence status are emotion specific.

Interrelationships between cortisol and fear perception

In the entire group the perception of vocal and facial fear was not significantly correlated (r = .161, n.s.). This was also true for the relationship between cortisol secretion and facial fear perception (r = .093, n.s.), and cortisol secretion and vocal fear perception (r = .079, n.s.).

Prediction of recurrence from cortisol or fear perception

Table 1 shows the mean levels of fear perception from ambiguous faces and vocal stimuli, together with levels of cortisol secretion, according to recurrence status.

Table 1 *Perception of fear from ambiguous faces and from vocal expressions by remitted patients with recurrence (Rec) or without recurrence of depression (Nonrec) within the following 2 years*

	Rec		Nonrec	
	M	SD	M	SD
% Facial fear	12.3	14.9	12.9	12.8
% Vocal fear	7.0	8.4	6.8	10.1
Cortisol[1]	99.7	47.2	98.9	46.0

[1]nmol/24h

Table 2, part A presents the results of the univariate Cox regression analyses, relating perception of facial and vocal fear, and cortisol to recurrence of depression. No significant main effects were found, indicating that neither levels of cortisol secretion nor levels of facial or vocal fear perception predicted recurrence of depression.

Table 2 *Cox regression analyses predicting the onset of recurrence from fear perception and cortisol secretion, adjusted for gender, age, and education*

Part A: univariate	B	HR	95% CI	p
Cortisol	-0.02	0.98	0.62–1.53	.922
% Facial fear	0.03	1.03	0.65–1.63	.907
% Vocal fear	0.05	1.05	0.68–1.63	.818
Part B: multivariate	**B**	**HR**	**95% CI**	**p**
1. Cortisol	0.18	1.20	0.71–2.04	.496
% Facial fear	-0.27	0.77	0.42–1.38	.375
Cortisol x facial fear	0.70	2.02	1.19–3.43	**.009**
2. Cortisol	-0.01	0.99	0.62–1.56	.955
% Vocal fear	-0.16	0.86	0.51–1.43	.553
Cortisol x vocal fear	0.63	1.89	1.04–3.41	**.036**
Part C: multivariate	**B**	**HR**	**95% CI**	**p**
Cortisol	0.18	1.20	0.71–2.01	.499
% Facial fear	-0.23	0.80	0.45–1.42	.438
% Vocal fear	-0.19	0.83	0.48–1.43	.501
Cortisol x facial fear	0.67	1.95	1.18–3.22	**.009**
Cortisol x vocal fear	0.64	1.89	1.02–3.48	**.042**

Prediction of recurrence from the interaction between cortisol and fear perception

The results of the multivariate regression analyses relating cortisol secretion and the perception of facial and vocal fear to recurrence of depression are presented in Table 2, part B. We found that the interaction between cortisol

secretion and facial fear perception (part B1) as well as the interaction between cortisol secretion and vocal fear perception (part B2) predicted recurrence of depression significantly. Figure 2 illustrates these interaction effects by depicting the percentage of recurrence in subgroups, differing in levels of cortisol secretion and fear perception (split half: high vs. low). The figure shows that remitted patients who had high levels of cortisol secretion and high levels of fear perception (either facial or vocal) were at substantially higher risk of becoming depressed again. Moreover, remitted patients with low levels of cortisol secretion and low levels of fear perception were at higher risk to experience recurrence as well.

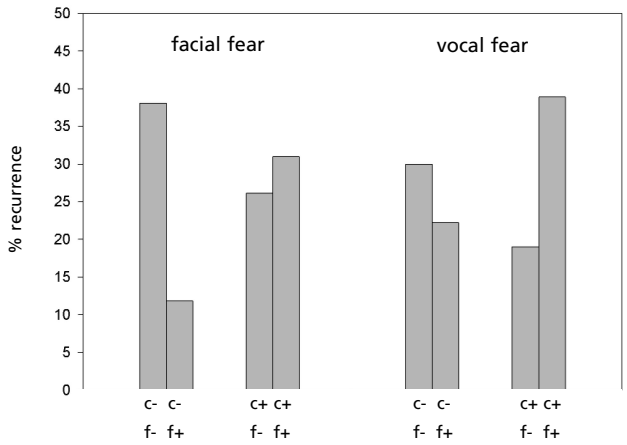

Figure 2 Percentage of recurrence in remitted patients differing in 24-h cortisol secretion (high: c+ and low: c-) and facial and vocal fear perception (high: f+ and low: f-).

The association between cortisol secretion and fear perception in the recurrent and the nonrecurrent groups, as depicted in Figure 3, helps to understand these significant interaction effects. The partial correlations between cortisol secretion and facial fear perception were in the recurrent group: r = .511 (p =. 030) and in the nonrecurrent group r = -.121 (p = .390). These correlation coefficients differed significantly from each other (Fisher's z test: p = .014). Hence, only for participants with a recurrent episode a significant association existed between cortisol secretion and facial fear

perception. A similar trend was found for the perception of fear from vocal expressions: the relationships between cortisol secretion and vocal fear perception were in the recurrent group r = .444 (p = .065) and in the nonrecurrent group r = -.031 (p = .823). The latter correlation coefficients tended to differ from each other (Fisher's z test: p = .067).

These results support our hypothesis that the association between cortisol secretion and fear perception sets persons at risk for depression recurrence.

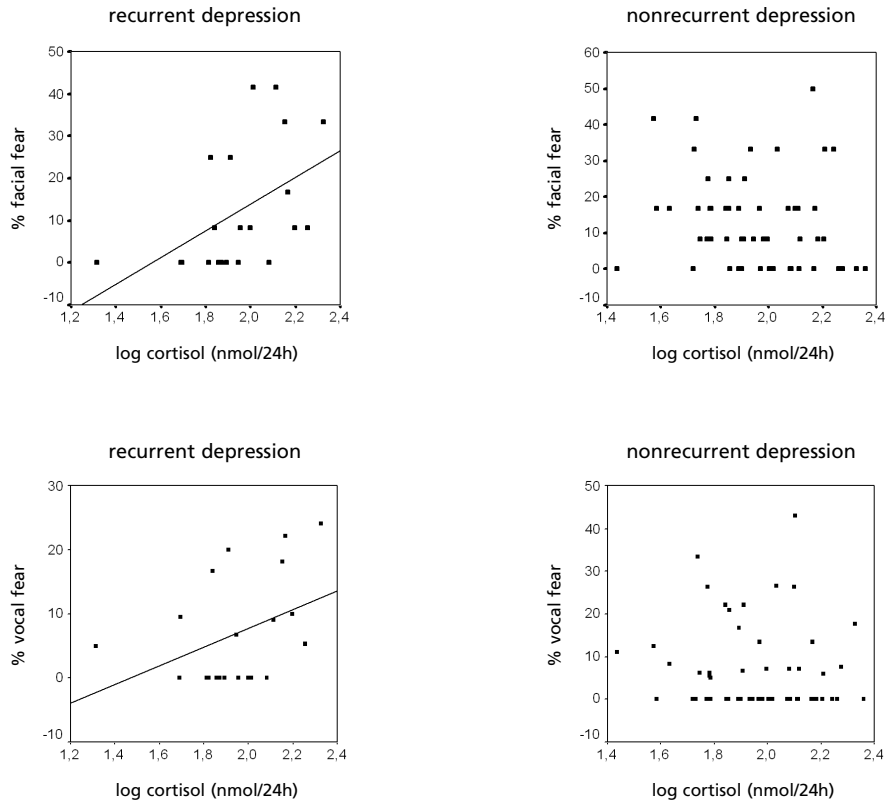

Figure 3 Association between 24-h cortisol secretion and perception of facial and vocal fear.

Additional analysis

We asked the question whether risk of recurrence connected to the one type of fear perception could be explained by the other type. A positive answer is not very likely as no direct relationship existed between the two types of fear perception. Indeed, Table 2, part C shows that both interaction terms contribute significantly and independently to the prediction of recurrence. Therefore, we must conclude that with regard to the prediction of recurrence, facial and vocal fear perception (both in interaction with cortisol secretion) are not interchangeable, and probably refer to different aspects of fear perception.

Confounding by residual symptom severity?

To be sure that our results cannot be ascribed to "residual symptoms", we performed the above analyses (Table 2, parts A and B) including HRSD depression score as an extra covariate. All effects remained significant. Thus, our results were not confounded by residual symptom severity.

DISCUSSION

Our hypothesis that an association between cortisol secretion and perception of fear operates as a risk factor for recurrence of depression was confirmed. Patients high or low on both variables were at substantially higher risk of becoming depressed within 2 years. This increased risk was also reflected by a significant correlation between cortisol secretion and facial fear perception in subjects who experienced recurrence. A trend in the same direction was found for vocal fear perception. The baseline levels of fear perception (via either channel) and cortisol secretion per se did not predict recurrence of depression. The results cannot be explained by gender, age, general cognitive impairment, education, psychoactive medication, residual symptoms, or diagnosis (retrospectively recurrent depression vs. single episode). This is the second study that demonstrates that the association between cortisol secretion and fear perception constitutes a risk for depression (Bouhuys et al., 2005). The previous cross-sectional results are now confirmed in a prospective design.

Levels and associations

Levels of cortisol secretion or fear perception per se did not exert risk for depression recurrence. We found the same in the cross-sectional study

(Bouhuys et al., 2005). However, other studies are at variance with this result (Ribeiro et al., 1993; Zobel et al., 1999; Zobel et al., 2001; Bouhuys et al., 1999a; Bouhuys et al., 1999b). This may be explained by methodological differences. Discrepancies may be caused by lack of refinement of analysis of the HPA system (24-h cortisol secretion vs. dexamethasone/CRH challenge test) or by the fact that other emotions were studied.

It is of particular interest that the *association* between cortisol secretion and fear perception places remitted patients at risk for recurrence. This association may be an indication of an *altered organization of the stress response*. It has been theorized that in persons who are vulnerable for depression the central stress response is impaired (Holsboer, 2000). Our data suggest that such impairment may (also) be expressed in a strengthened linkage between cortisol secretion and fear perception, rather than in altered levels per se.

The fear circuit and risk of recurrence

Although we did not assess amygdalar activity, it is of interest to relate our results to evidence that suggests that amygdalar activity is related to cortisol as well as to perception of negative emotions (LeDoux, 2003; Shinnick-Gallagher et al., 2003). Many studies suggest that the amygdala is a critical neural substrate for the processing of negative threatening emotional stimuli. This neural structure seems to be particularly involved in the processing of facial stimuli (Adolphs and Tranel, 2003), although the perception of fear from vocal expressions has been implicated as well (Phillips et al., 1998). In animal and human studies it has been shown that cortisol can potentiate the processing of threatening stimuli (Van Honk et al., 2000; Shinnick-Gallagher et al., 2003). Activation of the amygdala is also associated with cognitive processes including attention and memory (Zald, 2003). Negative thoughts and a negative memory bias, which have frequently been reported for depressed persons, can in turn affect amygdalar activity.

Some authors suggest that psychopathology may develop via the process of neural sensitization or kindling. They propose that increased activity or hyperexcitability of the amygdala develops through a process of neural sensitization, in which psychological stressors initiate changes in the brain's fear circuit, leading to enhanced perception and response to subsequent threat and danger (Rosen and Schulkin, 1998). Such hypothesis is in line with the cognitive kindling hypothesis in recurrent depression (Segal et al., 1996). One may speculate that the association we found between fear perception

and cortisol secretion is the result of such a sensitization process. In other words, our data may indicate that some remitted depressed persons have developed a "sensitive fear circuit", in which cortisol and fear perception have become directly linked. Whatever the origin of this altered fear circuit, our results make plausible that these deviations in stress-adaptive mechanisms constitute a risk for recurrence of depression.

We found some support for such interpretation in a positron emission tomography (PET) study on depressed patients and controls. An association between metabolic activity of the left amygdala and cortisol secretion was found in depressed patients but not in controls (Drevets et al., 2002). Hence, these data underscore the role of the amygdala and, as in our data, suggest the emergence of specific connections (in this case between amygdalar activity and cortisol secretion), which may exert risk for recurrence of depression.

Most of the above studies are based on experimental designs and refined analyses specifically developed to demonstrate links between cortisol, amygdalar activity, and fear perception. In contrast, our 24-h urinary cortisol assessment and self-reported fear perception may be considered rather rough and global indications of stress-adaptive mechanisms. Perhaps this explains why we did not find associations between fear perception and cortisol secretion in the nonrecurrent participants. However, one may argue that it is easier to detect relationships even between these rough measures when links between fear perception and cortisol are changed and/or strengthened. Since we did find a connection between fear perception and cortisol in participants who experienced recurrence of depression, we suggest that sensitization of fear circuits may have played a role.

Facial vs. vocal expressions

The amygdala has been implicated in fear perception, whether elicited by facial or vocal expressions (Phillips et al., 1998), but visual perception seems to be more strongly related to the amygdala than auditory fear perception (Anderson and Phelps, 1998). This stronger connection for facial stimuli may explain why in the recurrent group the association between fear perception and cortisol secretion is stronger for visually than for auditory perceived fear.

We found that both interaction terms between fear perception and cortisol secretion predicted recurrence of depression independently. This finding suggests that the two channels of perception may at least be partially dependent on different brain structures (see Anderson and Phelps, 1998).

Gender differences

Different mechanisms may be involved in the etiology of depression for men and women (Weissman and Klerman, 1977; Paykel, 1991). This seems to be true for assessments on the cognitive level (Nolen-Hoeksema, 1990; Bouhuys et al., 1999a; Bouhuys et al., 2005) as well as on the neuroendocrine level (Peeters et al., 2003; Bos et al., 2005). The earlier association we found between cortisol secretion, fear perception, and recurrence was confined to women (Bouhuys et al., 2005). We could not replicate this. However, gender effects were not easy to demonstrate by means of three-way interactions, since the number of patients that developed a depressive episode was rather small (12 women and 9 men). All in all, the role of gender in mechanisms that explain recurrence of depression is far from clear and need further attention.

In sum, the present study shows that, irrespective the channel of perception (eye or ear), the association between fear perception and cortisol secretion is related to recurrence of depression. These results, now found in two different samples, need to be replicated in other institutes and need more attention in the disentanglement of the complex role of stress responses in recurrence of depression. It would be of particular interest to assess sensitivity of the fear circuit directly within individuals (in contrast to the current group-wise approach) and relate this to future depression.

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