Original Paper

Neuropsychobiology

Neuropsychobiology 2007;55:143–150
DOI: 10.1159/000106056

Received: August 11, 2006
Accepted after revision: January 27, 2007
Published online: July 18, 2007

The Psychobiology of Burnout: Are There Two Different Syndromes?

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Key Words
Burnout · Cortisol · Prolactin · Attachment · Detachment · Oxytocin · Fatigue · Dopamine · Serotonin

Abstract
Background: Plasma prolactin levels are sensitive to dopamine and serotonin function, and fatigue. Low cortisol, dopamine and/or serotonin may be involved in burnout and detachment. ***Methods:*** In this double-blind within-subject study, we treated 9 female burnout subjects and 9 controls with 35 mg cortisol and placebo orally. We measured state affect and plasma prolactin, oxytocin, cortisol and adrenocorticotropic hormone levels, and administered an attachment questionnaire. ***Results:*** The burnout subjects displayed an extreme distribution of basal prolactin levels, displaying higher or lower levels compared to the controls. The low prolactin burnouts had profoundly low attachment scores and tended to have low oxytocin levels. The high prolactin burnout subjects tended to show cortisol-induced decreased prolactin and fatigue, and increased vigor. ***Conclusion:*** Results are consistent with the hypothesis that burnout subjects are either characterized by low serotonergic function or by low dopaminergic function, and that the latter group benefits from cortisol replacement. These preliminary results suggest that differentiating between two syndromes may resolve inconsistencies in research on burnout, and be necessary for selecting the right treatment strategy.

Introduction

We recently proposed that low function of the neuromodulator dopamine is importantly implicated in feelings of acute fatigue and listlessness, as well as in the chronic fatigue of syndromes including the highly similar syndromes of burnout and atypical depression [1]. The mesolimbic dopaminergic system is implicated in decisions to exert effort and cognitive control functions, and in the vigorousness of responding [1, 2]. Especially dopamine D_2 receptor function has been related to effects concerning energy expenditure [3, 4]. Pharmacological studies demonstrated that dopaminergic agents modulate feelings of vigor [5, 6] and D_2 receptor blockade increases subjective fatigue [7]. We recently reported several studies that found indirect support for the hypothesis that acute fatigue is associated with decreases in dopaminergically modulated cognitive control [8–11].

The phenomenology of burnout suggests an important role of decreased dopaminergic functioning also in burnout [1]. Together with emotional exhaustion and decreased perceived personal accomplishment, one of the defining characteristics of burnout is detachment/depersonalization. A recent review presented evidence for a relationship between attachment and dopaminergic function [12]. A replicated study found a significant correlation between dopamine D_2 receptor density in the putamen and scores on a detachment questionnaire [13,

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14]. Detachment may reflect decreased social approach motivation, i.e. social disengagement. Detachment may reflect a tuning or inhibition of dopaminergic systems such that less resources are invested in social approach.

Another abnormality that has been repeatedly reported in various fatigue syndromes including burnout and atypical depression is low levels of the hormone cortisol [15, 16]. A recent study found that subjects who reported high levels of chronic fatigue failed to show a cortisol mobilization response to a social stress challenge [17]. Several studies found that treatment with cortisol of fatigued patients decreased feelings of fatigue and increased feelings of vigor [18]. We recently found acutely decreased fatigue and increased vigor after the oral administration of 35 mg of cortisol in healthy women [19].

Singer [20] and Mason et al. [21] proposed the concept of an engagement-disengagement axis as the primary underlying dimension of the cortisol system. Indeed, extraversion has been related to higher task engagement-related cortisol mobilization [22]. Similarly, higher social engagement-related cortisol mobilization has been found in extraverted compared to inhibited children [23]. We recently found a relationship between higher socially motivated task engagement and higher cortisol mobilization [24]. These findings suggest that the hypocortisolemia in fatigue syndromes may reflect the detachment and disengagement that characterize such syndromes, and that cortisol administration may decrease fatigue and increase vigor perhaps by increasing dopaminergic activity. Interestingly, a recent positron emission tomography study found a positive correlation between individual differences in cortisol response and mesolimbic dopamine response to performance of a demanding task [25].

Plasma prolactin levels are sensitive to dopamine function and fatigue. Dopamine secretion in the arcuate nucleus inhibits prolactin release in the adenohypophysis via D_2 receptor stimulation [26]. Prolactin increases in response to dopamine D_2 antagonist but not to serotonergic agonist challenge correlated with exercise fatigability [27]. In the chronic fatigue syndrome increased serum prolactin levels have been reported, and prolactin was significantly correlated with daily fatigue severity, giving support to the hypothesis of decreased dopaminergic tone in chronic fatigue syndrome [7, 28].

There is evidence to suggest that basal prolactin levels are modulated not only by dopaminergic function but also by serotonin $5HT_{1A}$ receptor function [29] and noradrenaline function [30]. Neuroendocrine studies suggest that the function of $5HT_{1A}$ receptors is important in depression [31]. Low serotonin function may be involved in atypical depression [32]. Selective serotonin reuptake inhibitor antidepressants increase basal prolactin levels [29]. Basal prolactin levels have been shown to correlate positively, and basal cortisol levels negatively, with the prolactin response to a serotonergic challenge [33, 34]. Interestingly, cortisol decreases both basal and serotonergically stimulated prolactin release in humans [35]. Noradrenaline has also been implicated in the modulation of prolactin levels. For instance, the selective noradrenaline reuptake inhibitor antidepressant reboxetine stimulates both prolactin and cortisol secretion [30].

In the present study, we treated female subjects who fulfilled criteria for burnout and healthy control subjects with 35 mg of cortisol and placebo orally, in a double-blind within-subject design. We measured individual differences in attachment, state fatigue/vigor and in plasma prolactin. To measure attachment we used the Attachment-detachment subscale of the Reward Dependency scale from the Temperament and Character Inventory [36]. We also measured plasma oxytocin levels, as this neuropeptide hormone is thought to be an important modulator of attachment [37]. We hypothesized that subjects complaining of burnout may have decreased dopamine and/or decreased serotonin activity, as suggested by respectively increased/decreased plasma prolactin levels. Furthermore, above we reviewed results that suggest that administration of cortisol may increase dopamine activity. Especially burnout subjects showing increased prolactin levels, which may reflect reduced dopaminergic activity, are expected to show a cortisol-induced increase in vigor and decrease in plasma prolactin level.

Methods

Participants

Nine healthy volunteers (mean age = 34, SD = 8) and 9 subjects fulfilling criteria for burnout (mean age = 35, SD = 9), all females, were enlisted by an advertisement in a local newspaper and were paid for participation. The advertisement for burnouts asked for volunteers in a scientific study who were suffering from work-related fatigue. Each participant passed a health screening based on self-report. Inclusion criteria included right-handedness, Dutch as their native language, normal or corrected to normal vision, no personal history of psychiatric, metabolic, or neurological disorders, premenopausal status, and no use of relevant medication including steroid, psychotropic and contraceptive medication. Volunteers who reported noxious health behaviors (drug abuse including excessive alcohol, smoking and caffeine, and abnormal sleeping habits, e.g. too little sleep), chronic health problems or psychopathology were excluded from the study. Additionally, participants were screened for depression using the 13-item Beck

Depression Inventory (BDI) (healthy controls <6) [38]. All participants read and signed an informed consent statement approved by the Medical Ethical Committee of the University Medical Center of Groningen.

Subjects were tested within 3 weeks after administration of the Utrecht Burnout Scale (UBOS) and BDI. Subjects were working in various occupations and not on sick leave for longer than 4 weeks. They were not presently being treated for burnout or related disorders. The subjects self-reported the phase of their menstrual cycle based on days since onset of their last menstrual period.

Burnout

We measured burnout using the UBOS, which is a 16-item Dutch version of the Maslach burnout inventory, adapted to measure burnout across occupations [39]. The UBOS measures emotional exhaustion, distance and competence. The UBOS inclusion criterion for burnout was emotional exhaustion >2.21 and either distance >2.21 or competence <3.50 [39, 40].

Procedure

We used a within-subjects double-blind design. Placebo and treatment sessions, the order of which was counterbalanced, were separated by 1 week. The participants arrived at 9 a.m. First, a capsule was ingested. In the experimental condition, participants received a capsule containing cortisol (35 mg of hydrocortisone), whereas in the control condition they received a placebo (Avicel capsule) double-blind orally. The participants were allowed to read while they waited for a blood sampling that took place 70 min after capsule ingestion. Next, participants performed a number of tasks for 1 h, the results of which will not be presented here.

Questionnaire Measures

Temperament and Character Inventory

Only the temperament subscales of the Temperament and Character Inventory were used. These subscales consist of a total of 60 items, assessing novelty seeking, harm avoidance, reward dependency and persistence [36, 41]. Attachment-detachment is a subscale of the reward dependency scale and measures the tendency to express and share emotions and feelings with friends versus keeping emotional distance.

Mood Measures

The Profile of Mood States (POMS) short version [42] was filled out by the participants before ingestion of the capsule (T_0), before the start of task performance (T_1) and after the final task (T_2). The POMS consists of five subscales: fatigue, vigor, depression, anger, and tension, and has been translated and validated for a Dutch population. Additionally, at the start of each session the subjects filled out the state version of the State-Trait Anxiety Inventory [43].

Hormones

The blood samples were collected in ice-chilled tubes. After centrifugation, the plasma was removed and the samples were stored at –80°C until analysis. Plasma concentrations of cortisol and ACTH were determined using an in-house radio immunoassay [44]. Prolactin was determined with a chemiluminescence micropartial immunoassay (Abbott Laboratories, Diagnostic Division, Ill., USA). These analyses were performed at the University Medical Center of Groningen.

Before oxytocin was analyzed, plasma was extracted with acetone (guarantee reagent, GR; Merck, Darmstadt, Germany) and petroleum benzene (GR; boiling point range 40–60°C; Merck) with a recovery of 92%. Oxytocin levels were measured by radioimmunoassay at the Swedish University of Agricultural Sciences in Uppsala, Sweden, at the Department of Animal Physiology. The antibody KA_{19} was used for the analysis (Milab, Sweden). The limit of detection was 4.68 pM and interassay coefficients of variation low 22.06% CV = 9.57; medium 37.83% CV = 8.81; high 529.8% CV = 6.81; intra-assay %CV < 10 conc. = 20.90–1,026 [45].

Statistical Analyses

For the analyses of the hormone and mood levels, we employed General Linear Model (GLM) analyses for repeated measures with treatment condition (treatment vs. placebo) as the within-subjects factor, group (burnout vs. control) as the between-subjects factor and attachment scores as covariate. Additionally, multivariate analyses of covariance (MANCOVAs) for repeated measures were used to analyze mood measures, with time (T_1, T_2) and treatment condition as the within-subjects factors and measures before ingestion of the capsule (at T_0) as covariate, and group as the between-subjects factor. This analysis controls for differences between the sessions at baseline, that is, before ingestion of the capsule. We included age as a covariate in all GLM and MANCOVA analyses. The assumptions of GLM repeated measures and MANCOVA repeated measures of homogeneity of covariance structure (by Box's M tests) and normality or symmetry (by inspection of histograms and scatterplots of the data) were tested and found to hold.

As burnout may relate to high plasma prolactin levels but also to low prolactin levels (see 'Introduction'), we analyzed the basal prolactin levels using the Moses Test of Extreme Reactions. This nonparametric test is designed to test hypotheses in which it is expected that the experimental variable (e.g. burnout vs. control) will affect some subjects in one direction and other subjects in the opposite direction; it tests for extreme responses compared to the control group [46]. As shown in the 'Results' section, some of the burnout subjects were characterized by decreased prolactin levels (n = 4), while other burnout subjects were characterized by increased prolactin levels (n = 4). We compared these groups to each other and the controls using independent groups t tests. As these analyses involved very small numbers of subjects, we averaged mood scores over T_1 and T_2 before analyses using t tests.

Results

Hormones

Prolactin

Prolactin levels in the placebo condition were highly positively correlated with those in the cortisol condition ($r = 0.79$, $p < 0.001$). There was a main effect of treatment [$F(1, 13) = 5.33$, $p = 0.038$]. Treatment condition interacted with attachment [$F(1, 13) = 5.12$, $p = 0.041$] and with group [$F(1, 13) = 8.80$, $p = 0.011$]. There was a main effect of attachment [$F(1, 13) = 8.51$, $p = 0.012$]. In short, prolac-

Table 1. Results and descriptives (means and standard deviations), including cortisol-induced changes, of low prolactin burnouts, high prolactin burnouts, and controls

	Burnout low prolactin	SD	Burnout high prolactin	SD	Controls	SD
Burnout, depression						
Emotional exhaustion (UBOS)	4.35****	1.43	4.15***	1.30	1.48	1.14
Distance (UBOS)	3.75****	1.76	2.85**	2.09	1.13	0.69
Personal competence (UBOS)	3.71**	0.74	3.63**	0.62	4.83	0.82
BDI-13 depression	17.5****	4.6	15.3***	10.3	3.1	2.5
Personality						
Attachment-detachment[1]	1.6****	1.3	4.2##	1.3	4.0	0.7
Shyness with strangers[2]	3.2**	1.1	3.3**	1.5	1.1	1.4
State affect						
Vigor (POMS)	7.4**	2.8	11.5	3.3	12.5	3.9
Change in vigor	–0.75	2.75	4.75#	5.12	2.56	3.81
Fatigue (POMS)	7.1*	7.0	3.5	4.3	2.5	1.1
Change in fatigue	1.75	2.5	–3.00#	4.24	0.78	5.47
Depression (POMS)	5.2**	6.0	1.9	2.1	0.2	0.3
Tension (POMS)	3.8**	6.2	1.6	2.9	0.5	0.8
Anger (POMS)	5.0	8.0	1.0	1.2	0.2	0.3
STAI state anxiety	42**	8	33	8	29	6
Hormones						
Prolactin, mIU/l	144**	39	355*, ##	154	196	46
Change in prolactin	–20.8	34.2	–86*	112	11.5	44.4
Cortisol, nmol/l	190	58	186	37	218	73
Change in cortisol	1,120	150	1,119	141	1,012	649
ACTH, ng/l	14.4	6.4	13	5.2	15.6	5.0
Change in ACTH	–7.4	5.9	–3.9	7.5	–5.2	3.5
Oxytocin, nmol/l	46.3*	4.9	54.5#	6.1	54.3	7.4
Change in oxytocin	0.38	10.9	–0.08	5.28	3.19	4.42

* $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$, **** $p < 0.001$ (significance of a difference from the controls); # $p < 0.10$, ## $p < 0.05$ (significance of a difference between the two burnout groups).
[1] Subscale of Reward Dependency; [2] Subscale of Harm Avoidance.

tin levels were higher in the burnout group compared to controls. Treatment with cortisol decreased the prolactin levels only in the burnout group and in subjects scoring high on attachment. Prolactin levels were higher in subjects scoring high on attachment.

Cortisol, ACTH, Oxytocin

Treatment with cortisol increased plasma cortisol levels [$F(1, 14) = 277.93$, $p = 0.00001$] and suppressed plasma ACTH levels [$F(1, 14) = 11.25$, $p = 0.005$; table 1]. No interactions or effects of group or attachment were found on plasma levels of cortisol, ACTH or oxytocin.

Mood

No interactions with group or effects of treatment condition or attachment were found on any of the mood scores. For differences between the burnouts and controls on measures of burnout, depression, personality and mood, see table 1.

Comparison of Burnouts with Low and High Basal Prolactin Levels

The baseline prolactin levels of the burnout subjects were bimodally distributed about those of the controls (Moses Test of Extreme Reactions, trimmed control group span $s_h = 8$, extremes trimmed from each end of control group $h = 1$, $p = 0.025$). Four of the burnout subjects displayed a basal prolactin level that was lower (<175 mIU/l) than the levels of all but one healthy subjects, while 4 other burnout subjects displayed a basal prolactin level that was higher (>225 mIU/l) than the levels of all but one healthy subjects. Because high and low prolactin levels in subjects complaining of chronic fatigue may reflect different underlying mechanisms, not discriminating be-

tween these subgroups may obscure any relationships between the measures and manipulations in this study.

Table 1 shows the mean hormone levels, mood and personality scores, and changes after treatment with cortisol, separately for the control subjects, low prolactin burnouts and high prolactin burnouts. The groups did not differ in age and level of education (we coded the level of education ranging from 1, primary school, to 7, university or graduate school). Both burnout groups showed similarly high emotional exhaustion and depression scores, high scores on (only) the Harm Avoidance subscale Shyness with strangers and low competence compared to the controls. Distance seemed more elevated in the low compared to high prolactin group, though this was not significant. State negative affect was high, and vigor low, in both burnout groups, but more substantially and only significantly in the low prolactin group. In contrast to the low prolactin group, the high prolactin group tended to show a cortisol-induced increase in vigor, decrease in fatigue and decrease in prolactin levels. The low prolactin burnouts were characterized by low attachment and they tended to have low plasma oxytocin levels. The low cortisol levels in the burnouts, and high cortisol-induced suppression of ACTH levels in the low prolactin burnouts, did not approach significance.

We recently found that cortisol administration increased vigor and decreased fatigue in healthy female subjects [19]. From table 1 it appears that the low prolactin burnouts did not show these effects. We performed a post-hoc analysis excluding the low prolactin burnouts, to test if the other subjects showed the previously found effects. The 14 remaining subjects showed a cortisol-induced increase in vigor [$t(13) = 3.00$, $p = 0.010$], but no significant decrease in fatigue [$t(13) = 0.32$, n.s.].

Discussion

We found that treatment with cortisol decreased prolactin levels in the burnout group and in subjects scoring high on attachment. Prolactin levels were higher in subjects scoring high on attachment. The burnout subjects displayed a significantly bimodal extreme distribution of basal prolactin levels, either displaying higher or lower levels compared to the controls. Regardless of prolactin profile, burnout subjects had high scores on BDI depression, and the Harm Avoidance subscale Shyness with strangers. As also in larger studies, shyness proved to be the personality characteristic most consistently distinguishing burnout subjects from controls; this finding supports the representativeness of our small burnout sample [47].

We hypothesized that the burnout subjects showing high prolactin levels are characterized by low dopamine activity. These subjects showed an increase in vigor, decrease in fatigue and decrease in prolactin levels after treatment with cortisol. Although, in our small samples, some of these findings only approached significance, the total pattern of results supports our hypothesis that a subgroup of burnout subjects is characterized by low dopamine activity. The results further suggest that treatment with cortisol increases vigor and decreases fatigue by increasing dopaminergic activity. Cortisol treatment-induced increases in vigor and decreases in fatigue have been reported both in patients and in healthy subjects [18, 19]. When we analyzed all subjects with exclusion of the low prolactin burnouts, we replicated the cortisol-induced increase in vigor, but not the decrease in fatigue, that we previously found in a larger group of healthy women [19].

There may be parallels between the positive effects of cortisol treatment in some burnout subjects and the therapeutic effects of total sleep deprivation (TSD) in atypical forms of depression [48, 49]. TSD has rapid, individually variable, antidepressant effects, decreases plasma prolactin levels and increases vigor and cortisol levels [48–50]. Several lines of evidence linked TSD with an increase in the activity of brain dopamine pathways, and suggested that enhancement of brain dopamine function may be relevant for the clinical effect of TSD [51]. In patients with hyperprolactinemia who may have associated depressive symptoms, bromocriptine, a dopamine agonist that lowers prolactin, also has therapeutic effects [52]. As TSD is essentially a stressor, the associated increase in cortisol levels may be involved in its therapeutic effects. Perhaps future studies may investigate if cortisol treatment could be an alternative to TSD in patients showing indications of decreased dopamine activity. Indeed, rapid antidepressant effects of cortisol treatment have been reported in atypically depressed patients. A significant decrease in depression a day after cortisol treatment was found in a group of 6 patients that was selected from a larger group of nonpsychotic depressed patients that displayed significantly lower endogenous cortisol levels compared to controls [53, 54]. In a group of 6 treatment-resistant depressed patients with fatigue and hypocortisolemia, prednisone augmentation of antidepressant treatment was found effective [55].

According to recent results, the high basal prolactin levels and reactivity of prolactin and subjective vigor/fa-

tigue to cortisol challenge may be the result of increased dopamine D_2 receptor sensitivity, secondary to reduced dopamine levels. Porter et al. [34] found elevated prolactin responses to infusion of the serotonin precursor L-tryptophan in medication-free atypical depressed patients, but no change in $5HT_{1A}$ receptor-dependent growth hormone responses. L-Tryptophan competes with the dopamine precursor tyrosine for transport across the blood-brain barrier and may reduce dopamine synthesis by reducing brain tyrosine. There was a negative correlation between prolactin response and basal cortisol levels. Porter et al. [34] note that, over a normal physiological range, D_2 receptor function is inversely correlated with cortisol secretion, and suggest that the greater prolactin response to L-tryptophan infusion in the depressed subjects reflects increased dopamine receptor sensitivity, secondary to reduced dopamine levels.

In contrast, the burnout subjects showing low prolactin levels did not show cortisol-induced increases in prolactin, vigor or decreases in fatigue. This group was characterized by low attachment/high distance, and more severe state negative affect and anxiety. One explanation for the low prolactin levels in this group is low serotonin function. Low serotonin function may be involved in atypical depression, and especially atypical depression patients seem responsive to serotonergic medication [32]. Selective serotonin reuptake inhibitor antidepressants increase basal prolactin levels [29]. Alternatively, low noradrenaline function has been implicated in depression and may relate to low prolactin levels. For instance, the selective noradrenaline reuptake inhibitor antidepressant reboxetine stimulates both prolactin and cortisol secretion [30].

The hypothesis that low attachment would relate to low dopaminergic function is not supported. Instead, the burnout subjects that may have low serotonergic activity were characterized by profoundly low attachment scores. However, this is consistent with previous reports of positive relationships between serotonergic function and affiliative behavior [56]. The Attachment scale measures engagement in social interactions, and social interactions are believed to enhance the stress-protective $5\text{-}HT_{1A}$ receptor-mediated function of serotonergic neurotransmission [57]. Moreover, a serotonergic functioning impairment in detachment/depersonalization is indicated in different pharmacological studies [58]. Recent studies have demonstrated that oxytocin is released in response to treatment with selective serotonin reuptake inhibitors, opening up the possibility that oxytocin may mediate some of the social effects caused by serotonin [59, 60]. Low plasma levels of oxytocin have been found in fibromyalgia, a syndrome characterized by pain, fatigue and hypocortisolemia [59]. In a not yet published study on healthy women, we found a positive correlation between attachment scores and basal plasma oxytocin levels. The tendency of the low prolactin burnout subjects to display low basal oxytocin levels is consistent with their low attachment scores and with reduced serotonergic activity.

Despite higher anxiety and depression scores, the burnouts displayed lower plasma cortisol and ACTH levels compared to the controls, but the differences were not significant. However, the exceptionally low attachment scores in some of the burnout subjects suggest that hypocortisolemia that is reported in burnout, atypical depression and other fatigue syndromes may indeed be related to detachment when low serotonin and/or oxytocin function is involved. In addition, the favorable response to cortisol treatment in other burnout subjects suggests that some change in this hormonal system may be present when low dopamine function is involved.

Although both the high prolactin and the low prolactin burnout subjects scored high on chronic fatigue (burnout) and depression measures, the low prolactin burnout subjects scored higher on state negative affect measures. This may be related to their low attachment scores. Since this scale is a general trait measure of attachment-detachment, these subjects may also have been more detached during the sessions, and hence in certain ways less responsive to the experimental context. In contrast, the high prolactin burnout subjects, who scored high on attachment, may only display detachment related to their work (UBOS distancing), and hence they may have been more positively responsive to the social context of the experiment. In fact, strikingly high engagement during the sessions of some of the burnout subjects was noted by the experimenter. In these subjects, such high engagement in non-work-related situations may hypothetically obscure low cortisol mobilization responses occurring in other, work-related situations.

Many aspects define this study as preliminary. Besides the small number of subjects, these are reliance on single samples for hormone determination per session, and inclusion of subjects in various phases of their menstrual cycle. Although we partly employed a within-subject design, and we did not observe any relationships between menstrual cycle phase and the present findings, future studies would preferably have subjects participate in the same phase. Some larger studies of basal and serotonergic challenge-induced plasma prolactin levels found no effect of phase of cycle [61]. The high correlation between

the prolactin levels of both conditions, despite a treatment effect on those levels, suggests that many possible state-related confounding effects on prolactin levels exerted only limited influence, such that the prolactin measures showed sufficient reliability and stability to detect individual differences. Another limitation is the dependency on peripheral hormone levels: no definite conclusions can be drawn about the central mechanisms that modulated those levels. Moreover, those hormone levels are influenced by additional factors besides dopamine, serotonin and noradrenaline modulation. However, the overall consistency between different measures in this study and the presented theory strengthens our belief that we are presenting preliminary, but potentially important results. For instance, crucial effects that only approached significance in the small samples, such as the cortisol-induced increase in vigor and decrease in fatigue in high prolactin burnout subjects, were smaller in size but significant in a large group of healthy female subjects [19]. Other results, such as the low attachment scores in low prolactin burnout subjects, were actually very significant (and resulted in a main effect of attachment on prolactin levels in the GLM analysis of all subjects) and consistent with lower oxytocin in the same subjects; and we found a similar relationship between attachment scores and basal oxytocin levels in a larger sample of healthy female subjects. Finally, the cortisol-induced decrease in prolactin levels in burnouts, and in subjects scoring high on attachment, was significant in the more powerful GLM analysis; cortisol-induced decreases in plasma prolactin have been reported before [35].

To summarize, treatment with cortisol decreased the prolactin levels in burnout subjects compared to controls, and in subjects scoring high on attachment. The burnout subjects displayed an extreme distribution of basal prolactin levels, either displaying higher or lower levels compared to the controls. Indications that different central and psychological mechanisms are involved suggest that differentiating between the two syndromes may resolve inconsistencies in research on burnout, and be necessary for selecting the right treatment strategy, e.g. serotonergic or oxytocinergic medication in some, cortisol replacement or dopaminergic medication in others. Replication and extension of the present findings in a larger group of subjects and in patients may inform treatment strategies of various syndromes in which fatigue is a prominent feature.

Acknowledgements

Part of this research was supported by the Netherlands Concerted Research Action 'Fatigue at work' of the Netherlands Research Organization (580-02.100D) and by a grant (9910) of the Gratama Foundation.

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