Acta neurol. belg., 2006, **106**, 149-156

Review articles

Stress, depression and fibromyalgia

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Abstract

There is increasing evidence that stress and depression may play a crucial role in the aetiology and pathophysiology of fibromyalgia (FM). We first review recent studies on the possible role of life stress, including childhood trauma, in FM. Subsequently we focus on clinical and aetio-pathogenetic links between stress, depression and pain. We put forward the hypothesis that chronic stress / depression may contribute to a dysregulation of neuro-endocrine, immune and central pain mechanisms in FM. Finally, we discuss some future directions, including the use of new conceptual models, research topics and strategies, as well as potential implications from recent studies in affective disorders for the treatment of FM.

Key words : Depression ; childhood trauma ; chronic fatigue syndrome ; fibromyalgia ; life events ; neurobiology ; stress ; treatment.

Introduction

Fibromyalgia (FM) is a syndrome characterized by medically unexplained, widespread musculoskeletal pain, hyperalgesia and/or allodynia, physical and mental fatigue and effort intolerance, non-restorative sleep, mood disturbance as well as other functional (e.g. gastrointestinal) complaints (Mease *et al.* 2005). The syndrome shows substantial symptomatic and diagnostic overlap with chronic fatigue syndrome (CFS) (Clauw and Chrousos 1997 ; Sullivan *et al.* 2002 ; Meeus *et al.* in press) and other functional somatic syndromes such as irritable bowel syndrome (IBS) (Wessely *et al.* 1999 ; Aggarwal *et al.* 2006).

In the following paragraphs, we discuss (1) the precipitating, predisposing and perpetuating role of physical and psychosocial stressors in FM ; (2) evidence concerning clinical and aetio-pathogenetic links between stress, depression and FM ; (3) a pathophysiological hypothesis on the role of chronic stress and depression in dysregulating neuroendocrine, immune and central pain mechanisms in FM ; (4) important methodological issues with regard to stress and depression research in FM ; (5) lessons from recent therapeutic studies in affective disorders that may also inform FM treatment ; and (6) new conceptual models, topics and strategies for future research in this domain.

Life stress and FM

Precipitating stressors

Although clinical experience and retrospective studies suggest that the onset of FM is frequently associated with various types of negative life events (Anderberg *et al.* 2000 ; Poyhia *et al.* 2001) and personally-relevant daily hassles (Van Houdenhove *et al.* 2002), prospective studies could only partially confirm these findings (Raphael *et al.* 2002 ; Willliams *et al.* 2003 ; Kivimäki *et al.* 2004).

Whether *traumatic stressors* or *posttraumatic stress disorder (PTSD)* may precipitate FM still remains a controversial issue, although evidence for the frequent co-occurrence of PTSD and FM is increasing, in adult patients (Sherman *et al.* 2000 ; White *et al.* 2000 ; Cohen *et al.* 2002a ; Roy-Burne *et al.* 2004 ; Ciccone *et al.* 2005 ; Arguelles *et al.* 2006), as well as in children (Seng *et al.* 2005). The nature of the relationship remains unclear, but according to some authors, depression might be a mediating factor (Raphael *et al.* 2004a).

Predisposing stressors

Numerous retrospective case-control studies have shown that traumatic experiences (neglect, maltreatment or abuse) during childhood are more frequently reported by FM patients than by medically ill or healthy controls (for a review see e.g. Imbierowicz and Egle 2003 ; Davis *et al.* 2005 ; Van Houdenhove *et al.* in press). Although these findings suggest that *early life stress* may play a predisposing role in the aetio-pathogenesis of FM, such studies should be interpreted with caution due to confounding factors such as recall bias, response bias and health-care seeking bias (Hardt *et al.* 2004 ; Raphael 2005).

Traumatic experiences may augment vulnerability to FM via multiple and interacting mechanisms, notably psychophysiological mechanisms

associated with pathological arousal, such as muscle hypertension, hyperventilation and sleep problems ; hypothalamic-pituitary-adrenal (HPA-axis) dysfunction ; and inadequate stress coping resulting from negative affectivity, low self-esteem, proneness to depression and abuse-related personality disorders (Van Houdenhove *et al.* 2001a ; McLean *et al.* 2005 ; Weissbecker *et al.* 2006).

Furthermore, many FM patients appear to have created their own *lifestyle stress* – often since their early youth – by physically or mentally overexerting themselves, being too perfectionistic or overcommitted at work, or engaging in disproportionate self-sacrificing behaviour (Van Houdenhove *et al.* 1995, 2001b ; Smith *et al.* 2006).

Perpetuating stressors

Not accepting their condition and failing to adjust to their functional limitations (Viane *et al.* 2003), *low positive affect* (Davis *et al.* 2001), *high negative affect* (Geenen & Middendorp 2006), illness uncertainty (Reich *et al.* 2006), perceptual biases such as *somatic hypervigilance* (Crombez *et al.* 2004 ; Carillo-de-la-Pena *et al.* 2006) and dysfunctional cognitive coping such as *catastrophizing* (Edwards *et al.* 2006) undoubtedly enhances the patients' stress level and may lead to amplification and further persistence of FM symptoms.

Finally, not being accepted by significant others as suffering from a real and legitimate illness (*lack of social support)* can also be considered an important stress-generating factor that decreases quality of life and makes recovery from FM less probable (Schoofs *et al.* 2004).

Stress, depression and pain : what is the evidence ?

The clinical and aetio-pathogenetic relations between pain and depression have since long been recognized, but recently this issue has received renewed attention (Schatzberg 2004 ; Peveler *et al.* 2006 ; Kennedy *et al.* 2006). Assuming that mood disorders and FM are both stress-related conditions (Van Houdenhove and Egle, 2004 ; Hammen 2005), it is hardly surprising that there is high comorbidity between both (White *et al.* 2002 ; Thieme *et al.* 2004, Kassam *et al.* 2006 ; Tennen *et al.* 2006 ; Michielsen *et al.* 2006).

Studies have found comorbidity rates from 30 to 80 percent, depending on variations in definition and measurement of depression (Henningsen *et al.* 2003). A particular case is *atypical depression*, which is characterized by profound lethargia, daytime sleepiness and overeating, but also frequently involves diffuse somatic pain complaints and has been linked to stress-system underactivity (Gold and Chrousos 2002).

In FM patients, lifetime depression has been found to be much higher than in medical control groups and, moreover, to co-aggregate with mood disorders in family members (Arnold *et al.* 2004 ; Raphael *et al.* 2004b). Likewise, parents of children with primary juvenile FM reported higher levels of anxiety and depression than parents of healthy children or children with arthritis (Conte *et al.*, 2003). Thus, pain sensitivity, stress vulnerability and mood regulation may share common *familial-genetic factors* and FM may be categorized among the, genetically related, 'affective spectrum disorders' (Hudson *et al.* 2003, 2004).

More specifically, several recent studies have revealed genetic polymorphisms, i.e. in the serotonin transporter (Offenbaecher *et al.* 1999 ; Cohen *et al.* 2002b), the dopamine receptor (Buskila *et al.* 2004), the nordrenaline system (Gursoy *et al.* 2003) and the substance P receptor gene regulatory region (Ablin *et al.* 2005). However, it can be assumed that no single gene will be identified as the sole cause of FM. Much more likely, a combination of genetic traits coupled with a chain of environmental (physical and/or psychosocial) events will gradually emerge as an explanation (Ablin and Buskila 2006 ; Buskila and Sarzi 2006).

Stress, depression and the pathophysiology of FM

Stress-system dysfunction

The available evidence suggests that in FM the stress response system – notably the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system – is dysregulated (Okifuji and Turk 2002 ; Gupta and Silman 2004 ; Crofford *et al.* 2004 ; Gur *et al.* 2004 ; Adler and Geenen 2005 ; McBeth *et al.* 2005). Clinical observation and careful listening to patients' history, suggests that this abnormal functioning seems to occur mostly in the aftermath of a long period of overburdening by physical and / or emotional stressors, often associated with one or more depressive episodes. Eventually, the illness seems to be precipitated by an additional trigger in the shape of an acute physical or emotional event (Wentz *et al.* 2004 ; Van Houdenhove and Egle 2004 ; McLean *et al.* 2005).

We and others have proposed that this might imply a neurobiological 'switch' from *hyper*(re)-activity to *hypo*(re)activity of the HPA-axis, based on functional or even structural receptor changes, and followed by a cascade of disturbances in neurotransmitter functions, immunological and central pain processing mechanisms (Van Houdenhove and Egle 2004 ; Fries *et al.* 2005). In line with this, HPA-axis hypo-function following chronic stress has been found to lead to an inadequate neurohormonal stress response and impaired habituation to subsequent physical or psychosocial challenges

(Ostrander *et al.* 2006 ; Kudielka *et al.* 2006). Deficient HPA-axis functioning might foster pathological immune activation with release of pro-inflammatory cytokines, provoking the so-called sickness response (lethargia and malaise, social withdrawal, flu-like symptoms, concentration difficulties, mood lowering and pain threshold lowering), all of which characterize the symptom picture of FM (Wallace *et al.* 2001 ; Raison and Miller 2003).

Alternatively, stress system hypo-function might be considered a preceding 'trait' factor in some FM patients (Glass *et al.* 2004), possibly related to early adversities (Gunnar and Vazquez 2001). Interestingly, in this respect, recent population-based prospective investigations showed that HPA-axis hypo-function helped to predict the development of new chronic widespread pain in a group of psychologically 'at risk' subjects (Gupta *et al.* in press ; McBeth *et al.* in press).

Taken together, however, the exact significance of neuroendocrine dysfunction for the pathophysiology of FM remains to be elucidated (Cleare 2004).

Abnormal pain processing

Several recent studies strongly suggest that central pain processing is disturbed in FM. Indeed, 'generalized pain hypersensitivity' is now considered an important hallmark of the syndrome and has recently been confirmed by brain imaging studies (Gracely *et al.* 2002, 2004). Stress-related, cytokine-mediated activation of the inflammatory system may contribute to this central sensitization (Maier 2003 ; Khasar *et al.* 2005), but other factors such as inadequate descending pain inhibition (Mense 2000), including disturbed endogenous opioid system functioning (Kennedy *et al.* 2006), and low corticotropin releasing factor (CRF) (Larivière and Melzack 2000 ; Vit *et al.* 2006), may also play a role.

Furthermore, increasing evidence points towards peripheral tissues as relevant contributors to central sensitization, via neuroplastic changes in the spinal cord and brain. After central sensitization has been established, only minimal nociceptive input is required for the maintenance of the chronic pain state. Additional emotional and behavioural factors, such as pain-related negative affect and poor sleep may also play a role in pain threshold lowering (Price and Staud, 2005 ; Chiu *et al.* 2005 ; Staud 2006 ; Vierck 2006).

Studying the role of stress / depression in FM

The stress concept is rather vaguely defined and difficult to operationalize, which undoubtedly hampers its application in research (Van Praag 2004). Moreover, investigators on chronic pain disorders are not always aware of major methodological advances in the area of modern life stress studies. One example is the use of sophisticated interview-based strategies that may reveal not only external but also internal stressors associated with personality features and life history, and that focus on contextual features (and not only on stressors as such). Another example is the use of ecological momentary assessment methods and multivariate time series analyses that allow a detailed longitudinal view on the impact of daily life stressors on symptoms (Luyten and Van Houdenhove 2005).

Researchers should further recognize that causal relationships between FM and stress / depression are not linear, but recursive – so that patients often become trapped in a vicious cycle. Hence, future research should move away from simple linear etio-pathogenetic models but instead use 'multi-wave' studies to investigate recursive interactions between (pre- and post-morbid) stressors, coping styles / personality factors, and affective disorders in FM (Luyten and Van Houdenhove 2005).

Finally, FM researchers should study the relationship between stress, pain symptoms and HPA-axis functioning using objective stress measures and controlling for associated depression. By focusing on both biologic and psychosocial mediators and moderators, the complex interactions between these factors in the aetio-pathogenesis of FM may be unravelled (McLean *et al.* 2005b ; Luyten and Van Houdenhove 2006).

Treating FM : lessons from depression treatment research

Recent therapeutic guidelines for affective disorders emphasize the benefits of long-term maintenance / continuation treatment in preventing relapse, and recommend that therapists should aim at enduring changes in personality functioning and life style, as well as customize treatment to the patient's individual needs (Luyten *et al.* 2006). These guidelines are congruent with recent recommendations regarding the treatment of stress-related somatic syndromes such as CFS (Van Houdenhove, 2006) and FM (Dabadhoy & Clauw, 2006 ; Morley & Williams, 2006).

Moreover, depression treatment research has provided a compelling case for the importance of non-specific factors (such as the therapeutic alliance, and patient and therapist factors) in explaining outcome, beyond specific psychotherapeutic techniques and biological agents (Luyten *et al.* 2006). Treatment studies in FM should therefore consider these factors as well.

Finally, on a more general level, it may be expected that the growing interface between fundamental and treatment research in the study of affective disorders may inform a similar interface in FM research.

Future directions

Several new conceptual models may advance our understanding of the aetio-pathogenesis of various stress-related somatic syndromes, such as FM. Excellent examples are the concepts of 'stress system disorders' (Chrousos and Gold 1992), and 'allostasis / allostatic load' (McEwen 1998) that have recently been formulated within the 'bridging' sciences of psychoneuro-endocrinology and psychoneuro-immunology.

Furthermore, there is growing attention in stress research for 'nature-nurture' relationships (Meaney 2001 ; Moffit *et al.* 2005) including epigenetic mechanisms (Champagne and Meaney 2006) ; the role of positive and negative affect regulation (Zautra *et al.* 2005 ; Geenen and Middendorp 2006) ; and factors protecting against the impact of stressors (Champagne and Curley, 2005 ; Detert *et al.* 2004) including psychobiological determinants of resilience and vulnerability (Charney 2004) and consequences of childhood trauma and disordered early attachment (Waldinger *et al.* 2006) – all of which will open exciting heuristic avenues to study recursive interactions between life stress, personality, and genetic dispositions in stress-related illnesses.

Particularly growing insights in the role of the inflammatory response system, its links with the stress response system and its two-way relationships with the brain will augment our knowledge about cytokine-mediated pathological pain, fatigue, cognitive disturbances and mood disorders (Watkins and Maier, 2005 ; Glaser and Kiecolt-Glaser 2005).

It can be expected that these promising new developments will lay the groundwork for novel medications that will correct stress system dysregulations and abnormal pain processing (see e.g. Hendriksson and Sörensen 2002 ; Ledeboer *et al.* 2005 ; Crofford *et al.* 2005 ; Wood *et al.* 2005 ; Wallace 2006), and complement present pharmacological, cognitive-behavioural, rehabilitative and lifestyle interventions (Goldenberg *et al.* 2004 ; Jackson *et al.* 2006).

Conclusions

During the last years, evidence has accumulated that FM can be best understood psychologically as well as neurobiologically against the background of modern stress and depression research.

Nonetheless, our insights in the exact conditions under which stress and depression may play a predisposing, precipitating and / or perpetuating role in this syndrome remain fragmentary. Many uncertainties also remain with regard to the interference of physical and psychosocial stressors in the neurobiological processes giving rise to pain hypersensitivity, mood disturbance, fatigue and other FM symptoms.

On the other hand, it has become clear that FM treatment could benefit from lessons learned by recent research in depression, suggesting that therapeutic strategies in these patients should be personalized and maintained in the long run.

All these issues should be further investigated, based on new methodologies and theoretical concepts, and hopefully leading to more effective psychological and psychopharmacological therapies for those who suffer from FM.

REFERENCES

Ablin J. N., Bar-Shira A., Yaron M., Orr-Urtreger A. Possible association between fibromyalgia and a novel 1354>C polymorphism in the TACRI (substance P receptor) gene in Ashkenasi patients. *Arthritis Rheum.*, 2005, 52 (Suppl 9) : S269.

Ablin J. N., Buskila D. The genetics of fibromyalgia. Closing Osler's backdoor. *Isr. Med. Assoc. J.*, 2006, **8** : 428-429.

Adler G. K., Geenen R. Hypothalamic-pituitary-adrenal and autonomic nervous system functioning in fibromyalgia. *Rheum. Dis. Clin. N. Am.*, 2005, **31** : 187-202.

Aggarwal V. R., McBeth J., Zakrzewska J. M., Lunit M., MacFarlane G. J. The epidemiology of chronic syndromes that are frequently unexplained : do they have common associated factors ? *Int. J. Epidemiology*, 2006, **35** : 468-476.

Anderberg U. M., Marteinsdottir I., Theorell T., von Knorring L. The impact of life events in female patients with fibromyalgia and in female healthy controls. *Eur. Psychiatry*, 2000, **15** : 295-301.

Arguelles L. M., Afari N., Buchwald D. S., Clauw D. J., Furner S. *et al.* A twin study of posttraumatic stress disorder symptoms and chronic widespread pain. *Pain*, 2006, **124** : 150-157.

Arnold L. M., Hudson J. I., Hess E. V., Ware A. E., Fritz D. A. *et al.* Family study of fibromyalgia. *Arthritis Rheum.*, 2004, **50** : 944-952.

Buskila D., Cohen H., Neumann L. *et al.* An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and the relationship to novelty seeking personality traits. *Mol. Psychiatry*, 2004, **9** : 730-731.

Buskila D., Sarzi-Puttini P. Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome. *Arthritis Res. Ther.*, 2006, **8** : 218.

Carrillo-de-la-Pena M. T., Vallet M., Perez M. I., Gomez-Perretta C. Intensity dependence of auditory-evoked cortical potentials in fibromyalgia patients : a test of the generalized hypervigilance hypothesis. *J. Pain*, 2005, **115** : 316-321.

Champagne F. A., Curley J. P. How social experiences influence the brain. *Curr. Opin. Neurobiol.*, 2005, **15** : 704-709.

Champagne F. A., Meaney M. J. Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. *Biol. Psychiatry*, 2006, **59** : 1227-1235.

Charney D. S. Psychobiological mechanisms of resilience and vulnerability : implications for

successful adaptation to extreme stress. *Am. J. Psychiatry*, 2004, **161** : 195-216.

CHIU Y. H., SILMAN A. J., MACFARLANE G. J., RAY D., GUPTA A. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain*, 2005, **115** : 316-321.

CHROUSOS G. P., GOLD P. W. The concepts of stress and stress system disorders. Overview of physical and behavioural homeostasis. *JAMA*, 1992, **267** : 1244-1252.

CICCONE D. S., ELLIOTT D. K., CHANDLER H. K., NAYAK S., RAPHAEL K. G. Sexual and physical abuse in women with fibromyalgia syndrome. A test of the trauma hypothesis. *Clin. J. Pain*, 2005, **21** : 378-386.

CLAUW D., CHROUSOS G. P. Chronic pain and fatigue syndromes : overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation, 1997, **4** : 143-153.

CLEARE A. J. Stress and fibromyalgia – what is the link ? J. Psychosom. Res., 2004, **57** : 423-425.

COHEN H., NEUMANN L., HAIMAN Y., MATAR M. A., PRESS J. *et al.* Prevalence of posttraumatic stress disorder in fibromyalgia patients : overlapping syndromes or posttraumatic fibromyalgia syndrome ? Semin. *Arthritis Rheum.*, 2002a, **32** : 38-50.

COHEN H., BUSKILA D., NEUMANN L., EBSTEIN R. P. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. *Arthritis Rheum.*, 2002b, **46** : 845-847.

CONTE P. M., WALCO G. A., KIMURA Y. Temperament and stress response in children with juvenile primary fibromyalgia syndrome. *Arthritis Rheum.*, 2003, **48** : 2923-2930.

CROFFORD L. J., ROWBOTHAM M. C., MEASE P. J., RUSSELL I. J., DWORKIN R. H. *et al.* Pregabalin 1008-105 Study Group : Pregabalin for the treatment of fibromyalgia syndrome : results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.*, 2005, **52** : 1264-1273.

CROFFORD L. J., YOUNG E. A., ENGLEBERG C., KORSZUN A., BRUCKSCH C. B. *et al.* Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. *Brain Behav. Immun.*, 2004, **18** : 314-325.

CROMBEZ G., ECCLESTON C., VAN DEN BROECK A., GOUBERT L., VAN HOUDENHOVE B. Hypervigilance to pain in fibromyalgia : the mediating role of pain intensity and catastrophic thinking about pain. *Clin. J. Pain*, 2004, **20** : 98-102.

DABADHOY D., CLAUW D. J. Fibromyalgia : a different type of pain needing a different type of treatment. *Nat. Clin. Rheumatol.*, 2006, **2** : 364-372.

DAVIS D. A., LUECKEN L. J., ZAUTRA A. J. Are reports of childhood abuse related to the experience of chronic pain in adulthood ? A meta-analytic review of the literature. *Clin. J. Pain*, 2005, **21** : 398-405.

DAVIS M. C., ZAUTRA A. J., REICH J. W. Vulnerability to stress among women in chronic pain from fibromyalgia and osteoarthritis. *Ann. Behav. Med.*, 2001, **23** : 215-226.

DEDERT E. A., STUDTS J. L., WEISSBECKER I., SALMON P. G., BANIS P. L. *et al.* Religiosity may help preserve the cortisol rhythm in women with stress-related illness. Int. *J. Psychiatry Med.*, 2004, **34** : 61-77.

EDWARDS R. R., BINGHAM C. O. 3rd, BATHON J., HAYTHORNTHWAITE J. A. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Rheum.*, 2006, **55** : 325-332.

FRIES E., HESSE J., HELLHAMMER J., HELLHAMMER D. H. A new view on hypocortisolism. *Psychoneuroendocrinology*, 2005, **30** : 1010-1016.

GEENEN R., VAN MIDDENDORP H. The ostrich strategy towards affective issues in alexithymic patients with fibromyalgia. *Patient Educ. Couns.*, 2006, **60** : 97-99.

GLASER R., KIECOLT-GLASER J. K. Stress-induced immune dysfunction : implications for health. *Nat. Rev. Immunol.*, 2005, **5** : 243-251.

GLASS J. M., LYDEN A. K., PETZKE F., STEIN P., WHALEN G. *et al.* The effect of brief exercise cessation on pain, fatigue, and mood symptom development in healthy, fit individuals. *J. Psychosom. Res.*, 2004, **57** : 391-398.

GOLD P. W., CHROUSOS G. P. Organisation of the stress system and its dysregulation in melancholic and atypical depression. High vs low CRH/NE states. *Mol. Psychiatry*, 2002, **7** : 254-275.

GOLDENBERG D. L., BURCKHARDT C. S., CROFFORD L. Management of fibromyalgia syndrome. *JAMA*, 2004, **292** : 2388-2395.

GRACELY R. H., PETZKE F., WOLF J. M., CLAUW D. J. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum.*, 2002, **46** : 1333-1343.

GRACELY R. H., GEISSER M. E., GIESECKE T., GRANT M. A., PETZKE F. *et al.* Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain*, 2004, **127** : 835-843.

GUNNAR M. R., VAZQUEZ D. M. Low cortisol and a flattening of expected daytime rhythm : potential indices of risk in human development. *Dev. Psychopath.*, 2001, **13** : 513-538.

GUPTA A., SILMAN A. J. Psychological stress and fibromyalgia : a review of the evidence suggesting a neuroendocrinological link. *Arthritis Res. Ther.*, 2004, **6** : 98-106.

GUPTA A., SILMAN A. J., RAY D., MORRISS R., DICKENS C. *et al.* The role of psychosocial factors in predicting the onset of chronic widespread pain : results from a prospective population-based study. *Rheumatology*, (Oxford) (in press).

GUR A., CEVIK R., NAS K., COLPAN L., SARAC S. Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones. *Arthritis Res. Ther.*, 2004, **6** : R232-R238.

GURSOY S., ERDAL E., HERKEN H., MADENCI E., ALASEHIRLI B. *et al.* Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatol. Int.*, 2003, **23** : 104-107.

HAMMEN C. Stress and depression. *Annu. Rev. Clin. Psychol.*, 2005, **1** : 239-319.

HARDT J., RUTTER M. Validity of adult retrospective reports of adverse childhood experiences : review of the evidence. *J. Child Psychol. Psychiatr.*, 2004, **45** : 260-273.

HENDRIKSSON K. G., SÖRENSEN J. The promise of N-methyl-D-aspartate receptor antagonists in fibromyalgia. *Rheum. Dis. Clin. North Am.*, 2002, **28** : 343-351.

HENNINGSEN P., ZIMMERMANN T., SATTEL H. Medically unexplained physical symptoms, anxiety, and depression : a meta-analytic review. *Psychosom. Med.*, 2003, **65** : 528-533.

HUDSON J. I., MANGWETH B., POPE H. G. Jr, DE COL C., HAUSMANN A. *et al.* Family study of affective spectrum disorder. *Arch. Gen. Psychiatry*, 2003, **60** : 170-177.

HUDSON J. I., ARNOLD L. M., KECK Jr P. E., AUCHENBACH M. B., POPE Jr H. G. Family study of fibromyalgia and affective spectrum disorder. *Biol. Psychiatry*, 2004, **56** : 884-891.

IMBIEROWICS K., EGLE U. T. Childhood adversities in patients with fibromyalgia and somatoform pain disorder. *Eur. J. Pain*, 2003, **7** : 113-119.

JACKSON J. L., O'MALLEY P. G., KROENKE K. Antidepressants and cognitive-behavioral therapy for symptom syndromes. *CNS Spectr.*, 2006, **11** : 212-222.

KASSAM A., PATTEN S. B. Major depression, fibromyalgia and labour force participation : a population-based cross-sectional study. *BMC Musculoskelet. Disord.*, 2006, **7** : 4.

KENNEDY S. E., KOEPPE R. A., YOUNG E. A., ZUBIETA J. K. Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. *Arch. Gen. Psychiatry*, 2006, **63** : 1199-1208.

KHASAR S. G., GREEN P. G., LEVINE J. D. Repeated sound stress enhances inflammatory pain in the rat. *Pain*, 2005, **116** : 79-86.

KIVIMÄKI M., LEINO-ARJAS P., VIRTANEN M., ELOVAINO M., KELTIKANGAS-JARVINEN L. *et al.* Work stress and incidence of newly diagnosed fibromyalgia. A prospective cohort study. *J. Psychosom. Res.*, 2004, **57** : 417-422.

KUDIELKA B. M., VON KÄNEL R., PRECKEL D., ZGRAGGEN L., MISCHLER K. *et al.* Exhaustion is associated with reduced habituation of free cortisol responses to repeated acute psychosocial stress. *Biol. Psychol.*, 2006, **72** : 147-153.

LARIVIÈRE W. R., MELZACK R. The role of corticotropin-releasing factor in pain and analgesia. *Pain*, 2000, **84** : 1-12.

LEDEBOER A., SLOANE E. M., MILLIGAN E. D., FRANK M. G., MAHONY J. H. *et al.* Minocycline attenuates mechanical allodynia and proinfammatory cytokine expression in rat models of pain facilitation. *Pain*, 2005, **115** : 71-83.

LUYTEN P., BLATT S. J., VAN HOUDENHOVE B., CORVELEYN J. Depression research and treatment : are we skating to where the puck is going to be ? *Clin. Psychol. Rev.*, 2006, **26** : 985-999.

LUYTEN P., VAN HOUDENHOVE B. Beyond dualism. The role of life stress in chronic pain. *Pain*, 2005, **113** : 238-239.

LUYTEN P., VAN HOUDENHOVE B. Cortisol secretion and symptoms in patients xith fibromyalgia : comment on the article by McLean *et al. Arthritis Rheum.*, 2006, **54** : 2345-2346.

MAIER S. F. Bi-directional immune-brain communication : Implications for understanding stress, pain, and cognition. *Brain Behav. Immun.*, 2003, **17** : 69-85.

MCBETH J., CHIU Y. H., SILMAN A. J., RAY D., MORRISS R. *et al.* Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents. *Arthritis Res. Ther.*, 2005, **7** : R992-R1000.

MCBETH J., SILMAN A., GUPTA A., CHIU Y., RAY D. *et al.* Psychological risk factors are moderated through dysfunction of the hypothalamic pituitary adrenal stress axis in the onset of chronic widespread musculoskeletal pain. *Arthritis Rheum.* (in press).

MCEWEN B. S. Protective and damaging effects of stress mediators. *New Engl. J. Med.*, 1998, **338** : 171-179.

MCLEAN S. A., CLAUW D. J., ABELSON J. L., LIBERZON I. The development of persistent pain and psychological morbidity after motor vehicle collision : integrating the potential role of stress response systems into a biopsychosocial model. *Psychosom. Med.*, 2005a, **67** : 783-790.

MCLEAN S. A., WILLIAMS D. A., HARRIS R. E., KOP W. J., GONER K. H. *et al.* Momentary relationship between cortisol secretion and symptoms in patients with fibromyalgia. *Arthritis Rheum.*, 2005b, **52** : 3660-3669.

MEANEY M. J. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu. Rev. Neurosci.*, 2001, **24** : 1161-1192.

MEASE P. J., CLAUW D. J., ARNOLD L. M., GOLDENBERG D. L., WITTER J. *et al.* Fibromyalgia syndrome. *J. Rheumatol.*, 2005, **32** : 2270-2277.

MEEUS M., NIJS J., DE MEIRLEIR K. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome : A systematic review. *Eur. J. Pain* (in press).

MENSE S. Neurobiological concepts of fibromyalgia—the possible role of descending spinal tracts. *Scand. J. Rheumatol.*, Suppl., 2000, **113** : 24-29.

MICHIELSEN H. J., VAN HOUDENHOVE B., LEIRS I., VANDENBROECK A., ONGHENA P. Depression, attribution style and self-esteem in chronic fatigue syndrome and fibromyalgia patients : is there a link ? *Clin. Rheumatol.*, 2006, **25** : 183-188.

MOFFITT T. E., CASPI A., RUTTER M. Strategy for investigating interactions between measured genes and measured environments. *Arch. Gen. Psychiatry*, 2005, **62** : 473-448.

MORLEY S., WILLIAMS A. C. DE C. RCTs of psychological treatments for chronic pain : Progress and challenges. *Pain*, 2006, **121** : 171-172.

OFFENBAECHER M., BONDY B., DE JONGE S., GLATZEDER K., KRUGER M. *et al.* Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis Rheum.*, 1999, **42** : 2482-2488.

OKIFUJI A., TURK D. C. Stress and psychophysiological dysregulation in patients with fibromyalgia

syndrome. *Appl. Psychophysiol. Biofeedback*, 2002, **27** : 129-141.

OSTRANDER M. M., ULRICH-LAI Y. M., CHOI D. C., RICHTAND N. M., HERMAN J. P. Hypoactivity of the hypothalamo-pituitary-adrenocortical axis during recovery from chronic variable stress. *Endocrinology*, 2006, **147** : 2008-2017.

PEVELER R., KATONA C., WESSELY S., DOWRICK C. Painful symptoms in depression : under-recognised and under-treated ? *Brit. J. Psychiatry*, 2006, **188** : 202-203.

POYHIA R., DA COSTA D., FITZCHARLES M. A. Previous experiences of women with fibromyalgia and inflammatory arthritis and non-painful controls. *J. Rheumatol.*, 2001, **28** : 1888-1891.

PRICE D. D., STAUD R. Neurobiology of fibromyalgia syndrome. *J. Rheumatol.*, Suppl., 2005, **75** : 22-28.

RAISON C. L., MILLER A. H. When not enough is too much : the role of insufficient glucocorticoid signaling in the pathology of stress-related disorders. *Am. J. Psychiatry*, 2003, **160** : 1554-1565.

RAPHAEL K. G., NATELSON B. H., JANAL M. N., NAYAK S. A community-based survey of fibromyalgia-like pain complaints following the World Trade Center terrorist attacks. *Pain*, 2002, **100** : 131-139.

RAPHAEL K. G., JANAL M. N., NAYAK S. Comorbidity of fibromyalgia and posttraumatic stress disorder symptoms in a community sample of women. *Pain Med.*, 2004a, **5** : 33-41.

RAPHAEL K. G., JANAL M. N., NAYAK S., SCHWARTZ J. E., GALLAGHER R. M. Familial aggregation of depression in fibromyalgia : a community-based test of alternate hypotheses. *Pain*, 2004b, **110** : 449-460.

RAPHAEL K. G. Childhood abuse and pain in adulthood : more than a modest relationship ? *Clin. J. Pain*, 2005, **21** : 371-373.

REICH J. W., JOHNSON L. M., ZAUTRA A. J., DAVIS M. C. Uncertainty of illness relationships with mental health and coping processes in fibromyalgia patients. *J. Behav. Med.*, 2006, **29** : 307-316.

ROY-BYRNE P., SMITH W. R., GOLDBERG J., AFARI N., BUCHWALD D. Post-traumatic stress disorder among patients with chronic pain and chronic fatigue. *Psychol. Med.*, 2004, **34** : 363-368.

SCHATZBERG A. F. The relationship between chronic pain and depression. *J. Clin. Psychiatry*, 2004, **65** (Suppl 12) : 3-4.

SCHOOFS N., BAMBINI D., RONNING P., BIELAK E., WOEHL J. Death of a lifestyle : the effects of social support and healthcare support on the quality of life of persons with fibromyalgia and/or chronic fatigue syndrome. *Orthop. Nurs.*, 2004, **23** : 364-374.

SENG J. S., GRAHAM-BERMANN S. A., CLARK M. K., MCCARTHY A. M., RONIS D. L. Posttraumatic stress disorder and physical comorbidity among female children and adolescents : results from service-use data. *Pediatrics*, 2005, **116** : e767-e776.

SHERMAN J. J., TURK D. C., OKIFUJI A. Prevalence and impact of posttraumatic stress disorder-like symptoms on patients with fibromyalgia syndrome. *Clin. J. Pain*, 2000, **16** : 127-134.

SMITH W. R., WHITE P. D., BUCHWALD D. A case control study of premorbid and currently reported physical activity levels in chronic fatigue syndrome. *BMC Psychiatry*, 2006, **6** : 53.

SULLIVAN P. F., SMITH W., BUCHWALD D. Latent class analysis of symptoms associated with chronic fatigue syndrome and fibromyalgia. *Psychol. Med.*, 2002, **32** : 881-888.

STAUD R. Biology and therapy of fibromyalgia : pain in fibromyalgia syndrome. *Arthritis Res. Ther.*, 2006, **8** : 208.

TENNEN H., AFFLECK G., ZAUTRA A. Depression history and coping with chronic pain : a daily process analysis. *Health Psychol.*, 2006, **25** : 370-379.

THIEME K., TURK D. C., FLOR H. Comorbid depression and anxiety in fibromyalgia syndrome : relationship to somatic and psychosocial variables. *Psychosom. Med.*, 2004, **66** : 837-844.

VAN HOUDENHOVE B. What is the aim of cognitive behaviour therapy in patients with Chronic Fatigue Syndrome ? *Psychother. Psychosom.*, 2006, **75** : 396-397.

VAN HOUDENHOVE B., NEERINCKX E., ONGHENA P., HELLIN J. Does high 'action-proneness' make people more vulnerable to chronic fatigue syndrome ? A controlled psychometric study. *J. Psychosom. Res.*, 1995, **39** : 633-640.

VAN HOUDENHOVE B., NEERINCKX E., LYSENS R., VERTOMMEN H., VAN HOUDENHOVE L. *et al.* Victimization in chronic fatigue syndrome and fibromyalgia in tertiary care : a controlled study on prevalence and characteristics. *Psychosomatics*, 2001a, **42** : 21-28.

VAN HOUDENHOVE B., NEERINCKX E., ONGHENA P., LYSENS R., VERTOMMEN H. Premorbid "overactive" lifestyle in chronic fatigue syndrome and fibromyalgia. An etiological factor or proof of good citizenschip ? *J. Psychosom. Res.*, 2001b, **51** : 571-576.

VAN HOUDENHOVE B., NEERINCKX E., ONGHENA P., VINGERHOETS A., LYSENS R. *et al.* Daily hassles reported by chronic fatigue syndrome and fibromyalgia syndrome patients in tertiary care : a controlled quantitative and qualitative study. *Psychother. Psychosom.*, 2002, **71** : 207-213.

VAN HOUDENHOVE B., EGLE U. T. Fibromyalgia : a stress disorder ? Piecing the biopsychosocial puzzle together. *Psychother. Psychosom.*, 2004, **73** : 267-275.

VAN HOUDENHOVE B., LUYTEN P., EGLE U. T. The role of childhood trauma in chronic pain and fatigue. *J. Agress. Maltreatment Trauma* (in press).

VAN PRAAG H. The debit balance of present day stress research. *World J. Biol. Psychiatry*, 2004, **5** : 155-160.

VIANE I., CROMBEZ G., ECCLESTON C., POPPE C., DEVULDER J. *et al.* Acceptance of pain is an independent predictor of mental well-being in patients with chronic pain : empirical evidence and reappraisal. *Pain*, 2003, **106** : 65-72.

VIERCK C. J. Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain*, 2006, **124** : 242-263.

VIT J. P., CLAUW D. J., MOALLEN T., BOUDAH A., OHARA P. *et al.* Analgesia and hyperalgesia from CRF receptor modulation in the central nervous system of Fischer and Lewis rats. *Pain*, 2006, **121** : 241-260.

WALDINGER R. J., SCHULTZ M. S., BARSKY A. J., AHERN D. K. Mapping the road from childhood trauma to somatization : the role of attachment. *Psychosom. Med.*, 2006, **68** : 129-135.

WALLACE D. J., LINKER-ISRAELI M., HALLEGUA D., SILVERMAN S., SILVER D. *et al.* Cytokines play an aetiopathogenetic role in fibromyalgia : a hypothesis and pilot study. *Rheumatology (Oxford)*, 2001, **40** : 743-749.

WALLACE D. J. Is there a role for cytokine based therapies in fibromyalgia. *Curr. Pharm. Des.*, 2006, **12** : 17-22.

WATKINS L. R., MAIER S. F. Immune regulation of central nervous system functions : from sickness responses to pathological pain. *J. Intern. Med.*, 2005, **257** : 139-155.

WEISSBECKER I., FLOYD A., DEDERT E., SALMON P., SEPHTON S. Childhood trauma and diurnal disruption in fibromyalgia syndrome. *Psychoneuroendocrinology*, 2006, **31** : 312-324.

WENTZ K. A. H., LINDBERG C., HALLBERG L. R. M. Psychological functioning in women with fibromyalgia : a grounded theory study. *Health Care Women Int.*, 2004, **25** : 702-729.

WESSELY S., NIMNUAN C., SHARPE M. Functional somatic syndromes : One or many ? *Lancet*, 1999, **354** : 936-939.

WHITE K. P., CARETTE S., HARDT M., TEASELL R. W. Trauma and fibromyalgia : is there an association and what does it mean ? *Semin. Arthritis Rheum.*, 2000, **29** : 200-216.

WHITE K. P., NIELSON W. R., HARTH M., OSTBYE T., SPEECHLEY M. Chronic widespread musculoskeletal pain with or without fibromyalgia : psychological distress in a representative community adult sample. *J. Rheumatol.*, 2002, **29** : 588-594.

WILLIAMS D. A., CLAUW D. J. Self-reported symptoms before and after September 11 in patients with fibromyalgia. *JAMA*, 2003, **289** : 1637-1638.

WOOD P. B., KABLINGER A. S., CALDITO G. S. Open trial of pindolol in the treatment of fibromyalgia. *Ann. Pharmacother.*, 2005, **39** : 1812-1816.

ZAUTRA A. J., FASMAN R., REICH J. W., HARAKAS P., JOHNSON L. M. *et al.* Fibromyalgia : evidence for deficits in positive affect regulation. *Psychosom. Med.*, 2005, **67** : 147-155.

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