Industrial Psychiatry Journal
Publication of the Association of Industrial Psychiatry of India
Home
Current issue
Instructions
Submit article

Ind Psychiatry J. 2011 Jan-Jun; 20(1): 4–10.
doi: 10.4103/0972-6748.98407
PMCID: PMC3425245

Gender differences in stress response: Role of developmental and biological determinants

Rohit Verma, Yatan Pal Singh Balhara,[1] and Chandra Shekhar Gupta[2]

Author information ► Copyright and License information ►

Abstract

Go to:

Stress response is associated with manifestations of various psychosomatic and psychiatric disorders. Hence, it is important to understand the underlying mechanisms that influence this association. Moreover, men and women tend to react differently with stress–both psychologically and biologically. These differences also need to be studied in order to have a better understanding in the gender difference observed for many disorders, which are likely to be contributed by the gender difference in stress reactivity and responses. Such an understanding would have a significant impact on our understanding about how adult health is set during early life and how adult disease could be prevented in men and women.

Keywords: Gender, psychiatric disorders, stress response

Stress can be defined as a real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and behavioral responses. In Eastern cultures, stress has been viewed as an absence of inner peace. On the other hand, the Western culture has viewed stress as a loss of control.

Gender is an important determinant of human health, and there is a clear pattern for the sex-specific prevalence rates of various mental and physical disorders. Susceptibility to infectious diseases, hypertension, aggressive behavior, and drug abuse is generally observed to be higher in men. Conditions such as autoimmune diseases, chronic pain, depression, and anxiety disorders are relatively more prevalent among women.[1–4] The observed gender-specific disease pattern may be partly attributed to effects of sex hormones as some of these gender differences emerge during reproductive years and gradually diminish after menopause.[5] Individual differences in stress reactivity have been proposed as a potentially important risk factor for gender-specific health problems in men and women.[2,6]

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND AUTONOMIC NERVOUS SYSTEM

Go to:

Assessment of gender differences in stress reactivity relies primarily on measuring physiological responses to acute stressors in laboratory settings. This includes activities of the Hypothalamic-Pituitary-Adrenal (HPA) axis (eg, cortisol) and sympathetic nervous system (eg, heart rate and blood pressure). Greater acute HPA and autonomic responses have been found in adult men as compared to adult women, with the help of standard performance-related psychosocial stressors such as public speaking.[2,3] Pathogenesis of cardiovascular disease, aggression, and immune suppression in men are likely to be influenced by this greater sympathoadrenal responsiveness.[4,7]

HPA response patterns differ markedly between males and females. This has been demonstrated in both animal and human studies. The biochemical profile of human beings varied from that of rodents with regard to stress-related neurochemicals such as basal Adrenocorticotropic Hormone (ACTH) and corticosterone levels.[8] While the basal level as well as variance in response to stress is uniformly higher in females of rodents, the picture is more complex in humans. A relatively higher secretion of ACTH with comparable total cortisol levels under basal conditions has been observed in men. This finding reflects an increased sensitivity of the adrenal cortex in women as compared to men.[9] However, no gender differences are observed at the pituitary level on challenging with synthetic Human Corticotropin-Releasing Factor (h-CRF) with or without pretreatment with dexamethasone.[10,11] The response is different to ovine CRF[12] or a combination of h-CRF and vasopressin with respect to ACTH secretion, with women being more responsive.[11]

GONADAL STEROIDS AND MENSTRUAL CYCLE

Go to:

Female sex hormones attenuate the sympathoadrenal and HPA responsiveness. This leads to sluggish cortisol feedback on the brain and less or delayed containment of the stress response. Tendency of women to develop depression is related to the compromised cortisol feedback effects on HPA arousal.[2,6] Ovariectomy leads to attenuated HPA responses, whereas estradiol substitution induces HPA stimulation in animal studies.[13] An increased HPA-axis response to stress in females is observed in gonadectomized or neonatally estrogenized rats. This effect is independent of differences in circulating gonadal steroid levels.[14] This suggests an innate or organized difference in the HPA-axis response to stress. Genomic differences, organizationally or developmentally programmed effects (caused by earlier differential gonadal steroid exposure), and/or acute, activational effects of recent gonadal steroid exposure are some of the possible underlying mechanisms reflected in the observed sex differences in the central nervous system function. The sex differences in HPA axis responses would be expected to disappear if gonadal steroids were removed. On the contrary, sexual dimorphism would persist if the responses were not dependent on the concurrent gonadal steroids. Low levels of estradiol are observed in the early follicular phase, which peak shortly before or during ovulation and slowly decrease throughout the luteal phase. Basal as well as stimulated ACTH and corticosterone levels are the highest around the time of ovulation in rats.[15] Human studies have produced inconsistent results with respect to possible changes in the HPA activity during the menstrual cycle.[16]

PSYCHONEUROIMMUNOLOGICAL MARKERS

Go to:

There is a difference in susceptibility of women and men to specific immunological disorders. This suggests gender dimorphism of the immune system. Gender may exert differential effects on the immune system by modulating Glucocorticoid (GC) sensitivity of proinflammatory cytokine production.[17] The HPA axis can be activated by a wide variety of psychosocial and physiological stressors. This results in the secretion of GCs and modulation of specific immune responses. Psychosocial stress, such as academic examinations, leads to decreased cellular immune function.[18] This is mediated by profound changes in cytokine secretion. GCs suppress major type 1 cytokines, interferon-alpha, and Interleukin (IL)-2, produced by TH1 helper cells. However, type 2 cytokines, IL-4, and IL-10 remain unchanged. Humoral immune responses are favoured, while cell-mediated immunity is suppressed by this shift toward a type 2 cytokine pattern.[19] GCs specifically inhibit the production of proinflammatory cytokines (IL-6, IL-1, and Tumor Necrosis Factor (TNF)-alpha) in monocytes and macrophages. The anti-inflammatory cytokines remain unaffected or are even stimulated.[20]

HPG axis exerts direct and indirect effects on the immune system. HPA axis acts as a regulatory feedback loop that shuts off inflammatory responses to invading antigens after the initial response or in a state of stress. Cellular immunity is inhibited by estrogen, as it induces a shift in cytokine balance toward a type 2 cytokine response.[21] Monocytes and macrophages are affected in a dose-dependent manner. Inhibition of proinflammatory cytokine production occurs at higher concentrations and stimulation at lower concentrations.[22] Proinflammatory cytokine production is inhibited by progesterone as well. This action of progesterone is mediated by its competitive binding to the GC receptor.[23] Testosterone inhibits immune functions to some extent.[21,24]

NEUROIMAGING CORRELATES AND TASK STRATEGY

Go to:

The understanding of neuroanatomical substrates underlying human emotional processes tightly related to stress has been facilitated by functional neuroimaging studies.[25,26] However, these studies suffer from a major limitation. The majority of emotional stimuli employed in existing Functional Magnetic Resonance Imaging (fMRI) studies (eg, fearful faces) lack critical features of a standard psychosocial stress paradigm. Such a paradigm comprises motivated performance tasks along with social-evaluative threat and/or subjective feelings of uncontrollability.[27] A gender-specific neural activation model underlying the central stress response has been observed in these studies. This includes asymmetric prefrontal activity in males and, primarily, limbic activation in females.[28]

Negative affective style and suppressed immune function have been associated with high levels of right-sided prefrontal activation.[29] The Right Parieto-Frontal Cortex (RPFC) plays a major role in regulating negative emotions. This effect is most evident in moderating and inhibiting Dorsal Anterior Cingulate Cortex (DACC) and amygdala hyperactivities associated with negative affect.[30,31]

Persistent DACC activation following stress observed in female subjects might predispose women to mood disorders and depression if there is no modulating effect of RPFC. RPFC may be a critical neural substrate mediating adaptation and coping under stress.[32] Activation of RPFC and right parietal regions has been associated with various cognitive control tasks, including working memory, response selection, and task switching, as well as inhibitory functions.[33] The role of ventral striatum along with several limbic regions has been implicated in learning, reward, motivation, and emotion.[34] The observed gender differences in central stress responses might be a result of computational roles subserved by these brain regions.

The general trend of greater acute HPA and autonomic responses in males as compared to females by using performance stress paradigms is supported by the neuroimaging findings.[2] A greater degree of emotional “rewinding” (melancholy thinking) or reflection of own emotional traits observed in females as compared to males after completion of stress tasks is a likely consequence of persistent cingulate activation.[35] However, such observations are not consistent across studies. Some studies have found that adoption of social rejection task as the stressor instead of achievement tasks resulted in either no gender difference in stress reactivity or greater cortisol elevation in females.[27] It has been proposed that women are more likely to be negatively affected by interpersonal events than men.[36]

The complex nature of gender-specific stress response is reflected in the differences in experimental findings and alternative theoretical models. The findings are likely to be influenced by type of stressor/challenge, experimental procedure, outcome measured, subject status, and modulation by other stress mediators.[27]

GENETIC MODULATION AND ENDOPHENOTYPE/ PERSONALITY PREDISPOSITION

Go to:

The tendency to display negative effect in response to minor stressors in daily life is a part reflection of genetic liability to depression. It has been postulated as a true depression endophenotype.[37,38] However, depressive disorder develops in only a small fraction of individuals exposed to stressful life events (SLEs).[39] This could be result from greater sensitivity to depression-inducing effects of SLEs among some individuals as compared to others.[40,41] Personality trait,[42–44] childhood adversity,[45] and indirect measures of genetic risk for depression and anxiety, derived from twin or family studies[46,47] are some of the factors shown to increase sensitivity to SLEs. A length polymorphism in the gene encoding the serotonin transporter (5-HTTLPR) could be responsible for the moderating effect of genetic risk on the relationship between life events and depression.[48] However, this effect was observed only for the mild stressors rather than the severe life events.[49] An interaction between a genetic polymorphism and a stable psychological trait to experience the environment as stressful may be the manifested sign of an underlying interaction between a genetic polymorphism and SLEs.[39] Additionally, the 5-HTTLPR genotype may moderate the association between depressive disorder and the tendency to experience the environment as stressful.

Patients with depression or anxiety tend to score higher on neuroticism, extraversion, and facets of agreeableness and conscientiousness than individuals without these conditions.[50] Neuroticism has been associated with social phobia, agoraphobia, panic disorder, obsessive–compulsive disorder, and major depression. Introversion has been associated with social phobia and agoraphobia. Neuroticism not only predicts the onset of depressive symptoms and depressive disorder,[51] but also increases the risk of exposure to SLEs.[52,53]

COGNITIVE STRUCTURE

Go to:

As characterized by Beck, sociotropy reflects a high need for interpersonal relationships with a focus on ‘pleasing others to avoid disapproval’ in order to secure attachments. However, an increased need for independence with an elaborated focus on “control” and personal freedom to reduce possibility of failure is reflected in autonomy.[54] Beck postulates that elevated levels of sociotropy and autonomy increase one's sensitivity to the depressogenic effects of certain types of stressful life events.

Cognitive styles reflective of ‘concern about disapproval’ and ‘need for control’ pose significant risk for depression independent of the effects of stressful life events.[55] Individuals rating higher on these two cognitive styles are likely to be at greater risk for depression in the presence of stressful life events.[56] Kendler *et al.* reported that women are more sensitive to depressogenic effects of interpersonal problems with individuals within their proximal network.[57] Ruminative thinking is also more common in women and is associated with an increased risk of depression.[58]

FIGHT-OR-FLIGHT V/S TEND-AND-BEFRIEND MODEL

Go to:

There is a difference in the stress response exhibited by men and women. It is characterized by ‘fight-or-flight’ in men and ‘tend-and-befriend’ in women.[59] This hypothesis is supported by neuroendocrine and behavioral evidence. The physiological stress response typically involves activation of the sympathetic nervous system and the HPA axis in both genders. However, the stress response specifically builds on attachment care-giving processes in females. This tends to buffer the sympathetic and HPA arousal.

It was observed that the RPFC is activated and Left Orbitofrontal Cortex (LOrF) is suppressed by stress. RPFC is an important part of both the negative emotion and vigilance systems and LOrF is associated with positive emotion and hedonic goals.[60] The hypothesis that stress responses in men may be primarily characterized as “fight-or-flight” is supported by the observation that RPFC activation and LOrF deactivation with stress is predominately observed in the male brain. Involvement of the limbic system including ventral striatum, putamen, insula, and cingulate cortex underlies the stress response in females.[61] The observed limbic activation to stress in female subjects is more consistent with a ‘tend-and-

befriend' rather than a 'fight-or-flight' model.

However, it is noteworthy that ventral striatum activation is not a unique marker for the involvement of the reward system and has been implicated in numerous processes.[62] Also, the isolated fMRI environment is hostile to the formation of social attachment under stress. Some authors have suggested that the gender difference in emotionality per se may be an ill-posed question.[63,64]

DEVELOPMENTAL IMPACT

Go to:

Attachment theory proposed by Bowlby provides a biological basis for understanding close, protective relationships.[65,66] The attachment theory is based on the premises that a child's desire for proximity to his/her mother is a biological drive, which has been selected in evolution. An infant maintains proximity to her or his mother through a complex system of communications and behaviors, which increase its probability of survival. An insecure attachment may increase perceived stress. Also, it may affect the intensity or duration of the physiological stress response. Finally, it may determine the success of social support in buffering stress.

A high prevalence of past psychological trauma, including sexual abuse, is reported by individuals with various physical conditions including gastrointestinal disorders,[67] fibromyalgia,[68,69] and pain syndromes.[70] Small size at birth is associated with a higher prevalence of cardiovascular and metabolic disease in a child's later life.[71]

Animal and human studies have suggested that *in utero* resetting of the Hypothalamic–Pituitary–Adrenal (HPA) axis may be an important change initiating the metabolic syndrome. A sexually dimorphic response to programming of the HPA axis has been found in animal studies. Female rats are more sensitive than male rats to activation of the HPA axis following fetal alcohol exposure[72] or prenatal stress.[73] Moreover, the HPA-activation associated glucose tolerance and insulin sensitivity has been found to be impaired in female guinea pigs.[74] Association between the simple measurement of fasting plasma cortisol with birthweight and the metabolic syndrome has been found in both men and women. However, most of the published cross-sectional studies exploring the role of cortisol levels in cardiovascular risk factors have been conducted in men.[75,76] A difference in metabolic clearance rates of cortisol among males and females is reflected in the fact that urinary cortisol metabolite excretion differs between them.[77] Prematurity at the time of birth affects the cortisol metabolite excretion rate only in women.[78] Also prematurely born women exhibiting lower cortisol responses to stress.[10,79] A more recent study failed to find a correlation between birth size and the adrenal response to synthetic ACTH.[80]

ASSOCIATION WITH DISORDERS

Go to:

Manifestations of psychosomatic and psychiatric disorders has been found to be associated with a dysfunctional HPA axis.[81] HPA hyperactivity is a common finding in major depression,[82] social phobia,[83] panic disorder,[84] generalized anxiety,[85] obsessive–compulsive disorder,[86] susceptibility to infectious diseases,[87] and cardiovascular disorders.[88] Evidence of hypercortisolism is one of the most consistent biological findings among psychiatric patients.[89–91] Different diagnostic subtypes of depression may be characterized by different types of stress system pathology. Melancholic depression is associated with HPA axis hyperactivity.[92] On the other hand, atypical depression is associated with HPA axis downregulation.[93] Lupus erythematosus,[94] multiple sclerosis,[95] and neurodermatitis[96] are associated with hyporeactivity of the HPA system. A clear relationship between stressful life events and the onset of breast cancer has not yet been established.[97] However, a few studies suggest that stress may influence the progression and recurrence of cancer. Severe life event stress is associated with an increased rate of early HIV disease progression.[98] Specific types of chronic difficulty such as caring for a relative with dementia can be associated with increased cortisol secretion.[99,100] A study found lowered plasma tryptophan levels and increased cortisol secretion in carers of patients with clinical dementia.[100]

A noteworthy point here is that some studies have found that patients suffering from depression hypersecrete cortisol.[101] Also, elevated cortisol levels after life events are not necessarily associated with the development of depressive disorder. In addition, the majority of patients suffering from moderate depression in the community probably do not hypersecrete cortisol.

CONCLUSION

Go to:

Prevention of emergence of various disorders could be helped significantly by improving our understanding in the psychobiological impact of stress. Men and women tend to react differently to stress—both psychologically and biologically. The neurobiological underpinnings of this difference continue to be explored. At the same time, the research needs to explore the determinants of the environmental influence on the stress reaction. Better planned and designed interventions would help individuals deal more effectively with stress in their lives.

Footnotes

Go to:

Source of Support: Nil.

Conflict of Interest: None declared.

REFERENCES

Go to:

1. Holden C. Sex and the suffering brain. Science. 2005;308:1574. [PubMed]

2. Kajantie E, Phillips DI. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology. 2006;31:151–78. [PubMed]

3. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: A review. Biol Psychol. 2005;69:113–32. [PubMed]

4. Lundberg U. Stress hormones in health and illness: The roles of work and gender. Psychoneuroendocrinology. 2005;30:1017–21. [PubMed]

5. Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: Importance of gender. Psychoneuroendocrinology. 2005;30:80–91. [PubMed]

6. Goldstein JM, Jerram M, Poldrack R, Ahern T, Kennedy DN, Seidman LJ, et al. Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging. J Neurosci. 2005;25:9309–16. [PubMed]

7. Segerstrom SC, Miller GE. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130:601–30. [PMC free article] [PubMed]

8. Kitay JI. Pituitary-adrenal function in the rat after gonadectomy and gonadal hormone replacement. Endocrinology. 1963;73:253–60. [PubMed]

9. Roelfsema F, van den Berg G, Frölich M, Veldhuis JD, van Eijk A, Buurman MM, et al. Sex-dependent alteration in cortisol response to endogeneous adrenocorticotropin. J Clin Endocrinol Metab. 1993;77:234–40. [PubMed]

10. Kirschbaum C, Wust S, Hellhammer D. Consistent sex differences in cortisol responses to psychological stress. Psychosom Med. 1992;54:648–57. [PubMed]

11. Born J, Ditschuneit I, Schreiber M, Dodt C, Fehm HL. Effects of age and gender on pituitary-adrenocortical responsiveness in humans. Eur J Endocrinol. 1995;132:705–11. [PubMed]

12. Gallucci WT, Baum A, Laue L, Rabin DS, Chrousos GP, Gold PW, et al. Sex differences in sensitivity of the hypothalamic-pituitary-adrenal axis. Health Psychol. 1993;12:420–5. [PubMed]

13. Stroud LR, Salovey P, Epel ES. Sex differences in stress responses: Social rejection versus achievement stress. Biol Psychiatry. 2002;52:318–27. [PubMed]

14. Patchev VK, Almeida OF. Gender specificity in the neural regulation of the response to stress: New leads from classical paradigms. Mol Neurobiol. 1998;16:63–77. [PubMed]

15. Carey MP, Deterd CH, de Koning J, Helmerhorst F, de Kloet ER. The influence of ovarian steroids on hypothalamic-pituitary-adrenal regulation in the female rat. J Endocrinol. 1995;144:311–21. [PubMed]

16. Abplanalp JM, Livingston L, Rose RM, Sandwisch D. Cortisol and growth hormone responses to psychological stress during the menstrual cycle. Psychosom Med. 1977;39:158–77. [PubMed]

17. Rohleder N, Schommer NC, Hellhammer DH, Engel R, Kirschbaum C. Sex differences in glucocorticoid sensitivity of proinflammatory cytokine production after psychosocial stress. Psychosom Med. 2001;63:966–72. [PubMed]

18. Marshall GD, Jr, Agarwal SK, Lloyd C, Cohen L, Henninger EM, Morris GJ. Cytokine dysregulation associated with exam stress in healthy medical students. Brain Behav Immun. 1998;12:297–307. [PubMed]

19. Agarwal SK, Marshall GD., Jr Glucocorticoid-induced type1/type2 cytokine alterations in humans: A model for stress-related immune dysfunction. J Interferon Cytokine Res. 1998;18:1059–68. [PubMed]

20. Franchimont D, Martens H, Hagelstein MT, Louis E, Dewe W, Chrousos GP, et al. Tumor necrosis factor-α decreases, and interleukin-10 increases, the sensitivity of human monocytes to dexamethasone: Potential regulation of the glucocorticoid receptor. J Clin Endocrinol Metab. 1999;84:2834–9. [PubMed]

21. Bijlsma JW, Cutolo M, Masi AT, Chikanza IC. The neuroendocrine- immune basis of rheumatic diseases. Immunol Today. 1999;20:298–301. [PubMed]

22. Miller L, Hunt JS. Sex steroid hormones and macrophage function. Life Sci. 1996;59:1–14. [PubMed]

23. Miller L, Hunt JS. Regulation of TNF-α production in activated mouse macrophages by progesterone. J Immunol. 1998;160:5098–104. [PubMed]

24. Giltay EJ, van Schaardenburg D, Gooren LJ, Popp-Snijders C, Dijkmans BA. Androgens and ankylosing spondylitis: A role in the pathogenesis? Ann N Y Acad Sci. 1999;876:340–64. discussion 365. [PubMed]

25. Hamann S, Canli T. Individual differences in emotion processing. Curr Opin Neurobiol. 2004;14:233–8. [PubMed]

26. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. Neuroimage. 2002;16:331–48. [PubMed]

27. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. Psychol Bull. 2004;130:355–91. [PubMed]

28. Wang J, Korczykowski M, Rao H, Fan Y, Pluta J, Gur RC, et al. Gender difference in neural response to psychological stress. Soc Cogn Affect Neurosci. 2007;24:227–39. [PMC free article] [PubMed]

29. Davidson RJ, Jackson DC, Kalin NH. Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. Psychol Bull. 2000;126:890–909. [PubMed]

30. Beauregard M, Levesque J, Bourgouin P. Neural correlates of conscious self-regulation of emotion. J Neurosci. 2001;21:RC165. [PubMed]

31. Kalisch R, Wiech K, Herrmann K, Dolan RJ. Neural correlates of self-distraction from anxiety and a process model of cognitive emotion regulation. J Cogn Neurosci. 2006;18:1266–76. [PMC free article] [PubMed]

32. Christoff K, Ream JM, Geddes LP, Gabrieli JD. Evaluating self-generated information: Anterior prefrontal contributions to human cognition. Behav Neurosci. 2003;117:1161–8. [PubMed]

33. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 2004;8:170–7. [PubMed]

34. Poldrack RA, Rodriguez P. How do memory systems interact? Evidence from human classification learning. Neurobiol Learn Mem. 2004;82:324–32. [PubMed]

35. Papadakis AA, Prince RP, Jones NP, Strauman TJ. Self-regulation, rumination, and vulnerability to depression in adolescent girls. Dev Psychopathol. 2006;18:815–29. [PubMed]

36. Cyranowski JM, Frank E, Young E, Shear MK. Adolescent onset of the gender difference in lifetime rates of major depression: A theoretical model. Arch Gen Psychiatry. 2000;57:21–7. [PubMed]

37. Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. Am J Psychiatry. 2003;160:636–45. [PubMed]

38. Wichers M, Myin-Germey I. Genetic risk of depression and stress induced negative affect in daily life. Br J Psychiatry. 2007;191:218–223. [PubMed]

39. Goldberg EL, Comstock GW. Epidemiology of life events: Frequency in general populations. Am J Epidemiol. 1980;111:736–52. [PubMed]

40. Brown GW, Bifulco A, Harris TO. Life events, vulnerability and onset of depression: Some refinements. Br J Psychiatry. 1987;150:30–42. [PubMed]

41. Lora A, Fava E. Provoking agents, vulnerability factors and depression in an Italian setting: A replication of Brown and Harris's model. J Affect

Disord. 1992;24:227–35. [PubMed]

42. Bolger N, Schilling EA. Personality and the problems of everyday life: The role of neuroticism in exposure and reactivity to daily stressors. J Pers. 1991;59:355–86. [PubMed]

43. Ormel J, Oldehinkel AJ, Brilman EI. The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. Am J Psychiatry. 2001;158:885–91. [PubMed]

44. Fanous AH, Neale MC, Straub RE, Webb BT, O'Neill AF, Walsh D, et al. Clinical features of psychotic disorders and polymorphisms in HT2A, DRD2, DRD4, SLC6A3 [DAT1], and BDNF: A family based association study. Am J Med Genet B Neuropsychiatr Genet. 2004;125B:69–78. [PubMed]

45. Hammen C, Henry R, Daley SE. Depression and sensitization to stressors among young women as a function of childhood adversity. J Consult Clin Psychol. 2000;68:782–7. [PubMed]

46. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale M, Heath AC, et al. Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry. 1995;152:833–42. [PubMed]

47. Eaves LJ, Heath AC, Neale MC, Hewitt JK, Martin NG. Sex differences and non-additivity in the effects of genes on personality. Twin Res. 1998;1:131–7. [PubMed]

48. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science. 2003;301:386–9. [PubMed]

49. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: A replication. Arch Gen Psychiatry. 2005;62:529–35. [PubMed]

50. Bienvenu OJ, Samuels JF, Costa PT, Reti IM, Eaton WW, Nestadt G. Anxiety and depressive disorders and the five-factor model of personality: A higher- and lower-order personality trait investigation in a community sample. Depress Anxiety. 2004;20:92–7. [PubMed]

51. Rodgers B. Behaviour and personality in childhood as predictors of adult psychiatric disorder. J Child Psychol Psychiatry. 1990;31:393–414. [PubMed]

52. Van Os J, Jones PB. Early risk factors and adult person-environment relationships in affective disorder. Psychol Med. 1999;29:1055–67. [PubMed]

53. Headey B, Wearing A. Personality, life events, and subjective well-being: Toward a dynamic equilibrium model. J Pers Soc Psychol. 1989;57:731–9.

54. Beck AT. Cognitive therapy of depression: New perspectives. In: Clayton P, Barrett J, editors. Treatment of depression: Old controversies and new approaches. New York: Raven press; 1983. pp. 265–90.

55. Mazure CM, Raghavan C, Maciejewski PK, Jacobs SC, Bruce ML. Cognitive personality characteristics as direct predictors of unipolar major depression. Cognit Ther Res. 2001;25:215–25.

56. Mazure CM, Maciejewski PK. The interplay of stress, gender and cognitive style in depressive onset. Arch Womens Ment Health. 2003;6:5–8. [PubMed]

57. Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry. 2001;158:587–93. [PubMed]

58. Butler LD, Nolen-Hoeksema S. Gender differences in responses to depressed mood in a college sample. Sex Roles. 1994;30:331–46.

59. Taylor SE, Klein LC, Lewis BP, Gruenewald TL, Gurung RA, Updegraff JA. Biobehavioral responses to stress in females: Tend-and-befriend, not fight-or-flight. Psychol Rev. 2000;107:411–29. [PubMed]

60. Wang J, Rao H, Wetmore GS, Furlan PM, Korczykowski M, Dinges DF, et al. Perfusion functional MRI reveals cerebral blood flow pattern under psychological stress. Proc Natl Acad Sci U S A. 2005;102:17804–9. [PMC free article] [PubMed]

61. McClure SM, York MK, Montague PR. The neural substrates of reward processing in humans: The modern role of fMRI. Neuroscientist. 2004;10:260–8. [PubMed]

62. Poldrack RA. Can cognitive processes be inferred from neuroimaging data? Trends Cogn Sci. 2006;10:59–63. [PubMed]

63. Barrett LF, Robin L, Pietromonaco PR, Eyssell KM. Are women the "more emotional" sex? Evidence from emotional experiences in social context. Cogn Emot. 1998;12:555–78.

64. Fischer AH. Sex differences in emotionality: Fact or stereotype? Fem Psychol. 1993;3:303–18.

65. Bowlby J. Attachment. Vol. 1. New York: Basic Books; 1969. Attachment and loss.

66. Bowlby J. Separation: Anxiety and anger. Vol. 2. New York: Basic Books; 1973. Attachment and loss.

67. Drossman DA, Talley NJ, Leserman J, Olden KW, Barreiro MA. Sexual and physical abuse and gastrointestinal illness.Review and recommendations. Ann Intern Med. 1995;123:782–94. [PubMed]

68. Walker EA, Keegan D, Gardner G, Sullivan M, Bernstein D, Katon WJ. Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: II.Sexual, physical, and emotional abuse and neglect. Psychosom Med. 1997;59:572–7. [PubMed]

69. McBeth J, Macfarlane GJ, Benjamin S, Morris S, Silman AJ. The association between tender points, psychological distress, and adverse childhood experiences: A community-based study. Arthritis Rheum. 2000;42:1397–404. [PubMed]

70. Golding JM. Sexual assault history and headache: Five general population studies. J Nerv Ment Dis. 1999;187:624–9. [PubMed]

71. Barker DJ. Edinburgh: Churchill Livingstone; 1988. Mothers, Babies and Health in Later Life.

72. Redei E, Halasz I, Li LF, Prystowsky MB, Aird F. Maternal adrenalectomy alters the immune and endocrine functions of fetal alcohol-exposed male offspring. Endocrinology. 1993;133:452–60. [PubMed]

73. Weinstock M, Matilina E, Maor GI, Rosen H, McEwan BS. Prenatal stress selectively alters the reactivity of the hypothalamic-pituitary-adrenal system in the female rat. Brain Res. 1992;595:195–200. [PubMed]

74. Thavaneswaran P, Horton DM, Danilevica S, Kind KL, Robinson JS, Owens JA. San Francisco: American Endocrine Society; 2002. Gender specific prenatal programming of insulin resistance and diabetes in the aged guinea pig: A role for the HPA axis; pp. 3–395.

75. Phillips DI, Walker BR, Reynolds RM, Flanagan DE, Wood PJ, Osmond C, et al. Low birth weight and elevated plasma cortisol concentrations in adults from three populations. Hypertension. 2000;35:1301–6. [PubMed]

76. Levitt NS, Lambert EV, Woods D, Hales N, Andrew R, Seckl JR. Impaired glucose tolerance and elevated blood pressure in low birth weight, nonobese, young South African adults: Early programming of cortisol axis. J Clin Endocrinol Metab. 2000;85:4611–8. [PubMed]

77. Finken MJ, Andrews RC, Andrew R, Walker BR. Cortisol metabolism in healthy young adults: Sexual dimorphism in activities of A-ring reductases but not 11beta-hydroxysteroid dehydrogenases. J Clin Endocrinol Metab. 1999;84:3316–21. [PubMed]

78. Walker BR, Irving RJ, Andrew R, Belton NR. Contrasting effects of intrauterine growth retardation and premature delivery on adult cortisol secretion and metabolism in man. Clin Endocrinol (Oxf) 2002;57:351–5. [PubMed]

79. Kudielka BM, Hellhammer J, Hellhammer DH, Wolf OT, Pirke KM, Varadi E, et al. Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. J Clin Endocrinol Metab. 1998;83:1756–61. [PubMed]

80. Kajantie E, Eriksson J, Barker DJ, Forsén T, Osmond C, Wood PJ, et al. Birthsize, gestational age and adrenal function in adult life: Studies of dexamethasone suppression and ACTH1 – 24 stimulation. Eur J Endocrinol. 2003;149:569–75. [PubMed]

81. McCarty DJ, Manzi S, Medsger TA, Jr, Ramsey-Goldman R, LaPorte RE, Kwoh CK. Incidence of systemic lupus erythematosus.Race and gender differences. Arthritis Rheum. 1995;38:1260–70. [PubMed]

82. Björntorp P. Behavior and metabolic disease. Int J Behav Med. 1996;3:285–302. [PubMed]

83. Furlan PM, DeMartinis N, Schweizer E, Rickels K, Lucki I. Abnormal salivary cortisol levels in social phobic patients in response to acute psychological but not physicalstress. Biol Psychiatry. 2001;50:254–9. [PubMed]

84. Wedekind D, Bandelow B, Broocks A, Hajak G, Ruther E. Salivary, total plasma and plasma free cortisol in panic disorder. J Neural Transm. 2000;107:831–7. [PubMed]

85. Roy-Byrne PP, Uhde TW, Post RM, Gallucci W, Chrousos GP, Gold PW. The corticotropin-releasing hormone stimulation test in patients with panic disorder. Am J Psychiatry. 1986;143:896–9. [PubMed]

86. Altemus M, Pigott T, Kalogeras KT, Demitrack M, Dubbert B, Murphy DL, et al. Abnormalities in the regulation of vasopressin and corticotropin releasing-factor secretion in obsessive-compulsive disorder. Arch Gen Psychiatry. 1992;49:9–20. [PubMed]

87. Mason D. Genetic variation in the stress response: Susceptibility to experimental allergic encephalomyelitis and implications for human inflammatory disease. Immunol Today. 1991;12:57–60. [PubMed]

88. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338:171–9. [PubMed]

89. Carroll BJ. Clinical applications of the dexamethasone suppression test for endogenous depression. Pharmacopsychiatria. 1982;15:19–25. [PubMed]

90. Young EA, Lopez JF, Murphy-Weinberg V, Watson SJ, Akil H. Hormonal evidence for altered responsiveness to social stress in major depression. Neuropsychopharmacology. 2000;23:411–8. [PubMed]

91. Linkowski P. Neuroendocrine profiles in mood disorders. Int J Neuropsychopharmacol. 2003;6:191–7. [PubMed]

92. Anisman H, Ravindran AV, Griffiths J, Merali Z. Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. Mol Psychiatry. 1999;4:182–8. [PubMed]

93. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. Mol Psychiatry. 2002;7:254–75. [PubMed]

94. Weiner H. Social and psychosocial factors in autoimmune disease. In: Ader R, Felten DL, Cohen N, editors. San Diego: Psychoneuroimmunology Academic Press; 1991. pp. 955–1011.

95. Adams RD, Victor M. Principles of Neurology. New York: McGraw-Hill; 1989. Multiple sclerosis and allied demyelinative diseases; pp. 755–74.

96. Buske-Kirschbaum A, Jobst S, Wustmans A, Kirschbaum C, Rauh W, Hellhammer D. Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. Psychosom Med. 1997;59:419–26. [PubMed]

97. McGee R, Williams S, Elwood M. Are life events related to the onset of breast cancer? Psychol Med. 1996;26:441–7. [PubMed]

98. Evans DL, Leserman J, Perkins DO, Stern RA, Murphy C, Zheng B, et al. Severe life stress as a predictor of early disease progression in HIV infection. Am J Psychiatry. 1997;154:630–4. [PubMed]

99. Bauer ME, Vedhara K, Perks P, Wilcock GK, Lightman SL, Shanks N, et al. Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. J Neuroimmunol. 2000;103:84–92. [PubMed]

100. Da Roza Davis JM, Cowen PJ. Biochemical stress of caring. Psychol Med. 2001;31:1475–8. [PubMed]

101. Strickland PL, Deakin JF, Percival C, Dixon J, Gater RA, Goldberg DP, et al. Bio-social origins of depression in the community.Interactions between social adversity, cortisol and serotonin neurotransmission. Br J Psychiatry. 2002;180:168–73. [PubMed]