Q J Med 2005; **98**:323–329
doi:10.1093/qjmed/hci064

Advance Access publication 8 April 2005

Review

QJM

Type D personality: the heart, stress, and cortisol

L. SHER

From the Division of Neuroscience, Department of Psychiatry, Columbia University, New York, USA

Summary

Many studies have demonstrated the role of psychosocial and behavioural risk factors in the aetiology and pathogenesis of cardiovascular disorders. Recently, a new personality construct, the type D or 'distressed' personality, has been proposed. Type D behaviour is characterized by the joint tendency to experience negative emotions and to inhibit these emotions while avoiding social contacts with others. The observation that cardiac patients with type D personality are at increased risk for cardiovascular morbidity and mortality underlines the importance of examining both acute (e.g. major depression) and chronic (e.g. certain personality features) factors in patients at risk for coronary events. Both type D dimensions (negative affectivity and social inhibition) are associated with greater cortisol reactivity to stress. Elevated cortisol may be a mediating factor in the association between type D personality and the increased risk for coronary heart disease and, possibly, other medical disorders. Studies of the effect of age on hypothalamic-pituitary-adrenal (HPA) function in healthy humans have produced inconsistent results. This may relate to a different prevalence of type D individuals in study samples (i.e. some type D individuals may have alterations within the HPA axis that are similar to HPA axis changes in depressed patients). Further studies of the psychological and biological features of type D individuals may help develop treatment approaches to improve the psychological and physical health of individuals with type D personality.

Introduction

Many studies have demonstrated the role of psychosocial and behavioural risk factors in the aetiology and pathogenesis of cardiovascular disorders.[1–5] The most well known of these factors is type A behaviour pattern, which includes ambitiousness, aggressiveness, competitiveness, impatience, muscle tenseness, alertness, rapid and empathic vocal style, irritation, cynicism, hostility, and increased potential for anger.[1,5] Type A individuals are at increased risk for developing coronary heart disease.[1,2,5]

Recently, a new personality construct, the type D or 'distressed' personality, has been proposed.[6–8] This construct is a result of an investigation of coping styles in men with coronary heart disease. Type D personality subtype is characterized by the joint tendency to experience negative emotions and to inhibit these emotions while avoiding social contacts with others. In other words, the type D personality is a gloomy, anxious, and socially inept worrier. Type D individuals generally have fewer personal ties with other

Address correspondence to Dr L. Sher, Division of Neuroscience, Department of Psychiatry, Columbia University, 1051 Riverside Drive, Suite 2917, Box 42, New York, NY 10032, USA. email: ls2003@columbia.edu

people and tend to feel less comfortable with strangers.[6]

Type D characteristics

Type D individuals score highly on negative affectivity and social inhibition personality dimensions. Negative affectivity is defined as the 'tendency to experience negative emotions,' including depressed mood, anxiety, anger, and hostile feelings.[9,10] Individuals scoring high on negative affectivity are not only dysphoric but have a negative view of self, report more somatic symptoms, and have an attention bias towards adverse stimuli.[6,7] As Denollet[6] astutely notes, individuals who score high on negative affectivity seem to scan the world for signs of impending trouble.

Social inhibition is described as 'the avoidance of potential 'dangers' involved in social interactions such as disapproval or non-reward by others.'[11] Individuals scoring high on social inhibition frequently feel inhibited, tense, uncomfortable, and insecure when encounter with other people. Both negative affectivity and social inhibition are associated with the perception of a socially unsupportive environment.[8,12]

Type D is defined as the interaction of negative affectivity (which is closely related to neuroticism) and social inhibition.[6–8,12] Social inhibition is a moderator: the prevalence of cardiac events for individuals who score high in negative affectivity but low in social inhibition is less than for that for individuals scoring highly in both components. In other words, the type D concept suggests that the way people cope with negative emotions may be as important as the experience of negative emotions *per se*.[8]

Personality type D is assessed with a scale that measures negative affectivity and social inhibition.[13–15] Each item is rated according to a 5-point Likert scale from 0 (false) to 4 (true). Patients who score high on both negative affectivity and social inhibition, as determined by a median split, are classified as type D. The psychometric qualities and prognostic power of the scale have proven satisfactory in Belgian cardiac patients with Cronbach's α of 0.89 and 0.82 and test–retest reliability of 0.78 and 0.87 for the Negative Affectivity and Social Inhibition subscales, respectively.[14,16] The two-factor structure and the internal consistency of the Negative Affectivity and Social Inhibition subscales were recently confirmed in studies of Danish and German cardiac patients.[13,15]

The data on the relation of type D personality with mood and anxiety disorders are limited. There is evidence that type D personality is associated with depressive and anxiety symptoms, and with post-traumatic stress disorder.[8,13,17] Type D personality may be related to social phobia and panic disorder, because its clinical and biological correlates could be thus attributed. Type D individuals may also have a predisposition to develop avoidant personality disorder.

Type D and cardiac events

The inhibition of emotions has been associated with higher cardiovascular reactivity,[18] lower cardiovascular recovery,[19] lower heart rate variability,[20] and, in the long term, carotid atherosclerosis,[21] incidence of coronary heart disease,[22] and cardiac mortality.[23] In a sample of patients undergoing cardiac rehabilitation, deaths from cardiac causes were increased four-fold in those with type D personality, even after controlling for conventional risk factors.[24] This observation was later replicated in an independent sample of more than 300 patients with coronary heart disease.[16] Type D was an independent predictor of cardiac mortality and non-fatal myocardial infarction, and also of a composite endpoint of cardiac mortality, non-fatal myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty.

A study of cardiac patients with a decreased left ventricular ejection fraction demonstrated that type D personality was an independent predictor of a composite endpoint of mortality due to cardiac causes together with a decreased left ventricular ejection fraction.[25] In this study, type B behaviour, depression, anxiety, and anger did not add to the predictive power of type D personality. Appels *et al.*[26] investigated the effect of type D behaviour on sudden cardiac death. Next-of-kin of the sudden cardiac death victims were interviewed. Patients scoring high on negative affectivity and social inhibition were at seven-fold increased risk of sudden cardiac death, after controlling for biomedical risk factors. Type D personality and older age were independent predictors of the development of cancer in patients with coronary heart disease.[27]

A recent study suggests that type D personality is associated with increased depressive and anxiety symptoms in patients with an implantable cardioverter defibrillator.[17] Another recent study investigated the effect of type D personality on the occurrence of adverse events at 9 months in patients with ischaemic heart disease after percutaneous

coronary intervention with sirolimus-eluting stents or bare stents.[28] Type D patients were at a cumulative increased risk of adverse outcome, compared with non-type D subjects.

Type D personality (whether as a biological construct of temperament or a constellation of habitual behaviours) is a risk factor at least equivalent in importance to the other, 'conventional' coronary heart disease prognostic factors. Importantly, major depression is a very significant risk factor for cardiovascular disorders.[2–5] That cardiac patients with the type D personality are at increased risk for cardiovascular morbidity and mortality, underlines the importance of examining both acute (e.g. major depression) and chronic (e.g. certain personality features) factors in people who are at risk for coronary events. We need to adopt a personality approach in the early identification of those coronary patients who are at risk for stress-related cardiac events.[6,7] Psychological risk factors tend to cluster together, and clustering of these factors, in turn, considerably elevates the risk for cardiac events.

Type D, stress, and cortisol

Type D individuals tend to experience negative emotions such as depressed mood, anxiety, anger, hostile feelings, and to inhibit these emotions while avoiding social contacts.[6,7,12] Situations involving fear, anxiety, helplessness, and loss of control result in release of cortisol.[29–33] The relationship between negative affect and cortisol activity has been documented in several studies using structured laboratory stressors, such as public speaking and mental arithmetic[34] and aversive stimulation,[33] and in the scientific literature related to changes in the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients.[35–37] A recent study has documented relationships among negative affect, positive affect and cortisol in response to naturalistic stressors.[38] Both the experience of a current stressor and anticipating a stressor were associated with increased salivary cortisol levels. Negative affect was associated with higher cortisol levels and positive affect was associated with lower cortisol levels. Another study also found that stressful daily events were associated with increased cortisol secretion in healthy volunteers.[39] Distress, as reflected by the mood states 'negative affect' and 'agitation', was associated with higher cortisol levels. Mood plays a mediating role in the relationship between stressful events and cortisol secretion.[30,38,39] Negative affectivity is not just a confounder, but is related to elevated cortisol secretion during normal daily activities. In a recent study, both type D dimensions (negative affectivity and social inhibition) were associated with greater cortisol reactivity to stress,[12] although the results were not significant in more stringent regression analyses. However, it is reasonable to suggest that there is a difference in HPA regulation in type D individuals and in people with other personality types.

Elevated cortisol and medical illness

Depression appears to be an independent risk factor for the development of coronary heart disease and osteoporosis, and affects the prognosis of these and other medical disorders.[40–42] Considerable evidence suggests an association between depression and hypertension, peptic ulcers, and diabetes.[40,42] Elevated cortisol may be a mediating factor in these relationships. Cortisol has many effects that promote coronary heart disease. For example, cortisol inhibits the growth hormone and gonadal axes. Growth hormone deficiency is associated with higher relative risk for premature cardiovascular disease in adults.[43,44] Cortisol is a potent stimulus to visceral fat. Inhibition of the growth hormone and gonadal axes exacerbates visceral fat accumulation. Excess visceral fat leads to dyslipidaemia and, along with hypercortisolism, to insulin resistance, hyperinsulinism, and their sequelae.[45] Similar mechanisms may increase the vulnerability of type D individuals to cardiac and other medical illnesses. Elevated cortisol may be a mediating factor in the association between type D personality and the increased risk for coronary heart disease and, possibly, other medical disorders. It is important to note that cortisol is not the only mediating factor in this association. A recent study suggests that type D personality is associated with increased circulating levels of cytokine tumour necrosis factor α and its soluble receptors 1 and 2, which are predictors of mortality in chronic heart failure.[46]

HPA function, ageing, and type D personality

Depression is associated with impairment in feedback control of the HPA axis, contributing to higher cortisol levels during episodes of depression.[35,41,47–49] Prolonged exposure to elevated cortisol levels may be neurotoxic, especially for brain regions rich in corticosteroid receptors, and may mediate neuronal vulnerability to stressors.

Recurrent depression is associated with atrophy of the hippocampus and amygdala[50,51] as well as the prefrontal cortex.[52] A gradual deterioration of hippocampal feedback inhibition of the HPA axis due to down-regulation of glucocorticoid receptors from repeated stress has been demonstrated.[47,53,54] Evidence suggests that age and/or length of depression and/or the number of depressive episodes affect HPA regulation in depressed patients.[37,50,51] The potentiating or additive effect of age in conjunction with depression on pituitary adrenocortical activity was suggested by a number of studies.[37,51,55–64] Mean 24-h cortisol level increases with age in depression.[58] Elderly depressives who are cortisol non-suppressors after dexamethasone need more time for pituitary adrenocortical normalization to occur than do younger subjects.[60] An increase in post-dexamethasone cortisol levels with age has been reported in major depressive disorder.[61] A significant effect of age on cortisol release in depressed patients has been observed during the combined dexamethasone-corticotropin-releasing hormone test: older patients had higher post-dexamethasone cortisol levels.[63] In patients with endogenous depression, advancing age leads to higher baseline cortisol and a greater likelihood of being a dexamethasone non-suppressor.[64] Cortisol responses to fenfluramine administration in depressed patients increased with the number of major depressive episodes.[37] Other authors have reported similar observations.[55–57,59,62]

Studies of the effect of ageing on HPA function in healthy humans have inconsistent results. We recently found that age did not affect cortisol levels in healthy volunteers,[37] consistent with other reports.[63,65–68] Advanced age did not appear to affect the overnight dexamethasone suppression in healthy humans.[65] The 24-h mean cortisol concentration and the number of cortisol peaks as well as their amplitude and duration were studied in healthy volunteers, and no difference between younger and older subjects was found.[66] Basal and corticotropin releasing hormone-stimulated adrenocorticotropic hormone (ACTH) and cortisol secretion, as well as sensitivity of the ACTH-cortisol axis to glucocorticoid feedback suppression, were essentially unaltered with age in healthy men.[67] No difference in the results of combined dexamethasone-corticotropin-releasing hormone test was found between younger and older healthy volunteers,[63] and a recent study suggests that ageing has no effect on cortisol responses to fenfluramine administration in healthy elderly subjects.[68]

However, a number of authors suggest that age *does* affect HPA regulation in healthy humans.[56,69–76] Differences in the results of studies have been be explained by differences in a sample size, screening criteria, and some other factors, such as differences in sleeping patterns.[37,77] Equivocal results of these studies may be, in part, related to a different prevalence of type D individuals in study samples: i.e. some type D individuals may have alterations within the HPA axis that are similar to HPA axis changes in depressed patients.[78] Future studies of HPA function should control for the presence of type D individuals. Type D individuals should perhaps not participate in psychobiological studies as healthy controls. Studies of HPA function should also control for other personality traits that may affect the HPA axis. For example, individuals with borderline or antisocial personality features may have HPA axis abnormalities.[79–82]

Do type D individuals need treatment?

Individuals with type D personality are at increased risk for developing psychiatric and medical disorders.[6–8,12] Type D personality may be regarded as a psychopathological condition that may affect health and longevity, and requires psychological and/or pharmacological treatment. Are there psychological, pharmacological, or alternative medicine interventions that can help type D individuals? Cognitive behavioural therapy, social skills training, emotional support, interpersonal psychotherapy, progressive muscle relaxation, autogenic training, diaphragmatic breathing, guided imagery, various forms of meditation, hypnosis, biofeedback, exercise, and other treatments may all reduce stress in type D persons and improve their ability to socialize. For example, regular exercise may result in decreased anxiety and depression, greater ease in handling daily stress, longer and more restful sleep, improved sexual functioning, improvement in glucose tolerance and lipid parameters, etc.[83,84] Antidepressants may possibly help some type D individuals. It has been suggested that treatment with selective serotonin reuptake inhibitors may decrease harm avoidance (a tendency to respond intensely to signals of aversive stimuli), increase social confidence, and decrease hostility.[85–88] Further studies of psychological and biological features of type D individuals may help develop treatment approaches to improve psychological and physical health of individuals with type D personality.

References

1. Heilbrun AB Jr, Friedberg EB. Type A personality, self-control, and vulnerability to stress. *J Personality Assessment* 1988; **52**:420–33.
2. Williams RB, Littman AB. Psychosocial factors: role in cardiac risk and treatment strategies. *Cardiol Clinics* 1996; **14**:97–104.
3. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease. *Arch Gen Psychiatry* 1998; **55**:580–92.
4. Sher L. Effects of psychological factors on the development of cardiovascular pathology: role of the immune system and infection. *Med Hypotheses* 1999; **53**:112–13.
5. Ursano RJ, Epstein RS, Lazar SG. Behavioral responses to illness: personality and personality disorders. In: Wise MG, Rundell JR, eds. *The American Psychiatric Publishing Textbook of Consultation-Liaison Psychiatry. Psychiatry in the Medically Ill,* 2nd edn. Washington DC, American Psychiatric Publishing, 2002:107–25.
6. Denollet J. Type D personality. A potential risk factor defined. *J Psychosom Res* 2000; **49**:255–66.
7. Denollet J, Van Heck GL. Psychological risk factors in heart disease. What Type D personality is (not) about. *J Psychosom Res* 2001; **51**:465–8.
8. Pedersen SS, Denollet J. Type D personality, cardiac events, and impaired quality of life: a review. *Eur J Cardiovasc Prev Rehabil* 2003; **10**:241–8.
9. Watson D, Clark LA. Negative affectivity: the disposition to experience aversive emotional states. *Psychol Bull* 1984; **96**:465–90.
10. Watson D, Pennebaker JW. Health complaints, stress, and distress: exploring the central role of negative affectivity. *Psychol Rev* 1989; **96**:234–54.
11. Asendorpf JB. Social inhibition: a general-developmental perspective. In: Traue HC, Pennebaker JW, eds. *Emotion, Inhibition, and Health*. Seattle WA, Hogrefe and Huber Publishers, 1993:80–99.
12. Habra ME, Linden W, Anderson JC, Weinberg J. Type D personality is related to cardiovascular and neuroendocrine reactivity to acute stress. *J Psychosom Res* 2003; **55**:235–45.
13. Pedersen SS, Denollet J. Validity of the Type D personality construct in Danish post-MI patients and healthy controls. *J Psychosom Res* 2004; **57**:265–72.
14. Denollet J. Personality and coronary heart disease: the type-D scale-16 (DS16). *Ann Behav Med* 1998; **20**:209–15.
15. Grande G, Jordan J, Kummel M, Struwe C, Schubmann R, Schulze F, Unterberg C, von Kanel R, Kudielka BM, Fischer J, Herrmann-Lingen C. Evaluation of the German Type D Scale (DS14) and prevalence of the Type D personality pattern in cardiological and psychosomatic patients and healthy subjects. *Psychother Psychosom Med Psychol* 2004; **54**:413–22.
16. Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease: adverse effects of type D personality and younger age on 5-year prognosis and quality of life. *Circulation* 2000; **102**:630–5.
17. Pedersen SS, van Domburg RT, Theuns DA, Jordaens L, Erdman RA. Type D personality is associated with increased anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator and their partners. *Psychosom Med* 2004; **66**:714–19.
18. Gross JJ, Levenson RW. Hiding feelings: the acute effects of inhibiting negative and positive emotion. *J Abnorm Psychol* 1997; **106**:95–103.
19. Brosschot JF, Thayer JF. Anger inhibition, cardiovascular recovery, and vagal function: a model of the links between hostility and cardiovascular disease. *Ann Behavior Med* 1998; **20**:326–32.
20. Horsten M, Ericson M, Perski A, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Psychosocial factors and heart rate variability in healthy women. *Psychosom Med* 1999; **61**:49–57.
21. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Jansen-McWilliams L. Are hostility and anxiety associated with carotid atherosclerosis in healthy postmenopausal women? *Psychosom Med* 1998; **60**:633–8.
22. Haynes SG, Feinleib M, Kannel WB. The relationship of psychosocial factors to coronary heart disease in the Framingham Study: III. Eight-year incidence of coronary heart disease. *Am J Epidemiol* 1980; **111**:37–58.
23. Graves PL, Mead LA, Wang NY, Liang K, Klag MJ. Temperament as a potential predictor of mortality: evidence from a 41-year prospective study. *J Behavior Med* 1994; **17**:111–26.
24. Denollet J, Sys SU, Stroobant N, Rombouts H, Gillebert TC, Brutsaert DL. Personality as independent predictor of long-term mortality in patients with coronary heart disease. *Lancet* 1996; **347**:417–21.
25. Denollet J, Brutsaert DL. Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction. *Circulation* 1998; **97**:167–73.
26. Appels A, Golombeck B, Gorgels A, de Vreede J, van Breukelen G. Behavioral risk factors of sudden cardiac arrest. *J Psychosom Res* 2000; **48**:463–9.
27. Denollet J. Personality and risk of cancer in men with coronary heart disease. *Psychol Med* 1998; **28**:991–5.
28. Pedersen SS, Lemos PA, van Vooren PR, Liu TK, Daemen J, Erdman RA, Smits PC, Serruys PW, van Domburg RT. Type D personality predicts death or myocardial infarction after bare metal stent or sirolimus-eluting stent implantation: a Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry substudy. *J Am Coll Cardiol* 2004; **44**:997–1001.
29. Lundberg U. Catecholamine and cortisol excretion under psychologically different laboratory conditions. In: Usdin E, Kvetnanski R, Kopin I, eds. *Catecholamines and Stress: Recent Advances*. North Holland, Elsevier, 1980:455–60.
30. Buchanan TW, al'Absi M, Lovallo WR. Cortisol fluctuates with increases and decreases in negative affect. *Psychoneuroendocrinology* 1999; **24**:227–41.
31. Frankenhaeuser M. Psychobiological aspects of life stress. In: Levine S, Ursin H, eds. *NATO Conference Series III: Human Factors*. New York, Plenum, 1980:203–23.
32. Lovallo WR, Thomas TL. Stress hormones in psychophysiological research: emotional, behavioral, and cognitive implications. In: Cacioppo JT, Tassinary LG, Berntson G, eds. *Handbook of Psychophysiology*. New York, Cambridge University Press, 2000:342–67.
33. Lovallo WR, Pincomb GA, Brackett DJ, Wilson MF. Heart rate reactivity as a predictor of neuroendocrine responses to

aversive and appetitive challenges. *Psychosom Med* 1990; **52**:17–26.

34. al'Absi M, Bongard S, Buchanan TW, Pincomb GA, Licinio J, Lovallo WR. Cardiovascular and neuroendocrine adjustment to public speaking and mental arithmetic stressors. *Psychophysiology* 1997; **34**:266–75.
35. Holsboer F. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 2000; **23**:477–501.
36. Stokes PE. The potential role of excessive cortisol induced by HPA hyperfunction in the pathogenesis of depression. *Eur Neuropsychopharmacology* 1995; **5(Suppl.)**:77–82.
37. Sher L, Oquendo MA, Galfalvy HC, Cooper TB, Mann JJ. Age effects on cortisol levels in depressed patients with and without a history of posttraumatic stress disorder, and healthy volunteers. *J Affect Disord* 2004; **82**:53–9.
38. Smyth J, Ockenfels MC, Porter L, Kirschbaum C, Hellhammer DH, Stone AA. Stressors and mood measured on a momentary basis are associated with salivary cortisol secretion. *Psychoneuroendocrinology* 1998; **23**:353–70.
39. Van Eck M, Berkhof H, Nicolson N, Sulon J. The effects of perceived stress, traits, mood states, and stressful daily events on salivary cortisol. *Psychosom Med* 1996; **58**:447–58.
40. Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrouso S, Gold P. Bone mineral density in women with depression. *N Engl J Med* 1996; **16**:1176–81.
41. Gold PW, Drevets WC, Charney DS. New insight into the role of cortisol and the glucocorticoid receptors in severe depression. *Biol Psychiatry* 2002; **52**:381–5.
42. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: does cortisol play a role? *Biol Psychiatry* 2004; **55**:1–9.
43. Erfurth EM, Bulow B, Eskilsson J, Hagmar L. High incidence of cardiovascular disease and increased prevalence of cardiovascular risk factors in women with hypopituitarism not receiving growth hormone treatment: Preliminary results. *Growth Horm IGF Res* 1999; **9(Suppl. A)**:21–4.
44. Hew FL, O'Neal D, Kamarudin N, Alford FP, Best JD. Growth hormone deficiency and cardiovascular risk. *Baillieres Clin Endocrinol Metab* 1998; **12**:199–216.
45. 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.
46. Denollet J, Conraads VM, Brutsaert, DL, De Clerck LS, Stevens WJ, Vrints CJ. Cytokines and immune activation in systolic heart failure: the role of type D personality. *Brain Behav Immunity* 2003; **17**:304–9.
47. McEwen BS, Sapolsky RM. Stress and cognitive function. *Curr Opin Neurobiol* 1995; **5**:205–16.
48. Sher L, Mann JJ. Psychiatric pathophysiology: mood disorders. In: Tasman A, Kay J, Lieberman JA, eds. Chichester, John Wiley & Sons, 2003:300–15.
49. Sher L, Oquendo MA, Galfalvy HC, Zalsman G, Cooper TB, Mann JJ. Higher cortisol levels in Spring and Fall in patients with major depression. *Prog Neuropsychopharmacol Biol Psychiatry*, in press.
50. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 1996; **93**:3908–13.
51. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 1999; **19**:5034–43.
52. Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, Vannier M, Raichle ME. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 1997; **386**:824–7.
53. Sapolsky RM. *Stress, the Aging Brain and the Mechanisms of Neuron Death*. Cambridge MA, MIT, 1992:305–39.
54. McEwen BS. Stress and neuroendocrine function. Individual differences and mechanisms leading to disease. In: Wolkowitz OM, Rotschild AJ, eds. *Psychoneuroendocrinology. The Scientific Basis of Clinical Practice*. Washington DC, American Psychiatric Publishing, 2003: 513–46.
55. Asnis GM, Sachar EJ, Halbreich U, Nathan RS, Novacenko H, Ostrow LC. Cortisol secretion in relation to age in major depression. *Psychosom Med* 1981; **43**:235–42.
56. Oxenkrug GF, Pomara N, McIntyre IM, Branconnier RJ, Stanley M, Gershon S. Aging and cortisol resistance to suppression by dexamethasone: a positive correlation. *Psychiatry Res* 1983; **10**:125–30.
57. Alexopoulos GS, Young RC, Kocsis JH, Brockner N, Butler TA, Stokes PE. Dexamethasone suppression test in geriatric depression. *Biol Psychiatry* 1984; **19**:1567–71.
58. Halbreich U, Asnis GM, Zumoff B, Nathan RS, Shindledecker R. Effect of age and sex on cortisol secretion in depressives and normals. *Psychiatry Res* 1984; **13**:221–9.
59. Lewis DA, Pfohl B, Schlechte J, Coryell W. Influence of age on the cortisol response to dexamethasone. *Psychiatry Res* 1984; **13**:213–20.
60. Greden JF, Flegel P, Haskett R, Dilsaver S, Carroll BJ, Grunhaus L, Genero N. Age effects in serial hypothalamic-pituitary-adrenal monitoring. *Psychoneuroendocrinology* 1986; **11**:195–204.
61. Whiteford HA, Peabody CA, Thiemann S, Kraemer HC, Csernansky JG, Berger PA. The effect of age on baseline and postdexamethasone cortisol levels in major depressive disorder. *Biol Psychiatry* 1987; **22**:1029–32.
62. Brown RP, Stoll PM, Stokes PE, Frances A, Sweeney J, Kocsis JH, Mann JJ. Adrenocortical hyperactivity in depression: effects of agitation, delusions, melancholia, and other illness variables. *Psychiatry Res* 1988; **23**:167–78.
63. von Bardeleben U, Holsboer F. Effect of age on the cortisol response to human corticotropin-releasing hormone in depressed patients pretreated with dexamethasone. *Biol Psychiatry* 1991; **29**:1042–50.
64. Akil H, Haskett RF, Young EA, Grunhaus L, Kotun J, Weinberg V, Greden J, Watson SJ. Multiple HPA profiles in endogenous depression: effect of age and sex on cortisol and beta-endorphin. *Biol Psychiatry* 1993; **33**:73–85.
65. Tourigny-Rivard MF, Raskind M, Rivard D. The dexamethasone suppression test in an elderly population. *Biol Psychiatry* 1981; **16**:1177–84.
66. Sherman B, Wysham C, Pfohl B. Age-related changes in the circadian rhythm of plasma cortisol in man. *J Clin Endocrinol Metab* 1985; **61**:439–43.
67. Waltman C, Blackman MR, Chrousos GP, Riemann C, Harman SM. Spontaneous and glucocorticoid-inhibited adrenocorticotropic hormone and cortisol secretion are similar in healthy young and old men. *J Clin Endocrinol Metab* 1991; **73**:495–502.
68. Ramasubbu R, Flint A, Brown G, Awad G, Kennedy S. Neurohormonal responses to D-fenfluramine in healthy

elderly subjects. A placebo-controlled study. *Psychoneuroendocrinology* 2000; **25**:139–50.

69. Parnetti L, Mecocci P, Neri C, *et al*. Neuroendocrine markers in aging brain: clinical and neurobiological significance of dexamethasone suppression test. *Aging (Milano)* 1990; **2**:173–9.
70. Heuser I, Yassouridis A, Holsboer F. The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *J Psychiatr Res* 1994; **28**:341–56.
71. O'Brien JT, Schweitzer I, Ames D, Tuckwell V, Mastwyk M. Cortisol suppression by dexamethasone in the healthy elderly: effects of age, dexamethasone levels, and cognitive function. *Biol Psychiatry* 1994; **36**:389–94.
72. Ferrari E, Magri F, Dori D, Migliorati G, Nescis T, Molla G, Fioravanti M, Solerte SB. Neuroendocrine correlates of the aging brain in humans. *Neuroendocrinology* 1995; **61**:464–70.
73. Wilkinson CW, Peskind ER, Raskind MA. Decreased hypothalamic-pituitary-adrenal axis sensitivity to cortisol feedback inhibition in human aging. *Neuroendocrinology* 1997; **65**:79–90.
74. Magri F, Locatelli M, Balza G, Molla G, Cuzzoni G, Fioravanti M, Solerte SB, Ferrari E. Changes in endocrine circadian rhythms as markers of physiological and pathological brain aging. *Chronobiol Int* 1997; **14**:385–96.
75. Wilkinson CW, Petrie EC, Murray SR, Colasurdo EA, Raskind MA, Peskind ER. Human glucocorticoid feedback inhibition is reduced in older individuals: evening study. *J Clin Endocrinol Metab* 2001; **86**:545–50.
76. Ferrari E, Casarotti D, Muzzoni B, Albertelli N, Cravello L, Fioravanti M, Solerte SB, Magri F. Age-related changes of the adrenal secretory pattern: possible role in pathological brain aging. *Brain Res Rev* 2001; **37**:294–300.
77. Aeschbach D, Sher L, Postolache TT, Matthews JR, Jackson MA, Wehr TA. A longer biological night in long sleepers than in short sleepers. *J Clin Endocrinol Metab* 2003; **88**:26–30.
78. Sher L. Type D personality, stress, and cortisol. *J Psychosom Res* 2004; **57**:117–18.
79. Lieb K, Rexhausen JE, Kahl KG, Schweiger U, Philipsen A, Hellhammer DH, Bohus M. Increased diurnal salivary cortisol in women with borderline personality disorder. *J Psychiatr Res* 2004; **38**:559–65.
80. Rinne T, de Kloet ER, Wouters L, Goekoop JG, DeRijk RH, van den Brink W. Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. *Biol Psychiatry* 2002; **52**:1102–12.
81. Susman EJ, Schmeelk KH, Worrall BK, Granger DA, Ponirakis A, Chrousos GP. Corticotropin-releasing hormone and cortisol: longitudinal associations with depression and antisocial behavior in pregnant adolescents. *J Am Acad Child Adolesc Psychiatry* 1999; **38**:460–7.
82. Vanyukov MM, Moss HB, Plail JA, Blackson T, Mezzich AC, Tarter RE. Antisocial symptoms in preadolescent boys and in their parents: associations with cortisol. *Psychiatry Res* 1993; **46**:9–17.
83. Naughton JP. Physical activity and coronary heart disease. In: Wilson PK, ed. *Adult Fitness and Cardiac Rehabilitation*. Baltimore, University Park Press, 1975:200–18.
84. Sher L. The endogenous euphoric reward system that reinforces physical training: a mechanism for mankind's survival. *Med Hypotheses* 1998; **51**:449–50.
85. Andrews W, Parker G, Barrett E. The SSRI antidepressants: exploring their 'other' possible properties. *J Affect Disord* 1998; **49**:141–4.
86. Brody AL, Saxena S, Fairbanks LA, Alborzian S, Demaree HA, Maidment KM, Baxter LR Jr. Personality changes in adult subjects with major depressive disorder or obsessive-compulsive disorder treated with paroxetine. *J Clin Psychiatry* 2000; **61**:349–55.
87. Kramer PD. *Listening to Prozac*. New York NY, Viking, 1993.
88. Jacobsen FM. Can psychotropic medications change ethnoculturally determined behavior? *Cultural Diversity Mental Health* 1995; **1**:67–72.