Neurobiological Factors Linking Personality Traits and Major Depression

Jane A Foster, PhD[1]; Glenda MacQueen, MD, PhD[2]

Objective: To examine the neurobiological basis of personality and depression.

Method: We examined preclinical and clinical studies related to neuroanatomy, neuroendocrine, molecular, and genetic alterations in depressed patients. We considered whether common neurobiological factors might be shared between personality and depression.

Results: Preclinical studies provide insights into the neurobiological mechanisms underlying the pathophysiology of depression including neuroendocrine alterations in hypothalamic–pituitary–adrenal (HPA) function, neuroanatomical alterations in key brain regions, and alterations in neurotrophin and serotonergic signalling systems. Clinical studies show similar alterations in depressed patients. Evidence suggests that neuroendocrine alterations in HPA function may contribute to personality traits. Brain regions implicated in depression, including the hippocampus and the anterior cingulate cortex, might play a role in personality. Key molecules implicated in depression have been extensively studied with reference to personality traits, particularly neuroticism. To date, physiological measures (serum and positron emission tomography) provide the strongest evidence implicating brain-derived neurotrophic factor and serotonin in personality, while genetic evidence is less convincing.

Conclusions: A neurobiological link exists between personality and depression; however, more work is needed to provide an understanding of the nature of this relation and to link this work with clinical studies examining the influence of personality factors on depression.

Can J Psychiatry 2008;53(1):6–13

Information on funding and support and author affiliations appears at the end of the article.

Clinical Implications

- Neurobiological links exists between personality traits and risk for depression.
- Understanding the genetic and molecular basis of personality and depression will allow refinement of our clinical tools and provide novel targets for therapeutic development.

Limitation

- Differences in experimental design and exclusion criteria make it difficult to compare study results and there are no obvious reasons for discrepancies among reports.

Key Words: *depression, personality, genetics, serotonin, brain-derived neurotrophic factor*

Recent advances in neuroscience have yielded plausible, although partial, explanations for the neurobiological basis of MDD. Here we consider whether recent work in neurobiology can also address the etiologic relation between personality and MDD. First, however, it is fair to acknowledge that there remains a valid question regarding whether neuroscience has advanced to the point that useful comments on the biological underpinnings of complex traits such as personality can be made. Nonetheless, the question has not prevented an abundance of recent reviews that purport to summarize the neurobiology of intelligence,[1] morality,[2] evil,[3] hypnotic responsiveness,[4] sexual orientation,[5] suicide,[6] and the concept of self,[7] suggesting that discussing possible neurobiological underpinnings of reliably delineated personality traits and dimensions is fair, perhaps even modest. To consider the question of the relatedness of the neurobiological substrate of personality and MDD, we review clinical and preclinical studies related to dysregulation of neuroendocrine,

neuroanatomic, molecular, and genetic factors relevant to the pathophysiology of MDD, and we discuss studies suggesting that these factors may be shared with certain personality styles that confer risk for MDD.

Neuroendocrine Studies

The hypothesis that there is stress-like dysregulation of the HPA axis during a depressive episode is generally accepted, as is the idea that stress can predispose people to episodes of depression, including stress that is temporally proximate to the episode and stress that is remote, as in the case of early abuse.[8–11] The hypothalamus is a key CNS integrator of neuroendocrine and autonomic responses to both psychological and physiological stressors. Neuroendocrine neurons of the PVN are the primary source of CRH. PVN neurons secrete CRH into the pituitary portal circulation in response to stress, leading to increases in circulating ACTH, which stimulates synthesis and secretion of glucocorticoids from the adrenal gland.[12–17] Glucocorticoids act on multiple targets and can enhance or inhibit cellular activity in a wide range of physiological systems; in the brain, glucocorticoids inhibit HPA axis activity by negative feedback via direct and indirect pathways. The hippocampus indirectly regulates the release of hypothalamic CRH, as hippocampal neurons have glucocorticoid receptors resulting in a regulatory feedback loop with inhibitory afferents from the hippocampus suppressing hypothalamic release of CRH. Consideration of the links between stress, the HPA axis, and the hippocampus is important to the pathophysiology of MDD, but whether common deficits observed in HPA function and in the hippocampus in MDD are also related to personality is less well established.

Abbreviations used in this article

5-HT	serotonin
5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter protein promoter polymorphism
ACC	anterior cingulate cortex
ACTH	adrenocorticotrophic hormone
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CRH	corticotropin-releasing hormone
dex–CRH	dexamethasone–corticotropin-releasing hormone (test)
GABA	gamma-aminobutyric acid
HPA	hypothalamic–pituitary–adrenal
MDD	major depressive disorder
PVN	paraventricular nucleus of the hypothalamus
SSRI	selective serotonin reuptake inhibitor

In humans, the major glucocorticoid is cortisol, while in rats, and mice the major glucocorticoid is corticosterone. Plasma corticosterone and plasma ACTH levels are well-established output measures of HPA activation. Restraint stress and other psychological stressors are known to activate the HPA axis in rodents[18–28] and alterations in HPA function are linked to depressive and anxiety-like behaviours in animal models.[29–32] These preclinical studies and their related studies on neurobiology are applicable to the human condition as alterations in stress reactivity, circadian corticosterone, and behaviours are also seen in depressed patients. In fact, hyperactivity of the HPA axis is the most prominent neuroendocrine abnormality in major depression.[33] There are increased levels of basal cortisol, lack of suppression of cortisol levels by dexamethasone, and abnormal responses of the HPA to various physical and psychological stressors[34] in people with mood disorders. The normal diurnal variation of cortisol is perturbed: the cortisol troughs normally seen at night are not blunted[35] and the daytime peaks are higher.[36] Depressed patients have decreased glucocorticoid negative feedback in the dex–CRH test, and basal cortisol levels may also be elevated in healthy probands with a family history of mood disorders.[37] Successful resolution of depressive symptoms normalizes the HPA axis.[38,39] Further, HPA function may be an important clinical consideration as dysfunction in depressed patients may predict treatment response. A recent study found that in the absence of a treatment response, antidepressants did not alter the cortisol output on the dex–CRH test.[40] Studies have also shown that lithium augmentation in treatment resistant MDD increases the cortisol response to the dex–CRH test.[41]

Recent neurobiological studies linking alterations in HPA axis function to personality traits provide preliminary evidence of a common neuroendocrine basis for personality and depression. Several studies have considered personality traits and HPA axis function with mixed results.[42–49] Inconsistencies and difficulties relate to exclusion criteria because mixed population studies are difficult to interpret.[42] Differences in experimental design are related to the nature of HPA activation. When cortisol is measured it becomes even more difficult to compare study results. Sufficient evidence is present to suggest a link between HPA dysfunction and personality, nonetheless, and a few studies warrant specific comment.

Studies that have examined the relation between high neuroticism and HPA function in healthy volunteers provide insight and allow parallels to be drawn between these reports and HPA dysfunction in depressed patients. First, increased levels of morning cortisol observed in volunteers with high neuroticism reveals a subtle alteration in diurnal cortisol regulation. However, the full complement of daytime and nighttime alterations in cortisol regulation observed in

depressed patients was not seen in subjects with high neuroticism only.[36,46] Second, 2 studies have linked personality traits with an exaggerated HPA activation, measured by the cortisol response in the dex–CRH test.[43,49] In the first, high neuroticism was associated with greater HPA activation[43] and in the second, novelty seeking was inversely associated with greater HPA activation.[49] While a significant relation between harm avoidance and neuroticism with increased HPA activation was not reported in one study,[49] a trend toward increased activation might have reached significance with a larger sample size. Positive associations between personality traits and HPA dysfunction are likely to be strengthened with more work in this area.

Neuroanatomic Studies

Many brain regions are implicated in the pathophysiology of MDD, including frontal and temporal regions, particularly the hippocampus. Chronic stress in rodents constitutes a well-defined animal model to study the neurobiology of depression.[50] Chronic stress leads to decreased transcription of the neurotrophin BDNF and decreased neurogenesis, whereas chronic treatment with antidepressants increases transcription of BDNF and neurogenesis.[24,51–56] That is, chronic stress and chronic treatment have opposing effects on 2 types of hippocampal plasticity. Structural plasticity of the hippocampus refers to reorganization of synapses and changes in dendritic arborization. Cellular plasticity involves neurogenesis, new cell formation, in the subgranular zone of the dentate gyrus of the hippocampus.

In addition to preclinical studies on the effect of stress and antidepressants on the hippocampus, there are several lines of clinical evidence implicating the hippocampus in the pathophysiology of depression. First, as noted above, the hippocampus is a key region involved in the modulation of stress. The glucocorticoid negative feedback system between the hippocampus and the HPA is important in modulating stress and deficits in this feedback system may contribute to the altered HPA function observed in depressed patients.[33] As it is impossible to separate the hippocampal and hypothalamic contributions to stress regulation, the associations between personality traits and HPA dysfunction, discussed above, are likely driven both by hippocampal and by HPA alterations in glucocorticoid negative feedback. Second, metaanalytic studies[57] suggest that the cognitive processes that are most impaired when depressed people are compared with healthy people are hippocampal-dependent learning and memory, and these deficits may persist into euthymia.[58–60] Third, structural magnetic resonance imaging studies suggest that structural hippocampal changes occur in people with recurrent depression.[61,62]

Although there is much less evidence linking the hippocampus to neuroticism and other aspects of personality, the authors of a recent study[63] found that rats with intermediate levels of activity and depressivity had lower noradrenaline and hydroxyindoleacetic acid levels in the hippocampus than rats characterized by low activity and high depressivity. In contrast, however, there is little evidence that patients with temporal lobe epilepsy have greater levels of psychiatric symptoms or personality dysregulation, despite anecdotal evidence for a behavioural phenotype associated with temporal lobe seizures.[64]

Another region implicated in MDD is the ACC (see Caetano[65]), a region that is crucial for emotional processing and the integration of emotional, cognitive, and physiological stimuli.[66] An interesting and novel study recently suggested that personality traits and the ACC may be related by studying iris characteristics and their relation to scores on the NEO Personality Inventory.[67] Further, a recent multimodal imaging study reported that personality as well as concentrations of neuronal N-acetylaspartate were important in predicting ACC activation.[68] ACC activity may be more closely associated with novelty and sensation-seeking than with neuroticism, which would not preclude an association with MDD.

Molecular Studies

Molecular and cellular studies of stress, depression, and antidepressants conducted over the last decade have moved beyond a focus on changes in monoamines at the receptor level. Most studies have focused on the neurotrophin BDNF and the second messenger systems that may underlie regulation of this neurotrophin. An extensive series of studies have confirmed that chronic stress decreases the expression of BDNF in the hippocampus.[24,69–75] Administration of corticosterone decreases BDNF expression and removal of the adrenal glands increases the expression of BDNF; however, adrenalectomy does not completely block the effects of stress on BDNF. Blockade of serotonin 2A receptors also partially blocks the effects of stress on BDNF expression.[76]

In contrast to the actions of stress, antidepressant therapies increase the expression of BDNF in the hippocampus. The monoamine oxidase inhibitors and electroconvulsive therapy, which are 2 of the most effective although not the most tolerable or acceptable treatments of depression, are the most potent inducers of BDNF in animal studies.[77–79] Psychotropic drugs without antidepressant properties, such as opiates, typical antipsychotics, and psychostimulants, do not increase BDNF expression in the hippocampus.[80] Other treatments that may have antidepressant efficacy, including *N*-methyl-d-aspartate receptor antagonists, transcranial magnetic stimulation, and exercise do increase the expression of BDNF in the hippocampus.[81–84]

Progress in linking BDNF to human studies of MDD in the area of genetics is reviewed below. Here, we examine other human studies that support a role for BDNF in MDD and a possibly shared etiology with personality. First, postmortem work has demonstrated increased BDNF immunoreactivity in hippocampus from antidepressant-treated patients, compared with untreated patients.[85] Second, several papers have reported reduced serum BDNF levels in depressed patients.[86–89] The importance of serum or plasma BDNF to the CNS is not completely clear. However, an argument can be made of its importance based on the following observations: BDNF transport to blood occurs[90]; a correlation between CNS and peripheral BDNF has been reported in rats[91]; and alterations in plasma or serum in humans has been reported to be distinct from whole blood samples that would contain platelet-derived BDNF.[88] Importantly, in 2 of the clinical studies that measured BDNF in unmedicated depressed patients, BDNF peripheral levels returned to normal following antidepressant treatment.[87,89] These studies support using the measurement of peripheral BDNF as an indicator of CNS BDNF in clinical populations.

To our knowledge, only one study to date has considered the role of BDNF in personality by examining BDNF serum levels. Here, data mirrored the above observations in depressed patients, as lower BDNF serum levels in healthy volunteers was related to high neuroticism using the NEO Five-Factor Inventory.[92] The lowered BDNF levels may reflect central deficits in BDNF signalling that could contribute to the vulnerability of individuals with neuroticism to depression.

Genetic Studies

Neuroticism has a heritability of almost 50%[93] and is fairly stable across life. MDD has a similar degree of heritability[94]; the relative risk of MDD to a first-degree relative of a depressed person, compared with someone with no affected relative is 2 to 3, but may increase to as much as 5 if the population is restricted to relatives of people who have recurrent depression with onset by the third decade of life.[95,96] Thus there is reason to believe that neuroticism and depression are determined in part by genetic factors, and a reasonable question is whether these genetic factors are shared. In fact, there are now numerous genome-scan studies linking neuroticism and depression, and at least nine chromosomal regions that have support from more than one genome scan (see Levinson[97] for a review).

Although the field of personality genetics was largely launched by studies linking novelty seeking with the dopamine D4 exon III seven repeat (see Ebstein[14] for a review), neither novelty seeking nor dopamine have formed the core of work in mood disorders. Instead, the focus has been on serotonin and, to a lesser extent, BDNF, which have emerged as 2 key biological factors in both theories of MDD[98] and the genetics of neuroticism.[97] As such, these are good targets to consider the common genetic basis of personality and depression.

One of the major biological substrates in the pathogenesis of depression is the serotonergic system.[99,100] Serotonergic signaling in the CNS is clearly distinct from neurotrophin signalling in several ways. BNDF is produced in forebrain and hippocampal neurons and communicates locally via trkB receptors. In contrast, 5-HT-producing neurons are localized in the raphe nuclei of the brain stem and project to terminal regions throughout the brain including hypothalamus, cortex, hippocampus, and amygdala. BDNF mRNA and protein are synthesized in neurons. The 5-HT is produced in a 2-step reaction from tryptophan. Tryptophan is an essential amino acid and must be supplied from the diet via the circulation to the CNS. The rate limiting enzyme for 5-HT synthesis, tryptophan hyroxylase, is restricted to raphe neurons. In terminal regions numerous 5-HT receptor subtypes are present to participate in signaling. In addition, the 5-HTT regulates reuptake of extracellular 5-HT, which is recycled or degraded by monoamine oxidase A. Abnormalities in serotonergic activity can occur at many levels and therefore several genes and proteins involved in the serotonergic pathway could play a role in depression and related personality styles.

Most research has focused on the 5-HTT. The 5-HTT plays a key role in serotonergic neurotransmission via reuptake of 5-HT from the synaptic cleft and is the primary target for SSRIs.[101,102] The 5-HTTLPR polymorphism in the promoter region of the 5-HTT gene (*SLC6A4*) was identified with a 44-base pair insertion (*l* allele) or deletion (*s* allele),[103] which regulates gene transcription and 5-HTT availability at a physiological level.[103,104]

Several clinical studies have demonstrated an association of the *s* allele with anxiety-related traits,[105,106] increased risk for depression,[107,108] and drug response to SSRI treatment[109,110] and to lithium prophylaxis.[111] While these studies support the association of the *s* allele of the 5-HTT gene, both with increased risk of developing a mood disorder and with a worse response to serotonergic drugs, the associations are not robust. However, 3 recent, high-impact studies[112–114] provide additional evidence for a role for the 5-HTTLPR genotype in mood. In the first report,[112] healthy *s* allele carriers had greater amygdala reactivity to fearful stimuli. In the second report,[113] a role of the 5-HTTLPR genotype in gene-by-environment interaction was observed in patients with MDD. Specifically, the *s* allele endowed vulnerability to a depressive episode when the individual experienced stressful life events. In contrast, the presence of stressful life events had no effect on vulnerability of *l* allele homozygotes. In the third report,[114] the 5-HTTLPR genotype affected the structure and function of

neural circuitry (amygdala-cingulate) involved in emotional processing in healthy volunteers. Together, these reports suggest that the biological mechanisms underlying the impact of the 5-HTTLPR polymorphism on mood are complex and that gene–environmental interactions are important factors.

Over 25 studies have examined the association between a polymorphism in the 5-HTTLPR and anxiety- and depression-related personality traits. Investigators have struggled, however, to reconcile the conflicting results of metaanalyses by examining whether the 5-HTTLPR gene is associated with neuroticism as assessed with the NEO Five-Factor Inventory or harm avoidance as reflected by the Tridimensional theory of personality.[105,106,115] The most recent debate related to whether the use of different personality measurement scales determines whether a relation is found between polymorphism and personality trait is somewhat perplexing, given the substantial psychometric form equivalence between the constructs of neuroticism and harm avoidance.[116,117] Two recent reports, however, provide further support for an association of the *s* allele of the 5-HTTLPR gene and personality traits. In the first, an association between 5-HTTLPR and state anxiety, measured by the State-Trait Anxiety Measure, was found in healthy volunteers and migraineurs.[118] In the second, the authors report that neuroticism mediates the association between 5-HTTLPR and lifetime MDD.[119] Overall, the above studies support an association among serotonin genetics, personality, and depression. Additional support is provided by a recent imaging paper that showed decreased 5-HTT binding correlated with neuroticism,[120] suggesting that a good understanding of these relations might require imaging, genetics, and neurobiology.

Neuroticism and extraversion as assessed on the NEO Personality Inventory have also emerged in studies testing for associations between the specific polymorphisms of the BDNF Va166Met substitution and personality traits. Some[121,122] although not all[123–125] investigators have reported associations between these personality dimensions and the Va166Met genotype. These findings mirror the mixed findings of studies examining whether the various forms of the Va166Met BDNF polymorphism assign differential risk for depression. In a clinical study that will be very interesting if replicated, patients who were poor responders to cognitive-behavioural therapy for panic disorder had lower pretreatment levels of BDNF than good responders.[126] Another recent report suggests that BDNF polymorphism status may predict response to milnacipram or fluvoxamine.[127] Finally, in a high-profile animal study, mice that had the met/met phenotype were more anxious and were nonresponsive to the antidepressant fluoxetine.[128] In some ways, these studies mirror those of Bagby and colleagues,[129] which are reviewed in this issue, and it is thus tempting, if perhaps preliminary, to speculate about the potential relation among specific polymorphisms, personality dimensions, and responsiveness to various treatment modalities for mood and anxiety disorders.

Summary

Paris[130] recently noted that our understanding of neurobiology is insufficient to develop a model of personality that is only derived from biological variables, and this appears indisputable. We are also currently unable to link personality traits to illnesses such as depression via reliable, shared, biological markers. Lara and Akiskal[29] recently proposed an integrative neurobiological model of the spectrum of mood and personality disorders but it is difficult to discern whether their discussion of fear and anger as "traits" or "temperaments" were fair in this context. Further, linking fear with the vast serotonergic, noradrenergic, and GABA-ergic systems, and anger with dopaminergic and glutamatergic systems, arguably did not advance our conceptualization of these entities by much. Thus the current best attempts to uncover biological factors associated with risk for depression and particular personality phenotypes may not succeed. For example, the contributions of the BDNF Va166Met polymorphism or the 5-HTTLPR polymorphism to personality dimensions appear modest at best.

This returns us to the question of whether neuroscience can currently say anything useful about the biological factors that determine personality and the ways that personality traits relate to Axis I disorders such as depression. Perhaps what is notable at this stage is not so much the stability or validity of the results that have emerged but the fact that the questions are considered valid to ask. The convergence of these lines of research provides a window into a future where neurobiology, psychology, and psychiatry are integrated and we finally enter a post-Cartesian period. Gabbard[131] recently wrote about the continuing dissociation of "mind" and "brain" in psychiatry and the negative impact this has on the understanding and treatment of personality disorders. For anyone who believes that Canadian psychiatry has shaken off this perpetual trust inherited from Descartes, an interesting study by Miresco and Kirmayer[132] suggested that clinicians continue to resort to a mind–brain dichotomy when engaging in clinical reasoning, with consequences that might not always be favourable for patients. Surely as we study the neurobiological links between neuroticism and depression or personality dimensions and Axis I disorders, it opens the possibility of refinement at many levels: refinement in the way we clinically conceptualize the relation between Axis I disorders and personality, refinement in the behaviours that we select to test for associations with neurobiological measures, refinement in our choices of neurobiological candidates, and perhaps, as Epstein suggests,

an acceptance of a more qualitative evaluation of the impact of genes on complex behaviours.[133]

In a 1985 editorial entitled "The Fences in Psychiatry," Holzman[134] discussed the emerging relation between psychology, neuroscience, and psychiatry, arguing that psychiatry occupies a strategic position between the other sciences, but also that solutions to many of psychiatry's clinical problems would lie in solutions from other disciplines. Continued efforts at understanding the neurobiology of personality and depression might provide psychiatry with further insight into the best practices for diagnosis and treatment. Over the longer term, a contribution of neuroscience might be to clarify the relation between personality dimensions and illness. Perhaps the fences surrounding psychiatry will continue to fall.

Funding and Support

This work was supported by an honorarium to the authors.

References

1. Gray JR, Thompson PM. Neurobiology of intelligence: science and ethics. Nat Rev Neurosci. 2004;5:471–482.
2. Mendez MF. What frontotemporal dementia reveals about the neurobiological basis of morality. Med Hypotheses. 2006;67:411–418.
3. Stein DJ. The neurobiology of evil: psychiatric perspectives on perpetrators. Ethn Health. 2000;5:303–315.
4. Raz A, Fan J, Posner MI. Neuroimaging and genetic associations of attentional and hypnotic processes. J Physiol Paris. 2006;99:483–491.
5. Rahman Q. The neurodevelopment of human sexual orientation. Neurosci Biobehav Rev. 2005;29:1057–1066.
6. Bondy B, Buettner A, Zill P. Genetics of suicide. Mol Psychiatry. 2006;11:336–351.
7. Zimmer C. The neurobiology of the self. Sci Am. 2005;293:92–96, 98, 100–101.
8. Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol. 1997;48:191–214.
9. De Marco RR. The epidemiology of major depression: implications of occurrence, recurrence, and stress in a Canadian community sample. Can J Psychiatry. 2000;45:67–74.
10. de Beurs E, Beekman A, Geerlings S, et al. On becoming depressed or anxious in late life: similar vulnerability factors but different effects of stressful life events. Br J Psychiatry. 2001;179:426–431.
11. Nemeroff CC. Early-life adversity, CRF. Dysregulation, and vulnerability to mood and anxiety disorders. Psychopharmacol Bull. 2004;38:14–20.
12. Cummings S, Elde R, Ells J, et al. Corticotropin-releasing factor immunoreactivity is widely distributed within the central nervous system of the rat: an immunohistochemical study. J Neurosci. 1983;3:1355–1368.
13. Swanson LW, Sawchenko PE, Rivier J, et al. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. Neuroendocrinology. 1983;36:165–186.
14. Antoni FA. Hypothalamic control of adrenocorticotropin secretion: advances since the discovery of 41-residue corticotropin-releasing factor. Endocr Rev. 1986;7:351–378.
15. Berkenbosch F, van Oers J, del Rey A, et al. Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. Science. 1987;238:524–526.
16. Sapolsky R, Rivier C, Yamamoto G, et al. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science. 1987;238:522–524.
17. Whitnall MH. Regulation of the hypothalamic corticotropin-releasing hormone neurosecretory system. Prog Neurobiol. 1993;40:573–629.
18. Sternberg EM, Glowa JR, Smith MA, et al. Corticotropin releasing hormone related behavioral and neuroendocrine responses to stress in Lewis and Fischer rats. Brain Res. 1992;570:54–60.
19. Makino S, Smith MA, Gold PW. Increased expression of corticotropin-releasing hormone and vasopressin messenger ribonucleic acid (mRNA) in the hypothalamic paraventricular nucleus during repeated stress: association with reduction in glucocorticoid receptor mRNA levels. Endocrinology. 1995;136:3299–3309.
20. Anisman H, Lu ZW, Song C, et al. Influence of psychogenic and neurogenic stressors on endocrine and immune activity: differential effects in fast and slow seizing rat strains. Brain Behav Immun. 1997;11:63–74.
21. Bowers G, Cullinan WE, Herman JP. Region-specific regulation of glutamic acid decarboxylase (GAD) mRNA expression in central stress circuits. J Neurosci. 1998;18:5938–5947.
22. Wong YN, Cassano WJ Jr, D'Mello AP. Acute-stress-induced facilitation of the hypothalamic–pituitary–adrenal axis. Neuroendocrinology. 2000;71:354–365.
23. Bauer ME, Perks P, Lightman SL, et al. Restraint stress is associated with changes in glucocorticoid immunoregulation. Physiol Behav. 2001;73:525–532.
24. Butterweck V, Winterhoff H, Herkenham M. St John's wort, hypericin, and imipramine: a comparative analysis of mRNA levels in brain areas involved in HPA axis control following short-term and long-term administration in normal and stressed rats. Mol Psychiatry. 2001;6:547–564.
25. Marti O, Garcia A, Velles A, et al. Evidence that a single exposure to aversive stimuli triggers long-lasting effects in the hypothalamus–pituitary–adrenal axis that consolidate with time. Eur J Neurosci. 2001;13:129–136.
26. Tan Z, Nagata S. PVN c-fos expression, HPA axis response and immune cell distribution during restraint stress. J Uoeh. 2002;24:131–149.
27. Reyes TM, Walker JR, DeCino C, et al. Categorically distinct acute stressors elicit dissimilar transcriptional profiles in the paraventricular nucleus of the hypothalamus. J Neurosci. 2003;23:5607–5616.
28. Simpkiss JL, Devine DP. Responses of the HPA axis after chronic variable stress: effects of novel and familiar stressors. Neuro Endocrinol Lett. 2003;24:97–103.
29. MacNeil G, Sela Y, McIntosh J, et al. Anxiogenic behavior in the light–dark paradigm following intraventricular administration of cholecystokinin-8S, restraint stress, or uncontrollable footshock in the CD-1 mouse. Pharmacol Biochem Behav. 1997;58:737–746.
30. Harris RB, Gu H, Mitchell TD, et al. Increased glucocorticoid response to a novel stress in rats that have been restrained. Physiol Behav. 2004;81:557–568.
31. Van den Hove DL, Blanco CE, Aendekerk B, et al. Prenatal restraint stress and long-term affective consequences. Dev Neurosci. 2005;27:313–320.
32. Chotiwat C, Harris RB. Increased anxiety-like behavior during the post-stress period in mice exposed to repeated restraint stress. Horm Behav. 2006;50:489–495.
33. Barden N. Implication of the hypothalamic–pituitary–adrenal axis in the physiopathology of depression. J Psychiatry Neurosci. 2004;29:185–193.
34. Yehuda R. Stress and glucocorticoid. Science. 1997;275:1662–1663.
35. Cervantes P, Gelber S, Kin FN, et al. Circadian secretion of cortisol in bipolar disorder. J Psychiatry Neurosci. 2001;26:411–416.
36. Rybakowski JK, Twardowska K. The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. J Psychiatr Res. 1999;33:363–370.
37. Holsboer F, Lauer CJ, Schreiber W, et al. Altered hypothalamic–pituitary–adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology. 1995;62:340–347.
38. Heuser IJ, Schweiger U, Gotthardt U, et al. Pituitary–adrenal–system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. Am J Psychiatry. 1996;153:93–99.
39. Nickel T, Sonntag A, Schill J, et al. Clinical and neurobiological effects of tianeptine and paroxetine in major depression. J Clin Psychopharmacol. 2003;23:155–168.
40. Kunzel HE, Binder EB, Nickel T, et al. Pharmacological and nonpharmacological factors influencing hypothalamic–pituitary–adrenocortical axis reactivity in acutely depressed psychiatric in-patients, measured by the Dex-CRH test. Neuropsychopharmacology. 2003;28:2169–2178.
41. Bschor T, Adli M, Baethge C, et al. Lithium augmentation increases the ACTH and cortisol response in the combined DEX/CRH test in unipolar major depression. Neuropsychopharmacology. 2002;27:470–478.
42. McCleery JM, Goodwin GM. High and low neuroticism predict different cortisol responses to the combined dexamethasone—CRH test. Biol Psychiatry. 2001;49:410–415.
43. Zobel A, Barkow K, Schulze-Rauschenbach S, et al. High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic–pituitary–adrenocortical system in healthy volunteers. Acta Psychiatr Scand. 2004;109:392–399.
44. Bos EH, Bouhuys AL, Geerts E, et al. Cognitive, physiological, and personality correlates of recurrence of depression. J Affect Disord. 2005;87:221–229.
45. LeBlanc J, Ducharme MB. Influence of personality traits on plasma levels of cortisol and cholesterol. Physiol Behav. 2005;84:677–680.
46. Portella MJ, Harmer CJ, Flint J, et al. Enhanced early morning salivary cortisol in neuroticism. Am J Psychiatry. 2005;162:807–809.
47. Mangold DL, Wand GS. Cortisol and adrenocorticotropic hormone responses to naloxone in subjects with high and low neuroticism. Biol Psychiatry. 2006;60:850–855.
48. Oswald LM, Zandi P, Nestadt G, et al. Relationship between cortisol responses to stress and personality. Neuropsychopharmacology. 2006;31:1583–1591.
49. Tyrka AR, Mello AF, Mello MF, et al. Temperament and hypothalamic–pituitary–adrenal axis function in healthy adults. Psychoneuroendocrinology. 2006;31:1036–1045.
50. McEwen BS. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. Ann N Y Acad Sci. 2001;933:265–277.
51. Duman RS, Vaidya VA. Molecular and cellular actions of chronic electroconvulsive seizures. J Ect. 1998;14:181–193.

52. Xu H, Qing H, Lu W, et al. Quetiapine attenuates the immobilization stress-induced decrease of brain-derived neurotrophic factor expression in rat hippocampus. Neurosci Lett. 2002;321:65–68.
53. Pham K, Nacher J, Hof PR, et al. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. Eur J Neurosci. 2003;17:879–886.
54. Xu H, Luo C, Richardson JS, et al. Recovery of hippocampal cell proliferation and BDNF levels, both of which are reduced by repeated restraint stress, is accelerated by chronic venlafaxine. Pharmacogenomics J. 2004;4:322–331.
55. Luo C, Xu H, Li XM. Quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress. Brain Res. 2005;1063:32–39.
56. Rosenbrock H, Koros E, Bloching A, et al. Effect of chronic intermittent restraint stress on hippocampal expression of marker proteins for synaptic plasticity and progenitor cell proliferation in rats. Brain Res. 2005;1040:55–63.
57. Zakzanis KK, Leach L, Kaplan E. On the nature and pattern of neurocognitive function in major depressive disorder. Neuropsychiatry Neuropsychol Behav Neurol. 1998;11:111–119.
58. Adler CM, Holland SK, Schmithorst V, et al. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disord. 2004;6:540–549.
59. Campbell S, Macqueen G. The role of the hippocampus in the pathophysiology of major depression. J Psychiatry Neurosci. 2004;29:417–426.
60. Thompson JM, Gallagher P, Hughes JH, et al. Neurocognitive impairment in euthymic patients with bipolar affective disorder. Br J Psychiatry. 2005;186:32–40.
61. Sheline YI, Sanghavi M, Mintun MA, et al. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci. 1999;19:5034–5043.
62. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry. 2003;160:1516–1518.
63. Chumakov VN, Livanova LM, Krylin VV, et al. Effects of chronic neuroticization on the monoaminergic systems of different structures in the brains of rats with different typological characteristics. Neurosci Behav Physiol. 2006;36:605–611.
64. Swinkels WA, van Emde Boas W, Kuyk J, et al. Interictal depression, anxiety, personality traits, and psychological dissociation in patients with temporal lobe epilepsy (TLE) and extra-TLE. Epilepsia. 2006;47:2092–2103.
65. Caetano SC, Kaur S, Brambilla P, et al. Smaller cingulate volumes in unipolar depressed patients. Biol Psychiatry. 2006;59:702–706.
66. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain. 1995;118(Pt 1):279–306.
67. Larsson M, Pedersen NL, Stattin H. Associations between iris characteristics and personality in adulthood. Biol Psychol. 2007.
68. Yucel M, Harrison BJ, Wood SJ, et al. State, trait and biochemical influences on human anterior cingulate function. Neuroimage. 2007;34:1766–1773.
69. Smith MA, Makino S, Kvetnansky R, et al. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci. 1995;15:1768–1777.
70. Ueyama T, Kawai Y, Nemoto K, et al. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. Neurosci Res. 1997;28:103–110.
71. Vollmayr B, Faust H, Lewicka S, et al. Brain-derived-neurotrophic-factor (BDNF) stress response in rats bred for learned helplessness. Mol Psychiatry. 2001;6:471–474, 358.
72. Ashe PC, Chlan-Fourney J, Juorio AV, et al. Brain-derived neurotrophic factor (BDNF) mRNA in rats with neonatal ibotenic acid lesions of the ventral hippocampus. Brain Res. 2002;956:126–135.
73. Roceri M, Hendriks W, Racagni G, et al. Early maternal deprivation reduces the expression of BDNF and NMDA receptor subunits in rat hippocampus. Mol Psychiatry. 2002;7:609–616.
74. Roceri M, Cirulli F, Pessina C, et al. Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions. Biol Psychiatry. 2004;55:708–714.
75. Rasmusson AM, Shi L, Duman R. Downregulation of BDNF mRNA in the hippocampal dentate gyrus after re-exposure to cues previously associated with footshock. Neuropsychopharmacology. 2002;27:133–142.
76. Vaidya VA, Marek GJ, Aghajanian GK, et al. 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. J Neurosci. 1997;17:2785–2795.
77. Altar CA, Whitehead RE, Chen R, et al. Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biol Psychiatry. 2003;54:703–709.
78. Altar CA, Laeng P, Jurata LW, et al. Electroconvulsive seizures regulate gene expression of distinct neurotrophic signaling pathways. J Neurosci. 2004;24:2667–2677.
79. Li B, Suemaru K, Cui R, et al. Repeated electroconvulsive stimuli have long-lasting effects on hippocampal BDNF and decrease immobility time in the rat forced swim test. Life Sci. 2007.
80. Linden AM, Vaisanen J, Lakso M, et al. Expression of neurotrophins BDNF and NT-3, and their receptors in rat brain after administration of antipsychotic and psychotrophic agents. J Mol Neurosci. 2000;14:27–37.
81. Chen AC, Shin KH, Duman RS, et al. ECS-induced mossy fiber sprouting and BDNF expression are attenuated by ketamine pretreatment. J Ect. 2001;17:27–32.
82. Levkovitz Y, Grisaru N, Segal M. Transcranial magnetic stimulation and antidepressive drugs share similar cellular effects in rat hippocampus. Neuropsychopharmacology. 2001;24:608–616.
83. Adlard PA, Cotman CW. Voluntary exercise protects against stress-induced decreases in brain-derived neurotrophic factor protein expression. Neuroscience. 2004;124:985–992.
84. Garza AA, Ha TG, Garcia C, et al. Exercise, antidepressant treatment, and BDNF mRNA expression in the aging brain. Pharmacol Biochem Behav. 2004;77:209–220.
85. Chen B, Dowlatshahi D, MacQueen GM, et al. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry. 2001;50:260–265.
86. Karege F, Perret G, Bondolfi G, et al. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res. 2002;109:143–148.
87. Shimizu E, Hashimoto K, Okamura N, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry. 2003;54:70–75.
88. Karege F, Bondolfi G, Gervasoni N, et al. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry. 2005;57:1068–1072.
89. Aydemir C, Yalcin ES, Aksaray S, et al. Brain-derived neurotrophic factor (BDNF) changes in the serum of depressed women. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:1256–1260.
90. Pan W, Banks WA, Fasold MB, et al. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology. 1998;37:1553–1561.
91. Karege F, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci Lett. 2002;328:261–264.
92. Lang UE, Hellweg R, Gallinat J. BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. Neuropsychopharmacology. 2004;29:795–798.
93. Floderus-Myrhed B, Pedersen N, Rasmuson I. Assessment of heritability for personality, based on short-form of Eysenck Personality Inventory: a study of 12 898 twin pairs. Behav Genet. 1982;10:153–162.
94. Kendler KS, Neale MC, Kessler RC, et al. The lifetime history of major depression in women. Reliability of diagnosis and heritability. Arch Gen Psychiatry. 1993;50:863–870.
95. Weissman MM, Kidd KK, Prusoff BA. Variability in rates of affective disorders in relatives of depressed and normal probands. Arch Gen Psychiatry. 1982;39:1397–1403.
96. Weissman MM, Wickramaratne P, Merikangas KR, et al. Onset of major depression in early adulthood. Increased familial loading and specificity. Arch Gen Psychiatry. 1984;41:1136–1143.
97. Levinson DF. The genetics of depression: a review. Biol Psychiatry. 2006;60:84–92.
98. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry. 1997;54:597–606.
99. Lucki I. The spectrum of behaviors influenced by serotonin. Biol Psychiatry. 1998;44:151–162.
100. Reif A, Lesch KP. Toward a molecular architecture of personality. Behav Brain Res. 2003;139:1–20.
101. Blier P, de Montigny C. Serotonin and drug-induced therapeutic responses in major depression, obsessive–compulsive and panic disorders. Neuropsychopharmacology. 1999;21:91S–98S.
102. Murphy GM Jr, Kremer C, Rodrigues HE, et al. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatry. 2003;160:1830–1835.
103. Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science. 1996;274:1527–1531.
104. Heinz A, Goldman D. Genotype effects on neurodegeneration and neuroadaptation in monoaminergic neurotransmitter systems. Neurochem Int. 2000;37:425–432.
105. Schinka JA, Busch RM, Robichaux-Keene N. A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. Mol Psychiatry. 2004;9:197–202.
106. Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. Am J Med Genet B Neuropsychiatr Genet. 2004;127:85–89.
107. Lotrich FE, Pollock BG. Meta-analysis of serotonin transporter polymorphisms and affective disorders. Psychiatr Genet. 2004;14:121–129.
108. Nobile M, Cataldo MG, Giorda R, et al. A case–control and family-based association study of the 5-HTTLPR in pediatric-onset depressive disorders. Biol Psychiatry. 2004;56:292–295.
109. Arias B, Catalan R, Gasto C, et al. 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. J Clin Psychopharmacol. 2003;23:563–567.

110. Murphy GM Jr, Hollander SB, Rodrigues HE, et al. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry. 2004;61:1163–1169.
111. Rybakowski JK, Suwalska A, Czerski PM, et al. Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. Pharmacol Rep. 2005;57:124–127.
112. Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. Science. 2002;297:400–403.
113. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301:386–389.
114. Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci. 2005;8:828–834.
115. Munafo MR, Clark TG, Moore LR, et al. Genetic polymorphisms and personality in healthy adults: a systematic review and meta-analysis. Mol Psychiatry. 2003;8:471–484.
116. Munafo MR, Clark T, Flint J. Does measurement instrument moderate the association between the serotonin transporter gene and anxiety-related personality traits? A meta-analysis. Mol Psychiatry. 2005;10:415–419.
117. Schinka JA. Measurement scale does moderate the association between the serotonin transporter gene and trait anxiety: comments on Munafo et al. Mol Psychiatry. 2005;10:892–893; author reply 895–897.
118. Gonda X, Rihmer Z, Juhasz G, et al. High anxiety and migraine are associated with the s allele of the 5HTTLPR gene polymorphism. Psychiatry Res. 2007;149:261–266.
119. Munafo MR, Clark TG, Roberts KH, et al. Neuroticism mediates the association of the serotonin transporter gene with lifetime major depression. Neuropsychobiology. 2006;53:1–8.
120. Takano A, Arakawa R, Hayashi M, et al. Relationship between neuroticism personality trait and serotonin transporter binding. Biol Psychiatry. Epub: 2007 Mar 2.
121. Sen S, Nesse RM, Stoltenberg SF, et al. A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. Neuropsychopharmacology. 2003;28:397–401.
122. Itoh K, Hashimoto K, Kumakiri C, et al. Association between brain-derived neurotrophic factor 196 G/A polymorphism and personality traits in healthy subjects. Am J Med Genet B Neuropsychiatr Genet. 2004;124:61–63.
123. Lang UE, Hellweg R, Kalus P, et al. Association of a functional BDNF polymorphism and anxiety-related personality traits. Psychopharmacology (Berl). 2005;180:95–99.
124. Willis-Owen SA, Fullerton J, Surtees PG, et al. The Va166Met coding variant of the brain-derived neurotrophic factor (BDNF) gene does not contribute toward variation in the personality trait neuroticism. Biol Psychiatry. 2005;58:738–742.
125. Tochigi M, Otowa T, Suga M, et al. No evidence for an association between the BDNF Va166Met polymorphism and schizophrenia or personality traits. Schizophr Res. 2006;87:45–47.
126. Kobayashi K, Shimizu E, Hashimoto K, et al. Serum brain-derived neurotrophic factor (BDNF) levels in patients with panic disorder: as a biological predictor of response to group cognitive-behavioral therapy. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29:658–663.
127. Yoshida K, Sugawara Y, Higuchi H. Dramatic remission of treatment-resistant depression after the cessation of tricyclic antidepressants. Pharmacopsychiatry. 2006;39:114.
128. Chen ZY, Jing D, Bath KG, et al. Genetic variant BDNF (Va166Met) polymorphism alters anxiety-related behavior. Science. 2006;314:140–143.
129. Bagby RM, Quilty LC, McBride CC. Personality and the prediction of response in major depressive disorder: a randomized control trial comparing interpersonal therapy and pharmacotherapy. Paper presented at the Annual International Conference on Interpersonal Psychotherapy, Toronto (ON): 2006 Nov.
130. Paris J. Neurobiological dimensional models of personality: a review of the models of Cloninger, Depue, and Siever. J Personal Disord. 2005;19:156–170.
131. Gabbard GO. Mind, brain, and personality disorders. Am J Psychiatry. 2005;162:648–655.
132. Miresco MJ, Kirmayer LJ. The persistence of mind–brain dualism in psychiatric reasoning about clinical scenarios. Am J Psychiatry. 2006;163:913–918.
133. Ebstein RP. The molecular genetic architecture of human personality: beyond self-report questionnaires. Mol Psychiatry. 2006;11:427–445.
134. Holzman PS. The fences of psychiatry. Am J Psychiatry. 1985;142:217–218.

[1]Assistant Professor, Department of Psychiatry and Behavioural Neurosciences, McMaster University; Scientist, Brain–Body Institute, St Joseph's Healthcare, Hamilton, Ontario.
[2]Associate Professor, Department of Psychiatry and Behavioural Neurosciences, McMaster University; Scientist, Brain–Body Institute, St Joseph's Healthcare, Hamilton, Ontario.
Address for correspondence: Dr G MacQueen, St Joseph's Healthcare, Hamilton Centre for Mountain Health Services, 100 West 5th Street, PO Box 585, Hamilton, ON L8N 3K7; macqueng@mcmaster.ca

Résumé : Les facteurs neurobiologiques liant les traits de personnalité et la dépression majeure

Objectif : L'objectif de cette étude est d'examiner la base neurobiologique de la personnalité et de la dépression.

Méthode : Nous avons examiné les études précliniques et cliniques liées aux modifications neuroanatomiques, neuroendocriniennes, moléculaires et génétiques chez les patients déprimés. Nous avons étudié si les facteurs neurobiologiques communs pouvaient être partagés entre personnalité et dépression.

Résultats : Les études précliniques donnent un aperçu des mécanismes neurobiologiques qui sous-tendent la pathophysiologie de la dépression, y compris les modifications neuroendocriniennes de la fonction hypothalamo-hypophyso-surrénalienne (HHS), les modifications neuroanatomiques de régions clés du cerveau, et les modifications de la neurotrophine et des systèmes de signalisation sérotoninergique. Les études cliniques montrent des modifications semblables chez les patients déprimés. Les données probantes suggèrent que les modifications neuroendocriniennes de la fonction HHS peuvent contribuer aux traits de personnalité, que les régions du cerveau impliquées dans la dépression, y compris l'hippocampe et le cortex cingulaire antérieur peuvent jouer un rôle dans la personnalité, et que les molécules clés impliquées dans la dépression ont été beaucoup étudiées en rapport avec les traits de personnalité, en particulier le névrosisme. Jusqu'ici, les mesures physiologiques (sérum, tomographie par émission de positons) offrent les données probantes les plus fiables impliquant le facteur neurotrophique dérivé du cerveau et la sérotonine dans la personnalité, alors que les données probantes génétiques sont moins convaincantes.

Conclusions : Il existe un lien neurobiologique entre la personnalité et la dépression; toutefois, il faut plus de recherche pour offrir une compréhension de la nature de cette relation et pour relier cette recherche aux études cliniques qui examinent l'influence des facteurs de la personnalité sur la dépression.