In Review

Neurobiological Factors Linking Personality Traits and Major Depression

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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.


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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**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>serotonin</td>
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<tr>
<td>5-HTT</td>
<td>serotonin transporter</td>
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<tr>
<td>5-HTTLPR</td>
<td>serotonin transporter protein promoter polymorphism</td>
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<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotrophic hormone</td>
</tr>
<tr>
<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CRH</td>
<td>corticotropin-releasing hormone</td>
</tr>
<tr>
<td>dex–CRH</td>
<td>dexamethasone–corticotropin-releasing hormone (test)</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>HPA</td>
<td>hypothalamic–pituitary–adrenal</td>
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<tr>
<td>MDD</td>
<td>major depressive disorder</td>
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<tr>
<td>PVN</td>
<td>paraventricular nucleus of the hypothalamus</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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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 stressors34 in people with mood disorders. The normal diurnal variation of cortisol is perturbed: the cortisol troughs normally seen at night are not blunted35 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.42–46 Inconsistencies and difficulties relate to exclusion criteria because mixed population studies are difficult to interpret.47 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. Second, 2 studies have linked personality traits with an exaggerated HPA activation, measured by the cortisol response in the dex–CRH test. In the first, high neuroticism was associated with greater HPA activation and in the second, novelty seeking was inversely associated with greater HPA activation. While a significant relation between harm avoidance and neuroticism with increased HPA activation was not reported in one study, 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.

**Neuroanatonic 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. Chronic stress leads to decreased transcription of the neurotrophin BDNF and decreased neurogenesis, whereas chronic treatment with antidepressants increases transcription of BDNF and neurogenesis. 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. 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 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. Third, structural magnetic resonance imaging studies suggest that structural hippocampal changes occur in people with recurrent depression. Although there is much less evidence linking the hippocampus to neuroticism and other aspects of personality, the authors of a recent study 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.

Another region implicated in MDD is the ACC (see Caetano), a region that is crucial for emotional processing and the integration of emotional, cognitive, and physiological stimuli. 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. Further, a recent multimodal imaging study reported that personality as well as concentrations of neuronal N-acetylaspartate were important in predicting ACC activation. 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. 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.

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. Psychotropic drugs without antidepressant properties, such as opiates, typical antipsychotics, and psychostimulants, do not increase BDNF expression in the hippocampus. Other treatments that may have antidepressant efficacy, including N-methyl-d-asparate receptor antagonists, transcranial magnetic stimulation, and exercise do increase the expression of BDNF in the hippocampus.
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. Second, several papers have reported reduced serum BDNF levels in depressed patients. 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; a correlation between CNS and peripheral BDNF has been reported in rats; and alterations in plasma or serum in humans has been reported to be distinct from whole blood samples that would contain platelet-derived BDNF. Importantly, in 2 of the clinical studies that measured BDNF in unmedicated depressed patients, BDNF peripheral levels returned to normal following antidepressant treatment. 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. Neuroticism and, to a lesser extent, BDNF, which have emerged as 2 key biological factors in both theories of MDD and the genetics of neuroticism. 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. Serotonergic signaling in the CNS is clearly distinct from neurotrophin signaling in several ways. BDNF 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 hydroxylase, 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. 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), which regulates gene transcription and 5-HTT availability at a physiological level.

Several clinical studies have demonstrated an association of the s allele with anxiety-related traits, increased risk for depression, and drug response to SSRIs and to lithium prophylaxis. 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 provide additional evidence for a role for the 5-HTTLPR genotype in mood. In the first report, healthy s allele carriers had greater amygdala reactivity to fearful stimuli. In the second report, 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, the 5-HTTLPR genotype affected the structure and function of

Genetic Studies

Neuroticism has a heritability of almost 50% and is fairly stable across life. MDD has a similar degree of heritability; 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. 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 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 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
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. Some121,122 although not all123–125 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

Paris130 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 Akiskal131 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. Gabbard131 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 Kirmayer132 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,” Holzman134 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 relationship between personality dimensions and illness. Perhaps the fences surrounding psychiatry will continue to fall.

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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, neuroendocriennes, 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 neuroendocriennes de la fonction hypothalamo-hypophysaire-surrénalienne (HHS), les modifications neuroanatomiques de régions clés du cerveau, et les modifications de la neurotransphine et des systèmes de signalisation sérotoninergique. Les études cliniques montrent des modifications semblables chez les patients déprimés. Les données probantes suggèrent que les modifications neuroendocriennes 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.