

## *Cellular plasticity and resilience and the pathophysiology of severe mood disorders*

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*Recent advances in the identification of the neural circuits, neurochemicals, and signal transduction mechanisms involved in the pathophysiology and treatment of mood disorders have led to much progress toward understanding the roles of genetic factors and psychosocial stressors. The monoaminergic neurotransmitter systems have received the most attention, partly because of the observation that effective antidepressant drugs exert their primary biochemical effects by regulating intrasynaptic concentrations of serotonin and norepinephrine. Furthermore, the monoaminergic systems are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical neuronal circuits thought to support the behavioral and visceral manifestations of mood disorders. Increasing numbers of neuroimaging, neuropathological, and biochemical studies indicate impairments in cellular plasticity and resilience in patients who suffer from severe, recurrent mood disorders. In this paper, we describe studies identifying possible structural, functional, and cellular abnormalities associated with depressive disorders, which are potentially the cellular underpinnings of these diseases. We suggest that drugs designed to enhance cellular plasticity and resilience, and attenuate the activity of maladaptive stress-responsive systems, may be useful for the treatment of severe mood disorders.*

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**D**epression is a common, chronic, and often disabling psychiatric illness, which is estimated to affect 5% to 10% of the population. It frequently appears in early life, has a chronic course, and is considered a risk factor for other medical illnesses, such as coronary vascular disease, diabetes, and osteoporosis. This is not altogether surprising given the extensive bidirectional “mind-body” interactions mediated via the autonomic nervous system, immune system, and a host of neuroendocrine factors. According to the World Health Organization (WHO), depression is the leading global cause of years of life lived with disability and the fourth leading cause of disability-adjusted life-years. Disability-adjusted life-years is defined as the reduction in an individual’s productive life, and takes into account premature mortality.<sup>1,2</sup>

Considering the high morbidity and mortality associated with depression, it is unfortunate that the psychological and neurobiological underpinnings of depression have not been specifically defined. Although major depression is currently diagnosed by means of a diagnostic system (*Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition [DSM-IV]*) based upon phenomenology, this disorder most likely embodies a heterogeneous set of disorders with multiple causes. Therefore, one of the major goals of current and future research on depression is the development of a diagnostic system based on etiology.<sup>3</sup>

This goal is becoming increasingly closer to reality due to recent progress in the identification of neural circuits, neurochemicals, and signal transduction mechanisms

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## Selected abbreviations and acronyms

<b>BDNF</b>	<i>brain-derived neurotrophic factor</i>
<b>CREB</b>	<i>cyclic adenosine monophosphate (cAMP) response element binding protein</i>
<b>ERK</b>	<i>extracellular response kinase</i>
<b>HPA</b>	<i>hypothalamo-pituitary-adrenal (axis)</i>
<b>LTP</b>	<i>long-term potentiation</i>
<b>MAP</b>	<i>mitogen-activated protein</i>
<b>PFC</b>	<i>prefrontal cortex</i>

underlying the pathophysiology and treatment of depressive illness.<sup>4,5</sup> Advances toward specifying the contribution of genetic factors,<sup>6</sup> psychosocial stressors,<sup>7,8</sup> and gene–environment interactions to susceptibility to depression are also taking place.<sup>9,10</sup> It is anticipated that, in the next few years, combined use of genomic and proteomic strategies to refine complex psychiatric diseases into mechanism-based subcategories may ultimately facilitate the matching of specific target-based therapies to particular markers in certain patient subgroups.<sup>11</sup>

Of all brain systems, the monoaminergic neurotransmitter systems have received the greatest attention in neurobiological studies of depressive disorders. The implication of these systems in depression is based on several observations: (i) effective antidepressant drugs exert their primary biochemical effects by regulating intrasynaptic concentrations of serotonin and norepinephrine; and (ii) antihypertensives that deplete these monoamines sometimes precipitate depressive episodes in susceptible individuals.

Furthermore, the monoaminergic systems are extensively distributed throughout the network of limbic, striatal, and prefrontal cortical (PFC) neuronal circuits implicated in the behavioral and visceral manifestations of mood disorders.<sup>12</sup> Over the past 40 years, clinical studies have aimed to uncover specific flaws in these neurotransmitter systems in mood disorders by using various biochemical and neuroendocrine approaches. In fact, assessment of cerebrospinal fluid (CSF) chemistry, neuroendocrine responses to pharmacological challenge, and neuroreceptor and transporter binding have demonstrated a number of abnormalities of the serotonergic, noradrenergic, and other neurotransmitter and neuropeptide systems in mood disorders.

Although such studies have been useful in the past, they have proved to be of limited value in clarifying the particular pathophysiology of depressive disorders. In order to clarify the biological underpinnings of these disorders,

there should be an appreciation of the episodic and often intense mood disturbance, which can become progressive over the time. Furthermore, the phenotypic expression of the disease involves not only episodic and often profound mood disturbances, but also a constellation of cognitive, motor, autonomic, endocrine, and sleep/wake abnormalities. Additionally, while most antidepressants exert their initial effects by increasing the levels of serotonin and/or norepinephrine in the synapse, clinical antidepressant effects exclusively result after chronic administration (days to weeks). This suggests that a cascade of downstream effects is ultimately responsible for the clinical antidepressant effects of these medications. These observations have led to the recognition that, although monoaminergic neurotransmitter system dysfunction undoubtedly plays an important role in mediating some facets of the pathophysiology of depressive disorders, additional fundamental alterations in cellular plasticity cascades are most likely involved.<sup>13-15</sup>

The functional impairments during mood episodes have long been recognized; however, there is increasing evidence of significant interepisode impairment as well. The devastation of these disorders is further complicated by the fact that the medications currently used for their treatment are associated with variable rates of efficacy and not intolerable side effects. An appreciation for both the need for more efficacious treatment for mood disorders and the absence of significant advances in the development of truly innovative therapeutics has led to the investigation of intracellular signaling cascades and their role in the pathophysiology and treatment of mood disorders. Thus, while traditionally viewed exclusively as neurochemical disorders, recent evidence suggests the presence of impairments of cellular plasticity cascades, which produce not only functional, but also morphological impairments; this evidence has generated considerable excitement among the clinical neuroscience community and is reshaping views about the neurobiological underpinnings of these disorders. Thus, as we discuss in detail below, increasing neuroimaging, neuropathological, and biochemical studies suggest impairments in cellular plasticity and resilience in patients who suffer from severe, recurrent mood disorders. The term “neuroplasticity” encompasses diverse essential processes by which the brain perceives, adapts to, and responds to a variety of internal and external stimuli. Manifestations of neuroplasticity in the adult central nervous system (CNS) include alterations of dendritic function, synaptic remodeling, long-term potentiation (LTP),

axonal sprouting, neurite extension, synaptogenesis, and neurogenesis. In this perspective paper, we describe studies identifying possible structural, functional, and cellular abnormalities associated with depressive disorders—the potential cellular underpinnings of these micro- and macromorphological brain changes. We suggest that therapeutics designed to enhance cellular plasticity and resilience, and to attenuate the activity of maladaptive stress-responsive systems may have considerable utility for the treatment of severe mood disorders.

### Brain imaging studies in depressed patients

Positron emission tomography (PET) imaging studies have unveiled various abnormalities of glucose metabolism and regional cerebral blood flow (CBF) in limbic and PFC structures in patients with mood disorders. Although some disagreement exists regarding the specific locations and the direction of some of these abnormalities, unmedicated subjects with familial major depression show a consistent increase in regional CBF and metabolism in the amygdala, orbital cortex, and medial thalamus, and decreased metabolism and CBF in the dorsomedial/dorsal anterolateral PFC and anterior cingulate cortex ventral to the genu of the corpus callosum (ie, subgenual PFC) relative to healthy controls.<sup>16,17</sup> These abnormalities suggest that limbic-thalamic-cortical and limbic-cortical-striatal-pallidal-thalamic circuits, involving the amygdala, orbital and medial PFC, and anatomically related parts of the striatum and thalamus are involved in pathophysiology of depression. Additionally, these circuits have been implicated more generally in emotional behavior by electrophysiological, lesion analysis and brain mapping studies of humans and experimental animals.<sup>12,15</sup>

Some of these abnormalities reverse during symptom remission, suggesting that there are areas where neurophysiological activity may increase or decrease in order to mediate or respond to the emotional and cognitive manifestations of depression. However, CBF and metabolism do not completely normalize during effective antidepressant treatment in many of these areas.

Morphometric magnetic resonance imaging (MRI) and postmortem investigations have also demonstrated alterations in cerebral structure that persist regardless of mood state and may contribute to the corresponding abnormalities of metabolic activity.<sup>16,17</sup> Structural imaging studies have shown reduction in gray matter volumes in areas of the orbital and medial PFC, ventral striatum and

hippocampus, and enlargement of third ventricles in mood-disordered patients when compared to healthy controls. Complementary postmortem studies have demonstrated abnormal decreases in cortex volume, glial cell counts, and/or neuron size in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, and amygdala.<sup>12,14,15-17</sup>

It remains unclear whether these alterations in brain structure represent developmental abnormalities that may increase an individual's susceptibility to abnormal mood episodes, compensatory changes to other pathogenic processes, or the sequelae of recurrent affective episodes per se. The clarification of these issues will in part depend on investigations that outline the onset of such abnormalities within the illness course, as well as determine whether they precede depressive episodes in individuals with a high familial risk for mood disorders. The lack of complete reproducibility among neuroimaging or postmortem studies is not altogether surprising, and the disparities likely represent variations in experimental design and in patient populations. Further research is needed in order to understand whether more specifically defined subtypes of depression or mood disorders are associated with any specific abnormality.<sup>18</sup> The marked reduction in glial cells in these regions has been especially interesting, given the tremendous recent progress in our understanding of the critical roles of glial cells in regulating neuronal function. Thus, there is now compelling evidence that radial glial cells have the potential not only to guide newly born neurons, but also to self-renew and to generate *both neurons and astrocytes*. Furthermore, recent data have shown that astrocytes increase the number of mature, functional synapses on CNS neurons sevenfold, demonstrating that CNS synapse number can be profoundly regulated by glia. Glial cells are also known to play critical roles in regulating synaptic glutamate levels, CNS energy homeostasis, and the liberation of trophic factors, which in turn participate in the development and maintenance of synaptic networks formed by neuronal and glial processes.<sup>16,17,19-22</sup> Glial function abnormalities could thus prove essential to structural plasticity impairments and overall pathophysiology of mood disorders.

### Stress and brain morphology

The majority of studies of adaptive neuronal plasticity in response to stress, as well as hypothalamo-pituitary-adrenal (HPA) axis hormones, have focused on the hip-

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pocampus. This is partly due to early studies on neuronal populations of the limbic brain regions, including the dentate gyrus granule cell layer, and the CA1 and CA3 pyramidal cell layers. These cell layers and their connections (mossy fiber pathway and Schaffer collateral) have long been used as cellular models of learning and memory (ie, LTP). However, it is clear that stress and glucocorticoids also influence the survival and plasticity of neurons in other brain regions (such as PFC, *vide infra*) that have not yet been studied in the same detail as the hippocampus. Dendritic remodeling of hippocampal neurons is one of the best-characterized effects of stress on cellular morphology.<sup>23,24</sup> Dendritic remodeling is deeply observed in the CA3 pyramidal neurons as atrophy-decreased number and length of the apical dendritic branches. This stress-induced atrophy of CA3 neurons results after 2 to 3 weeks of exposure to restraint stress or more long-term social stress, and has been observed in rodents and tree shrews.<sup>23,24</sup> Although the effects of chronic stress in the CA3 layer tend to be most pronounced, slight structural changes are also found in the CA1 and dentate gyrus following a 1-month multiple stress paradigm.<sup>25</sup> Profound alterations in mossy fiber terminal morphology and significant synapse loss have also been described. The hippocampus has a very high concentration of glutamate and expresses both glucocorticoid (GR) and mineralcorticoid (MR) corticosteroid receptors, though these may be relatively scarce in the hippocampus of primates,<sup>26,27</sup> and more prevalent in cortical regions. MR activation in the hippocampus (CA1) is associated with reduced calcium currents, while GR activation leads to increased *N*-methyl-D-aspartate (NMDA) receptor throughput and increased calcium currents that could predispose to neurotoxicity. In fact, increasing evidence implicates glutamatergic neurotransmission in stress-induced hippocampal atrophy and death.

Histopathological changes in rat PFC after corticosterone administration have recently been described although this area has not been as comprehensively studied as the hippocampus. Using a Golgi-Cox procedure, Wellman<sup>28</sup> examined pyramidal neurons in layers II and III of the medial PFC, quantifying dendritic morphology in three dimensions. In this study, he demonstrated a significant rearrangement of apical dendrites in corticosterone-treated animals, with an increase in the dendritic material proximal to the soma and a decrease in distal dendritic material. This suggests that stress may result in a significant reorganization of the apical dendritic arbor in medial PFC in rats.

It is noteworthy that glucocorticoids may exert deleterious effects on neural plasticity and morphology, since a significant percentage of mood disorder patients show some form of HPA axis activation. It has been hypothesized that the depressive subtypes most frequently associated with HPA activation are also the most likely to be associated with reductions in hippocampal volume.<sup>23</sup> Many patients with Cushing's disease, in which pituitary gland adenomas cause cortisol hypersecretion, also show marked depressive symptoms, as well as hippocampal atrophy. Moreover, some patients with Cushing's disease also show reduced hippocampal volumes, correlating inversely with plasma cortisol concentrations. Corrective surgical treatment results in an enlargement of hippocampal volume in proportion to the treatment-associated decrease in urinary free cortisol concentrations.<sup>29,30</sup> HPA axis hyperactivity in mood disorder patients has been demonstrated by a variety of techniques/measures, including increased cortisol levels in plasma (especially at the circadian nadir), urine, and CSF, increased cortisol response to adrenocorticotropic hormone (ACTH), blunted ACTH response to corticotropin-releasing hormone (CRH) challenge, enlarged pituitary and adrenal glands, and reduced CRH receptor density in the brain (presumably reflecting a compensatory downregulation to sustained CRH elevations) at postmortem examination. In both unipolar and bipolar patients, reduced corticosteroid receptor feedback has been implicated in this process by challenge studies with dexamethasone and dexamethasone plus CRF.<sup>31,32</sup>

The results of recent longitudinal studies investigating the effects of early life stress and inherited variation in monkey hippocampal volumes underscore the need for caution when interpreting the clinical neuroimaging studies described above. These longitudinal studies in monkeys randomized paternal half-siblings (monkeys raised apart from one another by different mothers in the absence of fathers) to one of three postnatal conditions that interfered with various facets of early maternal care. Paternal half-siblings with small adult hippocampal volumes showed an initial larger relative increase in cortisol level following removal of all mothers after weaning.<sup>33</sup> However, plasma cortisol levels 3 and 7 days later did correlate with hippocampal size. These studies suggest that small hippocampal volume also reflects an inherited trait, and emphasize the need for caution in the simple attribution of causality in the cross-sectional morphometric studies of the hippocampus in humans.



## Stress effects on cellular plasticity and resilience

In addition to the cellular mechanisms described above, it is now clear that stressors may exert major effects on cellular plasticity and resilience by regulating the expression and function of growth factor cascades.<sup>33,34</sup> Neurotrophic factors (eg, nerve growth factor [NGF] and brain-derived neurotrophic factor [BDNF]), as well as cytokines, insulin-like growth factor-1 (IGF-1), and glial-derived neurotrophic factor (GDNF), increase cell survival.<sup>35,36</sup> These factors promote cell survival through the suppression of intrinsic, cellular apoptotic machinery, rather than by inducing cell survival pathways. This occurs via binding of these factors to membrane receptors and regulation of intracellular signal transduction pathways that can control apoptosis, including regulation of Bcl-2 family members. Mitogen-activated protein (MAP) kinase cascade, the phosphatidylinositol-3 kinase (PI-3K)/Akt pathway, and the PI-3K cascade are currently thought to be responsible for mediating many of the effects of neurotrophic factors.<sup>37</sup>

The family of receptors known as Trks, which contain an intrinsic tyrosine kinase domain, mediates neurotrophic factor signaling. Nerve growth factor binds to the TrkA receptor, while BDNF binds to TrkB. The resulting receptor activation results in phosphorylation and activation of effectors, including PI-3K, as well as protein coupling leading to of the MAP kinase cascade activation. Recent studies have shown that MAP kinase cascade activation can inhibit apoptosis by inducing the phosphorylation of Bad (a major proapoptotic protein) and increasing the expression of Bcl-2 (a major anti-apoptotic protein). This increased Bcl-2 expression likely involves a protein known as the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB).<sup>38,39</sup> Phosphorylation of Bad takes place via activation of a downstream target of the MAP kinase cascade, ribosomal S-6 kinase (Rsk). This phosphorylation by Rsk promotes the inactivation of Bad. Additionally, Rsk activation mediates the actions of the MAP kinase cascade and neurotrophic factors on the expression of Bcl-2. Rsk can phosphorylate CREB, leading to induction of Bcl-2 gene expression. A growing body of evidence indicates that not only is Bcl-2 neuroprotective, but also that it exerts neurotrophic effects and promotes neurite sprouting, neurite outgrowth, and axonal regeneration.<sup>40-43</sup>

Recently, it has been demonstrated that chronic stress (21 days' foot-shock) induces a marked and persistent hyperphosphorylation of an extracellular response kinase (ERK) in higher PFC layer dendrites, while phospho-CREB was reduced in the frontal cortex and other cortical regions.<sup>44</sup> Since CREB is phosphorylated and activated by phospho-ERK1/2 directly, this reduction indicates that chronic stress could downregulate CREB phosphorylation indirectly, and subsequently downregulate the transcription of some genes such as *Bcl-2* and *BDNF*. In this context, it is worth mentioning that a recent study revealed that severe stress exacerbates stroke outcome by suppressing Bcl-2 expression.<sup>45</sup> In this study, stressed mice expressed approximately 70% less Bcl-2 mRNA than unstressed mice following stroke. In addition, stress greatly exacerbated stroke in control mice, but not in transgenic mice that express increased neuronal Bcl-2. High corticosterone concentrations were significantly correlated with a greater stroke size in wild-type mice, but not in transgenic mice overexpressing Bcl-2. Therefore, enhanced Bcl-2 expression seems to offset the potentially harmful consequences of stress-induced neuronal endangerment, and suggests that pharmacologically induced upregulation of Bcl-2 may be useful in the treatment of a various disorders that have been linked to endogenous or acquired impairments of cellular resilience. It is now clear that the neurotrophic factor-ERK1/2-MAPK-Bcl-2 signaling cascade has a critical role in cell survival in the CNS and that a fine balance exists between the levels and activities of cell survival and cell death factors. BDNF-ERK1/2-CREB-Bcl-2 cascade dysregulation may be a key mechanism via which prolonged stress induces atrophy of select vulnerable neuronal subpopulations, distal dendrites, or both. Although dysregulation of this cascade most likely results in decreased neuronal survival, the differential survival is likely modulated not only by region-specific expression of protective factors, but also by the network properties of vulnerable structures. Therefore, it is likely that the dynamics of the impairments of cellular plasticity and resilience are determined by intrinsic properties of the affected regions.

There is emerging evidence—mainly from postmortem studies—supporting a role for abnormalities in neurotrophic signaling pathways in depression. Decreased levels of CREB, BDNF, and the TrkB receptor have been described in suicide victims.<sup>46-48</sup> Depressed individuals may also have genetic abnormalities in CREB and BDNF.

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Sequence variations in the *CREBI* gene have been observed in depressed women.<sup>6</sup> A coding variant of BDNF may be associated with the personality trait of neuroticism, which is a risk factor for depression.<sup>49</sup> Furthermore, two recent studies<sup>50,51</sup> suggest that a polymorphism in the pro-BDNF molecule is associated with bipolar disorder (a condition in which depressive episodes are accompanied by manic episodes). This polymorphism is associated with alterations in BDNF trafficking and secretion in vitro, as well as with alterations in hippocampal working memory in humans.<sup>52</sup> Therefore, an opportunity exists to study the interaction of life stress, signal transduction-related genes, neuroimaging abnormalities consistent with deficient structural plasticity, and susceptibility to depression.<sup>15</sup>

## Antidepressant mechanisms and neurotrophic signaling cascades

An increasing amount of evidence suggests that antidepressants regulate neurotrophic signaling cascades. Antidepressant treatment increases CREB phosphorylation and CREB-mediated gene expression in mice limbic brain regions.<sup>53</sup> Various classes of chronic antidepressant treatments, as well as electroconvulsive treatment (ECT), upregulate CREB and BDNF expression, suggesting that the CREB cascade and BDNF are common post-receptor targets of antidepressants.<sup>54,55</sup> This increase is exclusively seen after chronic use, thus corresponding to the onset clinical antidepressant effects with these therapies. Additional evidence that relates upregulation of these pathways and antidepressant treatment comes from antidepressant-like performance in behavioral models.<sup>56</sup> In rats, CREB overexpression in the dentate gyrus or BDNF injection leads to an antidepressant-like effect in the learned-helplessness paradigm and the forced swim test model of antidepressant efficacy.<sup>57-59</sup>

Chronic antidepressant treatment also increases the neurogenesis of dentate gyrus granule cells.<sup>60-62</sup> This effect has not been observed with acute antidepressant treatment. These studies show that chronic administration of different classes of antidepressants and ECT lead to an increase in the proliferation and survival of new neurons. Lithium, an effective antidepressant potentiating agent, also increases neurogenesis in the dentate gyrus.<sup>63</sup> It is noteworthy that in contrast to the findings seen with chronic antidepressant use, increases in neurogenesis do not occur with chronic administration of nonantidepressant psychotropic medications. Increases in neurogenesis have

been reported to occur with conditions that stimulate neuronal activity (eg, enriched environment, learning, exercise). This suggests that neurogenesis is positively regulated by, and might be reliant on, neuronal plasticity.

The enhancement of hippocampal neurogenesis following chronic antidepressant use highlights the level to which these efficacious treatments can regulate long-term neuroplastic processes in the brain. Since stress and antidepressants have opposite effects on hippocampal neurogenesis, it is likely that the clinical symptoms of depression are related to changes in hippocampal neurogenesis. In order to assess whether antidepressant-induced hippocampal neurogenesis is functionally relevant, Santarelli and associates<sup>64</sup> utilized both genetic and radiological methods to show that disruption of antidepressant-induced neurogenesis blocked behavioral responses to antidepressants. In this study, serotonin 1A receptor null mice were insensitive to the neurogenic and behavioral effects of fluoxetine, a serotonin selective reuptake inhibitor. In mice, X-irradiation of the hippocampus prevented the neurogenic and behavioral effects of two classes of antidepressants. Together, the above findings suggest that some of the behavioral effects observed with chronic antidepressant use may be mediated by the stimulation of neurogenesis in the hippocampus. However, as Kempermann<sup>65</sup> clearly articulated, much more research is required in order to adequately link changes in adult hippocampal neurogenesis to the pathophysiology and treatment of depression.

Agents capable of reversing the hypothesized impairments of cellular resilience, reductions in brain volume, and cell death or atrophy in depression have the potential of becoming new therapeutic classes of antidepressant drugs. New molecular targets might include phosphodiesterase inhibitors that increase CREB phosphorylation, MAP kinase phosphatase inhibitors that increase expression of the antiapoptotic protein bcl-2, presynaptic glutamate receptor subtypes that attenuate glutamate release,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) potentiators that increase BDNF expression, and NMDA antagonists that enhance plasticity and cell survival.<sup>14</sup>

## Concluding comments

A substantial body of evidence suggests that impairments in neuroplasticity and cellular resilience play a central role in the underlying biology of mood disorders. Additionally, there is a growing appreciation that new medications that

simply imitate “traditional” drugs, those aiming to directly or indirectly alter monoaminergic throughput, may be of limited benefit to those patients with refractory depression. Those strategies assume that the target circuits are functionally intact and that changes in synaptic activity will alter the postsynaptic throughput of the system. The evidence discussed here indicates that, in addition to neurochemical changes, many patients suffering from mood disorders also have marked structural alterations in crucial neuronal circuits. Therefore, in order to obtain an optimal treatment response, it will most likely be crucial to provide both trophic and neurochemical support. The aim of the trophic support would be to enhance and maintain normal synaptic connectivity, therefore permitting the chemical signal to restore maximum functioning of vital circuits essential for normal affective functioning. In fact, preliminary studies suggest that regional structural changes in the brains of patients with mood disorders may be related with not only severity and duration of the illness, but also with altered treatment response to pharmacotherapy and ECT.

The evidence also suggests that, somewhat similar to the treatment of other chronic medical conditions, such as hypertension and diabetes, prompt and sustained treatment may be necessary to prevent many of the injurious long-term sequelae associated with mood disorders. Although the evidence hints at an association between hippocampal atrophy and illness duration in depressed patients, it remains unclear whether the volumetric and cellular changes observed in other brain areas are related

to affective episodes. In fact, some studies have described reduced gray matter volumes and increased ventricle size in patients with mood disorders at the time of their first episode and in early onset of the disease.<sup>12,15</sup>

In conclusion, relevant genotypes for mood disorders are being identified, and clinical research techniques are now capable of defining neurobiological phenotypes. Similarly, results from transcriptomic and proteomic studies which identified neurotrophic signaling as targets for the long-term actions of antidepressants and mood stabilizers have played a role (along with neuroimaging and postmortem brain studies) in a reconceptualization about the pathophysiology, course, and optimal long-term treatment of severe mood disorders. These data suggest that, while mood disorders are clearly not classical neurodegenerative diseases, they are in fact associated with impairments of cellular plasticity and resilience. As a consequence, there is a growing appreciation that optimal long-term treatment will most likely be achieved by attempting to prevent the underlying disease progression and its attendant cellular dysfunction, rather than exclusively focusing on the treatment of signs and symptoms. We are optimistic that a new generation of research will clarify the relation among environmental and genetic risk factors to quantify the risk for the development of depression more precisely. These advances will result in a dramatically different diagnostic system based upon etiology, and ultimately in the discovery of new approaches to the prevention and treatment of some of mankind’s most devastating and least understood illnesses. □

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## **Plasticidad celular, resiliencia y fisiopatología de los trastornos afectivos graves**

Los avances recientes en la identificación de los circuitos neurales, los mecanismos neuroquímicos y de transducción de señales que participan en la fisiopatología y el tratamiento de los trastornos afectivos han conducido hacia un significativo progreso en la comprensión de los papeles de los factores genéticos y de los estresores psicosociales. Los sistemas de neurotransmisión monoaminérgica han concitado la mayor atención, en parte, debido a la observación que los antidepresivos eficaces ejercen sus efectos bioquímicos primarios a través de la regulación de las concentraciones intrasinápticas de serotonina y noradrenalina. Además, los sistemas monoaminérgicos se distribuyen extensamente a través de la red de circuitos neuronales límbicos, estriatales y corticales prefrontales, que se piensa son los responsables de las manifestaciones conductuales y viscerales de los trastornos afectivos. Un número creciente de estudios de neuroimágenes, neuropatológicos y bioquímicos revelan deterioros en la plasticidad celular y la resiliencia en pacientes que padecen trastornos afectivos graves y recurrentes. En este artículo se describen estudios que identifican posibles anomalías estructurales, funcionales y celulares que se asocian con los trastornos depresivos, los que constituyen potencialmente los fundamentos celulares de estas enfermedades. Se sugiere que los fármacos diseñados para incrementar la plasticidad celular y la resiliencia, y atenuar la actividad de los sistemas que determinan una mala adaptación al estrés, pueden ser útiles para el tratamiento de los trastornos afectivos graves.

## **Plasticité cellulaire, résilience et physiopathologie des troubles de l'humeur sévères**

Les progrès récents concernant l'identification des substances chimiques et circuits neuronaux et des mécanismes de transduction du signal impliqués dans la physiopathologie et le traitement des troubles de l'humeur ont amélioré la compréhension des rôles des facteurs génétiques et des facteurs psychosociaux de stress. Les systèmes de neurotransmetteurs monoaminergiques ont retenu le plus d'attention, en partie parce que l'on a remarqué que les principaux effets biochimiques des antidépresseurs efficaces s'exercent en régulant les concentrations intrasynaptiques de sérotonine et noradrénaline. De plus, les systèmes monoaminergiques sont largement distribués dans le réseau des circuits neuronaux limbiques, striataux et du cortex préfrontal supposés déterminer les manifestations comportementales et organiques des troubles de l'humeur. De plus en plus d'études de neuro-imagerie, neuropathologie et biochimie soulignent l'altération de la plasticité cellulaire et de la résilience chez les patients souffrant de troubles de l'humeur sévères et récurrents. Dans cet article, nous décrivons des études identifiant de possibles anomalies structurelles, fonctionnelles et cellulaires associées aux troubles dépressifs, qui constituent les bases cellulaires potentielles de ces pathologies. Nous suggérons que les médicaments conçus pour augmenter la plasticité cellulaire et la résilience et atténuer l'activité des systèmes inadaptés de réponse aux stress pourraient être utiles au traitement des troubles de l'humeur sévères.

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