And the Orchestra Played On: Activation of Distress Pathways—A Common Feature of Mood, Anxiety, Sleep, and Pain Disorders?

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As we begin this brief review of the neurobiology of major depressive disorder (MDD), we face these fundamental questions:

- Will the provided information be clinically relevant?
- Can current scientific research provide us with a coherent, comprehensive, and relatively accurate description of the underlying neurobiology of MDD?

Major depression, bipolar disorder (BD), and generalized anxiety disorder (GAD) are all characterized by a significant genetic contribution to their etiopathogenesis. Heritability estimates for MDD have exceeded 70% in some studies, and BD may be even more genetically based, with estimates reaching the 80% to 90% range. Interestingly, MDD is more frequently reported in the families of bipolar patients than is BD itself; this finding suggests a partially shared diathesis and likely a “correlated liability,” if not an affiliation with the same continuum. Similarly, the genetic and clinical overlap between MDD and GAD is so extensive that some authors have gone so far as to suggest that they are dual manifestations of the same underlying pathophysiology. It is becoming increasingly clear that relationships between MDD, GAD, and BD run deeper than symptomatic similarities shared by these conditions. Although not always consistent, studies point to shared genetic underpinnings for these disorders, emphasizing genes involved in the regulation of monoaminergic and peptide transmission, inflammatory responses, diurnal rhythms, and neurotrophic signaling. All of these are important modulators of anxiety, mood, and stress.
responses. Furthermore, symptoms of anger, depression, and anxiety are strongly correlated with one another.\(^8\) Stress, in turn, is a major precipitant, perpetuant, and aggravating factor of all 3 conditions. However, one must temper any rampant “clumping” enthusiasm with the recognition that—as with similarities—differences between symptom presentations have also frequently been found. Simple links between genes and symptom-based disorders are complicated by a number of factors, including:

- The most common “vulnerability genes” for mood and anxiety disorders account for relatively little variance.
- A gene for 1 product may produce an array of behavioral outcomes, given that its product is typically ensconced in larger circuits that tend to demonstrate final common pathway-type phenomena.
- Symptom presentations in any given person are likely to result from intricate interactions between multiple genes and environmental factors.\(^7,9\)

Examples of these types of interactions include epistasis (interactions between the genes) and epigenetic modulation (influences of life experience on gene expression).\(^10\) Acknowledging these important distinctions takes us a step closer to more effective personalized care.

It is no surprise that brain circuits involved in the regulation of mood, anxiety, and the stress response overlap to a significant degree with components of a “pain matrix” (areas mediating emotional and cognitive aspects of pain processing) as well as with structures involved in sleep regulation.\(^11–13\) From an evolutionary perspective, it is apparent that sleep deprivation, negative emotion, and physical pain all play key adaptive roles. All these apparently disparate phenomena provide a clear signal that current conditions are a threat to an organism’s survival.

Before we further elaborate on the roles and interactions between “danger, reward, and executive circuitries and pathways” in mood disorders, it is important to define these constructs more precisely. Reference to “circuitry and pathways” denotes discrete dynamic functional states of neural network rather than specific neuroanatomic entities. For example, depending on the pattern of “inputs,” nucleus accumbens, amygdala, hippocampus, anterior cingulate cortex (ACC), and paralimbic prefrontal cortex can be alternatively considered as components of either “reward/opportunity” or “danger/threat” pathways.\(^14,15\) Their cumulative interactions generate corresponding “outputs” or symptoms (much as one set of musical instruments can be used to produce a joyous or a mournful tune). Given the constant flow of internal and external information, there is a continuous flux of functional states, perpetuating the neural network’s adaptive and homeostatic roles.

In keeping with their shared role in alerting an organism to danger in the external or internal environment (ie, infection/tissue damage), peripheral and central “pathways” of anxiety, depression, and pain overlap significantly.\(^16–18\) They are all woven into the mammalian stress and immune response systems. While there are important differences in the sensory processing of anxiety, stress, and pain signals at the cortical and subcortical levels, (eg, dorsal column, thalamus, and primary and secondary somatosensory cortices [SI, and SII]), striking similarities are apparent in the involvement of limbic areas and paralimbic prefrontal cortex, amygdala, hippocampus, insula, ACC, ventromedial prefrontal cortex, as well as more “cognitive” and integrative brain areas, such as rostral ACC, dorsal ACC, dorsomedial prefrontal cortex, and dorsolateral prefrontal cortex.\(^12\) Imaging studies of persons experiencing depression, anxiety, spontaneous pain, social isolation, or sleep deprivation, bear more than little resemblance.

It is important to recognize that “stress circuitry,” “reward circuitry” (including nucleus accumbens, amygdala, hippocampus, ventral tegmental area, and orbital prefrontal cortex), and “executive circuitry” are not independent and mutually exclusive entities; they are better conceived of as intersecting and overlapping components of a common 3-dimensional neural network.\(^17,19,20\) Disruption in their dynamic balance may give rise to excessive negative emotions, combined with cognitive impairment and withdrawal of hedonic tone. Moreover, anxiety, pain, and depressed mood appear to have a shared capacity to engage autonomic, neuroendocrine, and neuroimmune components of the stress response.\(^21\) MDD, GAD,\(^22,23\) BD, chronic insomnia,\(^24\) and chronic pain\(^25\) are all associated with altered sympathetic/parasympathetic balance; neuroendocrine disturbance, manifested by insufficient HPA regulation; and altered immune function, characterized by inhibition of acquired immunity and enhancement of innate inflammatory signaling.\(^1,12,26\) In turn, these peripheral responses signal back to neural structures to further drive CNS danger pathway activation; this leads to a maladaptive feed–forward circuit that increasingly appears to be implicated in the production and maintenance of symptoms.
Within the CNS, microglia seem to be the principal recipients of bodily distress/pain signals. Microglia are increasingly implicated in the development of mood (depression and mania) and pain symptoms and disorders.\(^{27}\) Indeed, increasing evidence suggests that different patterns of interaction between microglia, astroglia, and neurons may engender diverse symptomatic manifestations (eg, pain, depression). Peripheral distress signals are “amplified” via reverberating communication between microglia, astrocytes, oligodendroglia, and neurons.\(^{12,28}\) The result is suppression of neurotophic trafficking and an increase in the production and release of proinflammatory cytokines and reactive oxygen and nitrogen species.\(^{26}\) The combined effect of this inflammatory and oxidative “surge” may damage astrocytes and oligodendroglia, thus contributing to demyelination and consequent disruption of CNS regulatory circuits required to restrain peripheral stress/inflammatory responses.\(^{12}\) Thus, the vicious circle closes.

Excessive excitatory glutamatergic transmission and compromised GABA-mediated inhibition (with ensuing excitotoxicity) appear to be common features of anxiety, mood, sleep, and pain disorders.\(^{31}\) Dysregulation in monoamine, substance P, galanin, and opiate-signaling also characterizes GAD, pain syndromes, and MDD. On the other hand, anxiety and mood and pain disorders are characterized by different patterns in the production of neurotrophic factors: depression and mania are characterized by reduced serum levels of brain-derived neurotrophic factor (BDNF), fibromyalgia is associated with increased BDNF,\(^{12}\) while fear and anxiety appear to be accompanied by elevated levels of nerve growth factor.\(^{32}\) Nonetheless, anxiety, pain, stress, and depression have a similar, possibly even synergistic, effect on neurotrophic signaling in the hippocampus, given that all of them are associated with reduced BDNF synthesis in this critical limbic region.\(^{33,34}\) This finding is of particular interest, given that the hippocampus represents a veritable “intersection” of pathways involved in emotional regulation, reward, memory, and coordination of neuroendocrine response.\(^{33}\)

MDD, BD, and chronic pain are all associated with neuroplastic changes in the CNS. In pathological pain states, facilitation of pain signaling, presumably on the basis of neuropastic changes in pain pathways, is often designated as “central sensitization.”\(^{35,36}\) Similarly, the recurrent and progressive nature of MDD and BD is often attributed to “kindling,” which—like central sensitization—reflects neuroplastic changes.\(^{37}\) Given this, MDD, BD,\(^{38}\) and chronic pain\(^{39}\) may all be characterized by adaptive processes gone awry as a result of complex interactions between genetic vulnerabilities and environmental factors. In this scenario, persistent aberrant processing of emotional, painful, and stressful signals eventually becomes “hard-wired,” presumably from ensuing neuroplastic alterations.

In some ways, chronic pain and disorders of sleep, mood, and anxiety share dysfunctional psychosomatic and somatopsychiatric communication patterns—indeed they can be seen as behavioral read-outs for these dysfunctional communication patterns.\(^{12}\) Their synergistic and simultaneous occurrence may give rise to a “symphony” of misery. If we assume that a shared biological underpinning gives origin to the clinical symptoms of MDD, BD, GAD, and chronic pain, it is clear that a full understanding of this “synergy” has critical diagnostic and treatment implications. Despite these powerful commonalities, however, it is important to realize that diverse underlying biological processes may generate similar symptoms and vice versa; that is, similar pathophysiology may drive diverse clinical manifestations. A synthesis of these dialectical perspectives suggests that understanding shared etiopathogenesis may provide an opportunity for the development of new preventive and treatment strategies that transcend diagnostic boundaries. A full appreciation of each person’s symptoms—as the unique result of interactions between genetic vulnerability, adversity, positive life experiences, individual coping skills, and overall health—offers the clearest way forward in our field’s attempt to develop personalized treatment approaches.

References:

References


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