The Critical Relationship Between Anxiety and Depression

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Anxiety and depressive disorders are among the most common psychiatric illnesses; they are highly comorbid with each other, and together they are considered to belong to the broader category of internalizing disorders. Based on statistics from the Substance Abuse and Mental Health Services Administration, the 12-month prevalence of major depressive disorder in 2017 was estimated to be 7.1% for adults and 13.3% for adolescents (1). Data for anxiety disorders are less current, but in 2001–2003, their 12-month prevalence was estimated to be 19.1% in adults, and 2001–2004 data estimated that the lifetime prevalence in adolescents was 31.9% (2, 3). Both anxiety and depressive disorders are more prevalent in women, with an approximate 2:1 ratio in women compared with men during women's reproductive years (1, 2).

Across all psychiatric disorders, comorbidity is the rule (4), which is definitely the case for anxiety and depressive disorders, as well as their symptoms. With respect to major depression, a worldwide survey reported that 45.7% of individuals with lifetime major depressive disorder had a lifetime history of one or more anxiety disorder (5). These disorders also commonly coexist during the same time frame, as 41.6% of individuals with 12-month major depression also had one or more anxiety disorder over the same 12-month period. From the perspective of anxiety disorders, the lifetime comorbidity with depression is estimated to range from 20% to 70% for patients with social anxiety disorder (6), 50% for patients with panic disorder (6), 48% for patients with posttraumatic stress disorder (PTSD) (7), and 43% for patients with generalized anxiety disorder (8). Data from the well-known Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study demonstrate comorbidity at the symptom level, as 53% of the patients with major depression had significant anxiety and were considered to have an anxious depression (9).

Anxiety and depressive disorders are moderately heritable (approximately 40%), and evidence suggests shared genetic risk across the internalizing disorders (10). Among internalizing disorders, the highest level of shared genetic risk appears to be between major depressive disorder and generalized anxiety disorder. Neuroticism is a personality trait or temperamental characteristic that is associated with the development of both anxiety and depression, and the genetic risk for developing neuroticism also appears to be shared with that of the internalizing disorders (11). Common nongenetic risk factors associated with the development of anxiety and depression include earlier life adversity, such as trauma or neglect, as well as parenting style and current stress exposure. At the level of neural circuits, alterations in prefrontal-limbic pathways that mediate emotion regulatory processes are common to anxiety and depressive disorders (12, 13). These findings are consistent with meta-analyses that reveal shared structural and functional brain alterations across various psychiatric illnesses, including anxiety and major depression, in circuits involving emotion regulation (13), executive function (14), and cognitive control (15).

Anxiety disorders and major depression occur during development, with anxiety disorders commonly beginning during preadolescence and early adolescence and major depression tending to emerge during adolescence and early to mid-adulthood (16–18). In relation to the evolution of their comorbidity, studies demonstrate that anxiety disorders generally precede the presentation of major depressive disorder (17). A European community-based study revealed, beginning at age 15, the developmental relation between comorbid anxiety and major depression by specifically focusing on social phobia (based on DSM-IV criteria) and then asking the question regarding concurrent major depressive disorder (18). The findings revealed a 19% concurrent comorbidity between these disorders, and in 65% of the cases, social phobia preceded major depressive disorder by at least 2 years. In addition, initial presentation with social phobia was associated with a 5.7-fold increased risk of developing major depressive disorder. These associations between anxiety and depression can be traced back even earlier in life. For example, childhood behavioral inhibition in response to novelty or strangers, or an extreme anxious temperament, is associated with a three- to fourfold increase in the likelihood of developing social anxiety disorder, which in turn is associated with an increased risk to develop major depressive disorder and substance abuse (19).

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It is important to emphasize that the presence of comorbid anxiety symptoms and disorders matters in relation to

treatment. Across psychiatric disorders, the presence of significant anxiety symptoms generally predicts worse outcomes, and this has been well demonstrated for depression. In the STAR*D study, patients with anxious major depressive disorder were more likely to be severely depressed and to have more suicidal ideation (9). This is consistent with the study by Kessler and colleagues (5), in which patients with anxious major depressive disorder, compared with patients with nonanxious major depressive disorder, were found to have more severe role impairment and more suicidal ideation. Data from level 1 of the STAR*D study (citalopram treatment) nicely illustrate the impact of comorbid anxiety symptoms on treatment. Compared with patients with nonanxious major depressive disorder, those 53% of patients with an anxious depression were less likely to remit and also had a greater side effect burden (20). Other data examining patients with major depressive disorder and comorbid anxiety disorders support the greater difficulty and challenge in treating patients with these comorbidities (21).

This issue of the *Journal* presents new findings relevant to the issues discussed above in relation to understanding and treating anxiety and depressive disorders. Drs. Conor Liston and Timothy Spellman, from Weill Cornell Medicine, provide an overview for this issue (22) that is focused on understanding mechanisms at the neural circuit level that underlie the pathophysiology of depression. Their piece nicely integrates human neuroimaging studies with complementary data from animal models that allow for the manipulation of selective circuits to test hypotheses generated from the human data. Also included in this issue is a review of the data addressing the reemergence of the use of psychedelic drugs in psychiatry, particularly for the treatment of depression, anxiety, and PTSD (23). This timely piece, authored by Dr. Collin Reiff along with a subgroup from the APA Council of Research, provides the current state of evidence supporting the further exploration of these interventions. Dr. Alan Schatzberg, from Stanford University, contributes an editorial in which he comments on where the field is in relation to clinical trials with psychedelics and to some of the difficulties, such as adequate blinding, in reliably studying the efficacy of these drugs (24).

In an article by McTeague et al. (25), the authors use meta-analytic strategies to understand the neural alterations that are related to aberrant emotion processing that are shared across psychiatric disorders. Findings support alterations in the salience, reward, and lateral orbital nonreward networks as common across disorders, including anxiety and depressive disorders. These findings add to the growing body of work that supports the concept that there are common underlying factors across all types of psychopathology that include internalizing, externalizing, and thought disorder dimensions (26). Dr. Deanna Barch, from Washington University in St. Louis, writes an editorial commenting on these findings and, importantly, discusses criteria that should be met when we consider whether the findings are actually transdiagnostic (27).

Another article, from Gray and colleagues (28), addresses whether there is a convergence of findings, specifically in major depression, when examining data from different structural and functional neuroimaging modalities. The authors report that, consistent with what we know about regions involved in emotion processing, the subgenual anterior cingulate cortex, hippocampus, and amygdala were among the regions that showed convergence across multimodal imaging modalities.

In relation to treatment and building on our understanding of neural circuit alterations, Siddiqi et al. (29) present data suggesting that transcranial magnetic stimulation (TMS) targeting can be linked to symptom-specific treatments. Their findings identify different TMS targets in the left dorsolateral prefrontal cortex that modulate different downstream networks. The modulation of these different networks appears to be associated with a reduction in different types of symptoms. In an editorial, Drs. Sean Nestor and Daniel Blumberger, from the University of Toronto (30), comment on the novel approach used in this study to link the TMS-related engagement of circuits with symptom improvement. They also provide a perspective on how we can view these and other circuit-based findings in relation to conceptualizing personalized treatment approaches.

Kendler et al. (31), in this issue, contribute an article that demonstrates the important role of the rearing environment in the risk to develop major depression. Using a unique design from a Swedish sample, the analytic strategy involves comparing outcomes from high-risk full sibships and high-risk half sibships where at least one of the siblings was home reared and one was adopted out of the home. The findings support the importance of the quality of the rearing environment as well as the presence of parental depression in mitigating or enhancing the likelihood of developing major depression. In an accompanying editorial (32), Dr. Myrna Weissman, from Columbia University, reviews the methods and findings of the Kendler et al. article and also emphasizes the critical significance of the early nurturing environment in relation to general health.

This issue concludes with an intriguing article on anxiety disorders, by Gold and colleagues (33), that demonstrates neural alterations during extinction recall that differ in children relative to adults. With increasing age, and in relation to fear and safety cues, nonanxious adults demonstrated greater connectivity between the amygdala and the ventromedial prefrontal cortex compared with anxious adults, as the cues were being perceived as safer. In contrast, neural differences between anxious and nonanxious youths were more robust when rating the memory of faces that were associated with threat. Specifically, these differences were observed in the activation of the inferior temporal cortex. In their editorial (34), Dr. Dylan Gee and Sahana Kribakaran, from Yale University, emphasize the importance of developmental work in relation to understanding anxiety disorders, place these findings into the context of other work, and suggest the possibility that these and other data point to neuroscientifically informed age-specific interventions.

Taken together, the papers in this issue of the *Journal* present new findings that shed light onto alterations in neural function that underlie major depressive disorder and anxiety disorders. It is important to remember that these disorders are highly comorbid and that their symptoms are frequently not separable. The papers in this issue also provide a developmental perspective emphasizing the importance of early rearing in the risk to develop depression and age-related findings important for understanding threat processing in patients with anxiety disorders. From a treatment perspective, the papers introduce data supporting more selective prefrontal cortical TMS targeting in relation to different symptoms, address the potential and drawbacks for considering the future use of psychedelics in our treatments, and present new ideas supporting age-specific interventions for youths and adults with anxiety disorders.

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