Recent advances in the study of the comorbidity of depressive and anxiety disorders

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Abstract

Depressive and anxiety disorders often comorbid, which causes more severe impairments. The high comorbidity and shared genetic and psychological factors between the 2 disorders have brought arguments about whether they represent a common construct, and whether the current classification is meaningful. In this editorial, a state-of-the-art overview of recent studies on the underlying mechanism of such comorbidity, and the association between and differentiation of the 2 disorders is provided. Recent studies employing data-driven approaches such as latent class analysis (LCA) and network analysis to investigate the symptomatology of depression and anxiety have indicated unique characteristics and bridging symptoms of their comorbidity. Whereas previous neurobiological and neuroendocrinological studies reported common alterations in prefrontal–limbic pathways, serotonergic projections and the hypothalamic–pituitary–adrenal (HPA) axis, recent research suggests that distinct neural circuits and heterogeneous changes in HPA activity may exist in depression when compared to anxiety. Lastly, both depression and anxiety have been long associated with decision-making deficits; however, emerging evidence from computational psychiatry demonstrate that there may be unique neurocognitive and computational alterations in each disorder. By investigating the common and unique symptomatic characteristics and underlying neurobiological and neurocomputational mechanisms of the 2 disorders as well as their comorbidity, it can be concluded that recent studies have greatly advanced our understanding of the etiology and neuropathophysiology of these disorders.

Keywords: depression, anxiety, comorbidity, data-driven, computational psychiatry

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Introduction

Depressive and anxiety disorders are 2 common mental disorders and affect 4.4% and 3.6% of the world population, respectively.[1] The 2 disorders, however, often comorbid.[2–7] For instance, it has been reported that 42% of people with 12-month major depressive disorder (MDD) also have 12-month anxiety disorders, and that 46% of people with lifetime MDD also have lifetime anxiety disorders.[5] Importantly, comorbid depression and anxiety causes more severe functional impairment, slower recovery and higher rate of suicidal ideation than each disorder alone.[2–7] Anxiety symptoms, even those not meeting the diagnostic criteria, often cause serious clinical concerns when they co-occur with depressive disorders: over half of patients with MDD have anxious depression, and these patients experience poorer treatment outcomes than those with non-anxious depression.[8] Given this high comorbidity and shared genetic and psychological risk factors (e.g., early life stress), it has been argued that the 2 disorders may represent a single, common construct of negative affect or psychological distress.[9] Therefore, a full understanding of the underlying mechanism of such comorbidity and the association between and differentiation of the 2 disorders is an urgent issue. In this editorial, an overview of recent studies focused on the symptomatology and neurobiological and neurocomputational mechanisms of the 2 disorders and their comorbidity is provided.

Symptomatology

Recent research has employed data-driven approaches such as latent class analysis (LCA) to investigate the typologies of depression and anxiety. Latent class analysis uses the full range of symptoms to classify individuals into homogeneous subtypes or the so-called latent classes, based on the patterns of symptom occurrence. So far, by employing LCA, a class of individuals with comorbid depression and anxiety has been consistently identified in samples from the general population at different ages and from different countries.[9–13] In several studies, the comorbidity occurs at multiple levels of symptom severity, for instance, low, moderate and high.[10,11] In some[9,12] but not other[10,11,13] studies, a depression or anxiety class only was also identified. Importantly, these studies have reported unique demographic and psychological characteristics of the comorbid class compared to other classes, for instance, being female, younger age, having fewer years of education, and experiencing more negative life events.

Another technique, the network approach, proposes that individual symptoms play a causal role in the psychopathology (by causing the onset of other symptoms) and seeks to clarify the connected network of symptoms which constitutes a disorder.[14] Network analysis of symptoms in patients with depressive and anxiety disorders has identified psychomotor agitation/retardation and irritability as the most important bridge symptoms connecting the 2 disorders and underlying the comorbidity.[15,16] Symptoms such as appetite change and suicidality are found to be unique to depression.[16]

Neurobiological mechanism

At the neurobiological level, the alterations in prefrontal-limbic pathways[17,18] and serotonergic projections arising from the raphe nuclei[19–21] have been proposed to underlie both depression and anxiety, which also explains why antidepressants such as selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors are effective for anxiety disorders. Nevertheless, a recent transcranial magnetic stimulation (TMS) was able to identify 2 distinct circuit targets for symptom clusters of depression (e.g., sadness) and anxiety (e.g., irritability). Specifically, TMS targeting the dorsomedial prefrontal cortex relieves anxiety symptoms, while TMS targeting the dorsolateral prefrontal cortex reduces depressive symptoms.[22]

From the neuroendocrinological point of view, dysfunctional hypothalamic–pituitary–adrenal (HPA) axis and elevated cortisol have been considered common to both depression and anxiety.[23,24] Nevertheless, comorbid depression and anxiety compared to each disorder alone[25] and anxious depression compared to non-anxious depression[26] may have more emphasized abnormalities in HPA axis and cortisol activity. It has to be noted that hypercortisolemia has also been reported in anxiety disorders,[27,28] which calls for a closer look at the potential heterogeneity of HPA abnormalities within the subtypes of anxiety disorders, as well as a reconsideration of the functional role of cortisol.[23]

Neurocomputational mechanism

Another recent trend is the neurocomputational approach known as computational psychiatry.[29–31] This approach builds mathematical models to simulate the neural and/or cognitive processes underlying behaviors including decision-making, which allows for the precise assay of fundamental neurocomputational constructs. Therefore, the parameters of these neural and cognitive processes may serve as useful biomarkers.[29–31]

Although both depression and anxiety have long been associated with decision-making deficits, emerging evidence from computational psychiatry suggest unique neurocomputational alterations in each disorder. Whereas depression is associated with reduced reward-seeking behaviors, including slower learning of reward contingencies and increased estimation of effort required to pursue rewards,[31–34] anxiety is associated with heightened sensitivity to threat and increased threat avoidance behaviors.[34]

For instance, 1 study reported that patients with generalized anxiety disorder have elevated risk aversion as indicated by a more concave utility function.[31] Furthermore, symptoms of anxiety are correlated with elevated risk aversion after controlling depression; however, symptoms of depression are not correlated with elevated risk aversion after controlling anxiety, suggesting a unique link between anxiety and risk aversion.[35] Somewhat contradictorily, a subsequent study with healthy adults employing 3 different methods to tease apart the comorbidity of depression and anxiety showed that neither depression nor anxiety is associated with risk aversion, while depression but not anxiety is associated with probability weighting of reward outcomes.[36] As the symptoms of depression increase, people's tendency to overweight small probabilities and underweight large probabilities is attenuated or even reversed. While these studies advance our understanding of the neurocomputational changes of the disorders, future research is required to address the inconsistencies and further clarify potential sex differences.[37]

By investigating the common and unique symptomatic characteristics and underlying neurobiological and neurocomputational mechanisms of the 2 disorders and their comorbidity, it can be concluded that recent studies have greatly advanced our understanding of the etiology and neuropathophysiology of these disorders. The insights provided by these studies also shed light on several treatment targets that may be of particular clinical interest, including bridge symptoms, distinct brain circuit targets and distinct neurocomputational alterations. We believe that future research will propel us towards a better, more refined understanding of depression, anxiety and their comorbidity, and bring us closer to personalized precision psychiatry.

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