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Anxiety – depression comorbidity – bête noire or quick fix?

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Summary

The common territory shared by anxiety and depression has always been a contentious subject. Research in favor of anxious depression as a potentially treatment-relevant subtype has been limited by diagnostic dilemmas and crude measurement. The most recent evidence from genetics, neuropeptide systems and functional neuroimaging suggests a valid diagnostic construct.

The peripatetic journey of psychiatric nosology has triggered a wealth of reactions, from militant antipsychiatry to philosophical anchorage (1), from warnings of “brainlessness” and “mindlessness” drifts to derision of high-tech creeds. Psychiatrists have been often portrayed as either obsessional splitters or narcissistic wizards, spreading imaginary epidemics to quench an Adlerian thirst for power or just to get rich.

More sympathetic attempts to understand these vacillations describe models like epistemic iteration, according to which successive stages of knowledge build increasingly accurate estimations of a diagnostic model (2). This would involve a stable, objective model – in other words, an entity that exists “out in the world”, but eludes for now our ability to define it. That brings us to the crux of this editorial.

Comorbidity between anxiety and depression has received constant attention for generations of researchers. But does anxious depression exist “out there”? Any clinician would say yes, as they encounter and treat the mixed version more often than pure depression. However, as dichotomizers have ruled the DSM for some time (1), the US psychiatrist will have to write two diagnoses to accommodate the symptomatology to the nosology.

Several theoretical models argued that a diagnosis of ‘anxious-depression’ is a quick fix, an artifact forced upon naturally dimensional psychopathologies by the dominant neo-Kraepelinian paradigm. Others support the view of two different entities sharing some common psychopathological territory or representing, in their mixed state, the stable, deepest core of neurotic symptoms (3). Models like the tripartite model of Clark & Watson rely on psychological constructs such as positive affectivity, physiological hyperarousal, and negative affectivity (4). Empirical research has supported the tripartite model's utility, especially with regard to the two dimensions that separate depression and anxiety (low positive affect and high physiological hyperarousal, respectively), which have proven to be

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orthogonal. The comorbidity is explained almost exclusively by an increase in negative affect in both conditions, which links anxiety and depression with constructs such as neuroticism. Other models, such as the approach-withdrawal model or the valence-arousal model, rely on affective styles stemming from the interaction of motivation and emotion, as well as on the neural circuits assumed to underlie these constructs (5). The approach system (positive affect and reward response) and the withdrawal system (avoidance and negative affect) involve overlapping, yet dissociable neural circuits: left prefrontal cortex and the basal ganglia for the approach system, right prefrontal cortex for the withdrawal system, with the amygdala playing a crucial role in both systems (5). These models propose various permutations among the basic factors as the source of comorbidity, but as a rule, they advance endophenotypes designed to increase the diagnostic validity.

More recently, bipolar vulnerability has also been suggested as a source of comorbidity. The study in the current issue of the journal supports the prognostic importance of anxiety symptoms in the long-term outcome of both unipolar and bipolar depression (Coryell et al, this issue).

Further insights into the sources of comorbidity have come from gene-by-environment interactions studies. These studies have shown that genetic risk factors for major depression and generalized anxiety are strongly correlated, but that the majority of the genetic covariance between the two disorders results from factors not shared with neuroticism (which counted for only about 25% of this correlation)(6). Such results contradict the architecture of the tripartite model, in which the negative affect is the intermediate phenotype of comorbid anxious-depression. In addition, neuroticism-independent genetic factors seem to significantly increase the risk for major depression, generalized anxiety disorder, and panic disorder, showing that there is substantial, but not complete, overlap between the genetic factors that influence individual variation in neuroticism and those that increase liability for both depression and anxiety (6).

As epistemic iteration requires building on incremental knowledge, the construct of comorbid depression and anxiety is currently being deliberated not through sophisticated psychological models, but through progress in the biological realms of receptor changes, neuropeptide systems alterations, dysregulation in intracellular signaling, changes in gene sequence or expression, or alteration in brain circuits (7). How relevant are these advances to the pathophysiology of anxious depression? A brief overview is required.

Serotonin plays an important modulatory role in emotion, motivation and cognition, and its dysfunction contributes to many disorders, including mood and anxiety disorders, psychosis and substance abuse. Serotonin transporter knockout rodents have been extensively characterized in well-validated tests for anxiety- and depression-like behavior. However, depression and anxiety-like symptoms are less robust in these animal models, suggesting that the monoaminergic dysregulation is most likely intermingled with dysregulation in other systems such as the glutamatergic or peptidergic systems, in particular neuropeptide Y (NPY) and vasopressin (AVP) (7). The importance of AVP, Corticotropin Releasing Hormone (CRH), oxytocin, prolactin, NPY, and neuropeptide S as neuromodulators of emotionality is becoming increasingly apparent. Differences in these peptides' behavior in depression vs. anxiety models are frequently reported (7). Thus, specific agonists of NPY1 receptor are purely anxiolytic, while NPY2 antagonist have anxiolytic and antidepressant potential; urocortin 1 has no effect in depressive models, while it has anxiogenic properties; oxytocin has been extensively studied for its anxiolytic effect, while its antidepressant effect is still unclear. So far, there are no studies addressing neuropeptides changes in comorbid anxious depression, so we cannot make inferences regarding their role in supporting a distinct diagnosis of anxious depression. One relevant neurotrophin that has been connected

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to comorbid anxious depression is the brain-derived neurotrophic factor (BDNF). Recent data showed that the BDNF Val66Met allele was significantly more abundant in individuals with comorbid anxious depression than in individual with pure depression or pure anxiety. Proinflammatory cytokines (interferon-alpha, interleukin-2, IL-1beta, IFN gamma) have been implicated in the pathophysiology of mood disorders, through their influence of monoaminergic metabolism and the hypothalamic-pituitary-adrenocortical (HPA) axis, but again, there are no studies addressing their role in anxious depression. This brings us to the most studied system - the HPA axis. Clinical and preclinical studies have reported HPA axis dysregulation in mood and anxiety disorders, with higher cortisol levels in comorbid anxious depression than in pure Major Depressive Disorder (MDD) or pure Generalized Anxiety Disorder (GAD). The association of HPA axis and the tripartite model of Clark and Watson has shown that morning cortisol was not linked to DSM-IV diagnoses of anxiety disorders or MDD, but to specific symptoms such as anhedonia, worry and negative affect, making thus an argument for the a dimensional diagnostic model.

Although neuroimaging studies pertinent to either depression or anxiety have flooded Medline in the last two decades and transformed the amygdala into a star, a surprisingly small number of studies explored the neural marke(8)rs of anxiety-depression comorbidity. Anxiety-depression comorbidity has been characterized by more right than left anterior activity in MDD subjects, consistent with a key role of the right prefrontal cortex in anxiety disorders (5). Sustained activation in the dorsal Anterior Cingulate Cortex (ACC) has been described as a marker of anxiety superimposed on depression, results confirmed by a voxel-based morphometry study indicating that reduced volume of dorsal ACC is a non-specific effect of comorbid anxiety and depression. Moreover, the connectivity patterns in the Default-Mode Network in late-life depression are modified by the presence of increased anxiety symptoms (8). The functional neuroimaging experiments have still to move the field forward clinically, to offer sensitive and specific biomarkers of diagnostic and treatment response, but the few results available suggest that comorbid anxious depression leaves a different neural imprint than pure depression or pure anxiety.

To return to the epistemic iteration model, it seems we generate increasingly accurate estimations of the biological features of the “out-in-the-world” anxious depression, but the asymptotic nature of the process doesn't allow for fast gratification. The overall direction of the most recent biological findings points toward a valid comorbid entity, one that has been for a long time a nosological pain due to its complexity. The current failure to allow the diagnosis of Mixed Anxiety-Depression (subthreshold MDD plus subthreshold anxiety disorder) has notable treatment consequences: practitioners may not provide optimal pharmacotherapy or psychotherapy [such as simple-to-deliver internet CBT (9)], or even fail to detect or treat the symptoms as they don't fall in the prescribed DSM category (10).”

We expect eventual applications from neuroscience and genetics to revolutionize the diagnosis and treatment of mental disorders. Current efforts, including those listed above, remind us though that we tackle the “most complexly organized structure in the universe [...] and the number of possible permutations and combinations of brain activity, in other words the numbers of brain states, exceeds the number of elementary particles in the known universe” (11).

Maybe attempts to achieve DSM validity, especially in contentious areas like comorbid anxious depression, will take more iterations, but some of the dismissive approaches reviewed in the first paragraph remind us of a story about the late Francis Crick: “All this stuff on the brain is interesting, Dr. Crick, but can you name any one single discovery in the last two decades that has really important implications?” “Well, my dear, “replied Crick, “one thing we have now learnt is that the brain is really plastic.”

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