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Growing Trends in Conceptualizing Geriatric Mental Health within a Neural Context

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Commentary on *Anxiety in Late Life Depression: Associations with Brain Volume, Amyloid Beta, White Matter Lesions, Cognition, and Functional Ability* by Kryza-Lacombe *et al.*

Conflict of interest

Nathan Hantke serves as the national co-director for the Mental Illness Research and Treatment VA Fellowship Program.

Description of authors' roles

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The Diagnostic and Statistical Manual of Mental Health Disorder (DSM), first published in 1952, proposed that mental health disorders should be conceptualized and diagnosed as discrete and unique entities. From a clinical perspective, this approach is intuitive and appealing. A patient presents to clinic, meets criteria for a specific mental health disorder, and is prescribed a treatment to address the symptoms. There are several key assumptions within this model: the symptoms related to each mental health disorder are mutually exclusive, mental health symptoms within each disorder present similarly between populations, clinical thresholds are fixed across the lifespan, and treatments prescribed are equally efficacious across patient demographics. However, over the past 70+ years, since the inception of the DSM, the field of psychology has experienced dramatic growth and many empirical studies appear to contradict several of these key assumptions about mental health disorders. Honing in on testing a few of these key assumptions, Dr. Kryza-Lacombe and colleagues (2024) provide new findings in their recent work that highlights cross-diagnosis symptom presentation and neurobiological correlates in an older adult population.

There is a growing body of research indicating that there are more neural similarities among psychiatric disorders than there are differences, and that there are common neural substrates associated with clinical symptoms that cross diagnostic boundaries (e.g., McTeague et al., 2020; Xie et al., 2023). For example, of older adults experiencing late-life depression (LLD), which is major depressive disorder that occurs among people age 65 and above, nearly half also demonstrate concurrent anxiety (Beekman et al., 2000). As a field, we often take the frequency of co-occurring psychiatric symptoms/disorders and the blurring diagnostic boundaries as a normal part of the complicated mosaic of mental health care. However, a paradigm shift has been brewing over the past decade that revolves around the key question of whether clinical presentation, alone, is sufficient to understand mental health disorders and, if not, asks how we can do better. Reflecting the expanding literature focused on identifying neurobiological and psychiatric intersections, psychopathology is increasingly recognized as a product of neural dysfunction. Taxonomy and nosology emphasizing biomarkers and multidimensional models, such as NIH Research Domains of Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP), are gaining traction within the field as alternative approaches to traditional DSM-based criteria with a goal of grounding psychopathological symptoms and

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mental health disorders within a framework of brain dysfunction (Cuthbert, 2015). Particularly given the growing aging population, leveraging research on potential biomarkers and using multidimensional models that expound on traditional diagnostic approaches is especially important to understand the etiology of mood disorders in older adults, such as LLD, so that future work builds toward more efficacious and applicable treatments.

It is at this juncture that Dr. Kryza-Lacombe and colleagues (2024) present their findings, examining the complex relationship of anxiety within older adults with LLD via factors associated with neurodegenerative conditions. Given the likely multifactorial nature of mood disorders in older adulthood, the authors investigated a rather comprehensive list of factors in their study, including regional brain volumes, amyloid beta (Aβ) deposition, white matter disease, APOE genotyping, cognitive dysfunction, and functional ability. The study comprised a sample of 121 older adults with primary major depressive disorder (MDD) and, thus, LLD. Expectedly, given the high comorbidity of depression and anxiety symptoms, 50% of the sample was found to have coincident moderate to severe anxiety, with over 25% of the total LLD sample also meeting criteria for a concurrent anxiety disorder. Although not unexpected, this high rate of comorbid anxiety and LLD within their sample punctuates the necessity of comprehensive studies, such as the authors', to explore how comorbid mental health symptoms and their intersection with neurobiological phenomena might differ from that of participants who fit neatly into a precisely singular mental health diagnostic box. Investigating those with these blurred symptoms/diagnostic presentations can advance the field by allowing for a deeper understanding and ability to conceptualize the interplay of psychiatric disorders and neurobiological correlates, particularly as it relates to varied demographic samples, such as in older adults.

Leveraging research demonstrating the importance of the orbitofrontal cortex (OFC) in a person's engagement with both reward-related behaviors and in their general hedonic experience, the authors investigated the interplay of total OFC volume as it correlates to cognitive functioning as well as anxiety and depression in older adulthood. What they found, which was a key outcome of their study, was that greater anxiety was associated with more cognitive dysfunction and reduced OFC volumes, even when controlling for severity of depression. In addition, global cognitive functioning was associated with anxiety severity, such that worse

cognition was seen in those with more anxiety, independent of OFC volumes and severity of depressive symptoms. These findings extend seminal work demonstrating an association between anxiety severity and reduced grey matter in the OFC in older adulthood, and that older adults with concurrent symptoms of anxiety and depression experience greater cognitive dysfunction than those with anxiety or depression alone (Andreescu et al., 2017; Beaudreau & O'Hara, 2009).

There is a large body of literature proposing that co-occurring depression and anxiety symptoms are prodromal symptoms of a neurodegenerative process (Pimontel et al., 2020). It has been specifically indicated that cerebrovascular disease burden and Alzheimer's disease are associated with mood symptoms, and prior research has shown that anxiety and Aβ deposition in older adults is related. One hypothesis supporting this is that anxiety-related elevated cortisol levels increase risk for AD-related neuropathology (Demnitz-King et al., 2023). However, in contrast with these studies, Dr. Kryza-Lacombe and colleagues' present study found that cognitive dysfunction and smaller OFC volumes were associated with anxiety symptoms in individuals with LLD, yet were not associated with biomarkers of possible emerging dementia. Additionally, they demonstrated that Aβ burden and white matter hyperintensities on neuroimaging were not associated with anxiety severity in older adults with LLD. The authors postulate that older adults with symptoms of anxiety and depression are more likely to experience cognitive impairment and future cognitive decline that are not directly tied to neurodegenerative biomarkers, such as Aβ. Consistent with this hypothesis, recent studies have demonstrated that severe and sustained depression and anxiety have longitudinally been associated with future cognitive decline (Kaup et al., 2016; Petkus et al., 2016). Additionally, other research has shown that the OFC has a unique relationship with mood symptoms, linking reduced OFC volume to depression and generalized anxiety disorder in older adults, possibly due to decreased cognitive flexibility and emotion dysregulation (Andreescu et al., 2015). It may be that the smaller OFC reflects dysfunction within the "executive control network" that results in an inability for the anterior cingulate and OFC to dampen and habituate to anxiety-inducing thoughts (Etkin & Schatzberg, 2011). This relationship may also explain dysfunction with cognitive control and working memory in older adults with anxiety symptoms (Hantke et al., 2017). In the current study, the reason for the lack of significant association of OFC volume and cognitive dysfunction is not

entirely clear, and the lack of findings may be a byproduct of sample size and/or the tests used in the cognitive battery, but highlights the necessity of ongoing and additional study in this area. Although the exact relationship between LLD, anxiety, and neuropathology remains unclear, what is clear is that additional research investigating the individual and related contributions of these factors in older adults is imperative.

The neuropsychological and anatomical underpinnings of mental health disorders in older adulthood, including LLD, have been substantially clarified over the past decade, but we still have a long way to go. It is quite possible that mood symptoms/disorders and cognitive dysfunction are a bidirectional relationship, with worsening mood resulting in cognitive inefficiency and cognitive difficulties reflecting dysfunction in neural networks key in mood regulation (Desai et al., 2020). The mixed findings within the field likely reflect the complicated relationship between mental health symptoms, neuropathology, and neuropsychology, emphasizing the difficulty of conceptualizing clinical symptoms into a neat and tidy box, further supporting a shift toward taxonomies and nosology that emphasize multidimensional approaches and use of neural correlates. Precision psychiatry approaches and conceptual frameworks, such as RDoC and HiTOP, reflect a zeitgeist of interdisciplinary approaches in the taxonomy of mood disorders that highlight cognitive, behavioral, genetic, and neurobiological contributing factors. Concordantly, *International Psychogeriatrics* has a body of recently published work that demonstrates reciprocal associations between depression, cognitive impairment, and modifiable factors such a night-time sleep duration (Zuidersma et al., 2022), and that individually tailored mood interventions may improve mood in older adults (Delhom et al., 2022). These studies, among others, enhance and improve the field's ability to address modifiable risk factors as well as understand and conceptualize mental health disorders, which, in turn, holds great promise for improving quality of life in older adults.

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