International Psychogeriatrics (2023), 35:12, 682–685 © International Psychogeriatric Association, 2023
doi:10.1017/S1041610223000674

COMMENTARY

Neurobiological underpinnings of geriatric depression: an imperative for enhanced diagnosis and targeted interventions

Commentary on "Regional grey matter volume correlates with anxiety, apathy, and resilience in geriatric depression" by Krause-Sorio *et al.*

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The prevalence of depression among older people has been reported to exceed 30% (Zenebe *et al.*, 2021). Geriatric depression (GD) is a significant public health concern due to its high rates of underdiagnosis and lack of appropriate treatment, resulting in compromised quality of life and increased vulnerability to physical and cognitive decline (Nelson *et al.*, 2008). The diagnostic and therapeutic challenges associated with depression in older people stem from several factors, including the coexistence of physical comorbidities that mask psychiatric symptoms, age-related alterations in brain structure and function, and the necessity for individualized interventions targeting distinct neurobiological profiles. GD is characterized by alterations in brain structure (Mackin *et al.*, 2013). Therefore, understanding the neurobiological mechanisms underlying GD is of utmost importance as it offers the potential for improved diagnostic precision and the development of more targeted interventions (Schumann *et al.*, 2014). Such knowledge can pave the way for personalized treatment strategies that align with the unique neurobiological characteristics of older adults with depression.

The study titled "Regional Grey Matter Volume Correlates with Anxiety, Apathy, and Resilience in Geriatric Depression" by Krause-Sorio *et al.* (Krause-Sorio *et al.*, 2023) in International Psychogeriatrics sheds light on the complex interplay between brain structure and psychological factors in older adults with depression. Using voxel-based morphometry, the researchers examined the associations between regional gray matter volume and psychological factors such as anxiety, apathy, and resilience in older adults with depression. To date, several studies, including meta-analyses, have reported specific brain regions or clusters associated with anxiety and apathy in younger adults using MRI morphometry. As the basis of these symptoms could be diverse depending on the causal psychiatric pathology, the symptoms have been investigated in specific disorders, such as been investigated mainly in anxiety disorders, such as generalized anxiety disorder and social anxiety disorder, and apathy has been investigated in various diseases, such as mood disorders, anxiety disorders, schizophrenia, and dementia. In addition, despite the important association between resilience and depression, studies on the brain associated with resilience, especially in old age, are limited. Krause-Sorio *et al.* aimed to comprehensively assess anxiety, apathy, and resilience in GD patients, offering valuable insights into clinical challenges for prevention and intervention.

As Krause-Sorio *et al.* mentioned, there are very few reports investigating apathy, anxiety, and resilience, especially in the context of GD. Conversely, numerous studies, including reviews, have explored the relationship between symptoms and brain structures in various diseases and conditions, such as anxiety disorders and dementia, and are not limited to GD. In previous studies, individual psychiatric symptoms have been associated with each brain region depending on the underlying clinical diagnosis and psychopathology, and comparisons with Krause-Sorio *et al.*'s study are instructive even if the population subjects do not match exactly.

Anxiety

In Krause-Sorio *et al.*'s study, anxiety was notably associated with the posterior cingulate cortices and large areas of multiple lobes, including the frontal,

parietal, and occipital regions, but not the temporal cortex. Meta-analyses conducted by Wang *et al.* and Kolesar *et al.* explored structural changes in the gray matter in adult patients with anxiety disorders, including panic disorder, social anxiety disorder, and generalized anxiety disorder (Kolesar *et al.*, 2019; Wang *et al.*, 2021). Both these reviews, similar to Krause-Sorio *et al.*, reported that anxiety disorders were linked to structural changes in the frontal and parietal lobes, while consistently identifying the temporal lobe as a significant site. Among the temporal lobes, the temporal-parietal cortices, hippocampus, and amygdala were found to be significantly associated and are recognized as particularly important regions for cognitive function and emotional processing (Kolesar *et al.*, 2019; Wang *et al.*, 2021). Additionally, Mincic *et al.*'s meta-analysis also reported associations between negative emotionality-related traits and the amygdala and anterior parahippocampal gyrus, which are parts of the temporal lobe (Mincic, 2015). Specific regions of the temporal lobe, such as the amygdala, hippocampus, and medial temporal lobe, have consistently been identified as sites of emotional and anxiety-related structural changes. Therefore, this is a notable difference from the results of Krause-Sorio *et al.*'s study, in which only the temporal lobe was not a significant region. Certainly, there are valid reasons for discrepancies with previous studies, such as differences between anxiety in anxiety disorders and depression, distinctions between young and older adults, and differences in statistical methodology. In this context, ensuring the certainty of disease diagnosis and age cohort sampling is an important premise.

Apathy

The present study reported that reduced gray matter volume in various extended clusters of all four lobes, including the left superior frontal cortex, stretching into the paracentral, precuneus, and posterior cingulate cortex was associated with greater apathy in GD. A meta-analysis of Alzheimer's disease and cognitively normal older adults reported that atrophy in the right putamen, inferior frontal gyrus, and middle temporal gyrus was associated with apathy independent of cognitive function and depression (Chaudhary *et al.*, 2022). In addition, in mild cognitive impairment and normal elderly individuals, apathy was associated with a lower inferior temporal cortical thickness (Guercio *et al.*, 2015). The common point between the study by Krause-Sorio *et al.* and these previous studies is that they focused on a part of the larger frontal cortex. However, the difference is that, as in the case of anxiety, the significance of the temporal lobe is a commonly focused site. Understanding the neural basis of apathy is crucial as it can significantly affect an individual's functional abilities and treatment adherence. Targeting the ACC and ventral striatum through behavioral interventions or pharmacological approaches may offer potential avenues for managing apathy in GD.

Resilience

In the current study, resilience was related to the extended regions across the cortex, including the frontal, parietal, and temporal lobes. Due to its history, most studies related to brain imaging of resilience have focused on children and young adults with post-traumatic stress disorder (PTSD), with limited research on older people. Much resilience research has been devoted to PTSD. One meta-analysis reported that the medial prefrontal cortex, amygdala, and hippocampus (limbic regions) structures are associated with resilience in PTSD (Moreno-López *et al.*, 2020). In a resilience study using MRI images of a large population cohort of older people, the cortical thickness of the posterior cingulate cortex and temporal pole was significantly associated with resilience (Shikimoto *et al.*, 2021). Additional research is needed, as it is inconclusive whether resilience in health status is altered in the brain during depression.

Nevertheless, the most remarkable feature of Krause-Sorio *et al.*'s study was that it found that the common aspects of anxiety, apathy, and resilience were gray matter volume in the inferior primary somatosensory cortex. To the best of our knowledge, no studies have reported simultaneous overlapping of brain regions for multiple psychiatric symptoms associated with depression. The primary somatosensory cortex processes tactile sensations and is crucial for tactile discrimination, body awareness, and the recognition of touch sensations from various body parts (Kaas *et al.*, 1979). GD, characterized by the emergence of psychosomatic symptoms, is a very interesting part of the brain. In vivo studies have shown that long-term depression is induced by sensory deprivation during cortical map plasticity (Allen *et al.*, 2003). The overlapping brain regions associated with GD and the somatosensory cortex in this study might be an extension of prior research. The finding that the somatosensory cortex plays a significant role in both long-term depression induced by sensory deprivation and GD suggests that the current study builds upon and extends previous research in this area. This provides further evidence of the involvement of the somatosensory cortex in depressive symptoms, especially in the

https://doi.org/10.1017/S1041610223000674 Published online by Cambridge University Press

context of GD. These findings have important clinical implications as they suggest that targeting the amygdala and prefrontal cortex through interventions such as cognitive-behavioral therapy or neuromodulation techniques could potentially alleviate anxiety symptoms in older adults with depression. The common brain basis of multiple symptoms in GD is expected to contribute greatly to the understanding of therapeutic intervention targets and pathophysiology.

Two strengths of this study are its focus on GD and its simultaneous assessment of multiple symptoms of depression, which may lead to practical insights in the real world. However, there are several concerns regarding the design that determine the validity of this study. First, one of the key concerns is bias regarding participant attributes. The mean age of depression onset was 42.8 (SD 18.3) years, and the current age was 67.9 (SD 6.12) years in the study, suggesting that some of the participants had experienced depression onset at a relatively younger age and that the depressive symptoms have persisted for a long time. GD, also known as late-life depression, is most commonly defined as depression occurring in adults aged 60 and older (MacQueen *et al.*, 2016). In addition, a long-term type of depression typically persists for at least two years and may be diagnosed with chronic depression or persistent depressive disorder by DSM-5-TR. Therefore, the participants in this study, characterized by early adolescent onset and chronicity of depression, potentially represent a demographically distinct subgroup compared to the narrowly defined GD that is commonly perceived. However, this is not limited to the current research but is a universal and fundamental problem in diagnosing GD. Whether late-onset GD and early-onset GD can be considered based on the same psychiatric pathology is controversial. However, considering the potential multiple pathologies of GD, it is not always possible to reach a consensus on a strict definition in the future. Therefore, the definition of GD in the current study does not necessarily negate the essential meaning of the research. The second concern is related to the adequacy of the sample size required to ensure the statistical validity and reliability of the analysis. While the authors' approach of investigating both complicated comorbid symptoms and protective factors of GD in the same sample population is commendable for providing a comprehensive understanding of the neural mechanisms, the use of only forty-nine subjects raises potential issues. With a small sample size, the statistical power diminishes, making it challenging to adequately adjust for multiple confounders and increasing the likelihood of obtaining false negatives. Simultaneously, data variability may lead to spurious results, thereby elevating the risk of false positives. Another concern is the lack of control for intracranial volume or head size and the application of multiple comparisons for various symptomatic variables, including anxiety, apathy, resilience, and depression. Failure to control for these factors could potentially confound the results and weaken the robustness and reliability of the study's findings. Given these limitations, it is essential to consider the implications and generalizability of this study's results. Future research with a larger and more diverse sample, rigorous control of confounding factors, and thoughtful consideration of statistical analyses is crucial to strengthen the validity and reliability of the findings.

Krause-Sorio *et al.*'s approach, which assessed related symptoms and resilience in the same sample of GD, offers valuable insights and contributes to a more comprehensive understanding of the neural mechanisms underlying this condition. However, caution must be exercised when interpreting the results of this study. The findings of this study do not conclusively establish specific brain regions or overlapping regions as potential markers of resilience, depression, and anxiety in GD. Further investigations with a more plausible definition of GD and larger sample sizes are warranted to advance our understanding of the diverse symptoms of GD and the underlying brain mechanisms of resilience. Nonetheless, this study represents a significant advancement in elucidating the intricate relationship between brain changes and psychological symptoms in GD. These findings provide a foundation for future research endeavors aimed at refining diagnostic and treatment approaches for this vulnerable population, ultimately improving their well-being and quality of life.

Conflict of interest

None.

Description of authors' roles

The author, Ryo Shikimoto, contributed to the manuscript, revised, read, and approved the submitted version.

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