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COMMENTARY

Can we promote cognitive resilience in late-life depression?

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Aging does not inevitably lead to cognitive impairment. Not only is there variability in age-related brain changes, but older adults also vary in the degree to which those brain changes predict cognitive decline (Stern *et al.*, 2019). Moreover, brain pathology associated with disorders such as Alzheimer's disease does not necessarily relate to cognitive decline, as some older adults are able to maintain high levels of performance despite a high burden of pathology (Aiello Bowles *et al.*, 2019).

Decades of research provide evidence for this heterogeneity in cognitive and brain aging, with more recent studies seeking to understand the mechanisms that might explain the variability. Several factors seem to confer protection against the development and cognitive consequences of age-related brain changes, including genetic influences, early life experiences, medical factors, and lifestyle behaviors (Burke *et al.*, 2019). This literature tends to focus on the development of dementia and related brain pathology; however, less focus has been placed on cognitive impairment in late-life depression (LLD). As highlighted by Szymkowicz *et al.* (2022) in this issue of *International Psychogeriatrics*, cognitive presentation varies in LLD, similar to the well-established variability in cognitive aging.

Szymkowicz *et al.* used a data-driven approach to identify cognitive profiles, or phenotypes, within a group of individuals with LLD. This method is in contrast to the more common approach of comparing cognitive functioning between depressed and non-depressed older adults. Considering the cognitive heterogeneity we know exists in late life, this type of intragroup examination clearly complements the body of research focused on between-group differences. The authors found that approximately 60% of older adults with LLD evinced cognitive deficits based on within-sample z-scores. Of this subsample, there were nearly equal numbers of participants who either had an isolated relative weakness in episodic memory recall or had the lowest scores of the sample across attention/working memory, processing speed, and executive functions. Notably, approximately 40% of the sample scored 0.30 standard deviations or higher above the mean across cognitive domains, including attention/working memory, processing speed, language, episodic recall, and executive functions. These findings mirror a recent study of depressed adults aged 18–65 that used a similar cluster analysis approach and identified 39% of the sample with preserved cognitive functioning, 38% with selective cognitive deficits, and 23% with significant cognitive deficits (Vicent-Gil *et al.*, 2020).

Perhaps most striking about the heterogeneity of cognitive phenotypes in these studies is that nearly 40% of people with depression exhibited no cognitive deficits. This finding begs the question, how are they able to maintain their cognitive functioning? More importantly, are there modifiable factors contributing to their cognitive preservation that can be incorporated into depression treatment to avoid or treat cognitive impairment in LLD?

As a starting point to answering these questions, geriatric psychiatry could leverage what we know about cognitive resilience from the broader cognitive and brain aging literature. We know that experiences and lifestyle behaviors continue to moderate brain–behavior relationships in late life, building upon the groundwork laid by early life experiences (Montine *et al.*, 2019). In particular, physical, cognitive, and social activity enhance and preserve cognitive functioning in later decades of life, possibly by both directly impacting brain structure and function and by enabling the brain to more flexibly respond to and compensate for brain changes (Burke *et al.*, 2019). To varying degrees, these enriching experiences affect several neurobiological mechanisms associated with both cognitive impairment and depression in older adults, including structural and functional alterations in frontolimbic regions, neurovascular changes, inflammation, and neurotrophic factors (Dotson *et al.*, 2021). The common underlying mechanisms impacting cognition and mood suggest the lifestyle behaviors that promote cognitive resilience in late life could inform prevention and intervention efforts for cognitive deficits in LLD.

Lifestyle behaviors such as physical, cognitive, and social activity are already common in psychotherapeutic interventions for LLD. Behavioral

activation is effective as a standalone treatment or a component of other behavioral treatments, such as cognitive-behavioral therapy (Orgeta *et al.*, 2017). The target of behavioral engagement is usually depressive symptoms rather than cognitive impairment; however, these existing interventions could be modified to prevent or treat cognitive as well as mood symptoms. For example, since aerobic exercise affects neurovascular mechanisms that contribute to both depression and cognitive impairment (Dotson *et al.*, 2021), behavioral engagement in therapy can specifically focus on increasing physical activities that include an aerobic component. Or, interventions that safely integrate cognitive and physical demands could be developed for LLD since combining a cognitive challenge with physical activity may provide an added cognitive benefit (e.g. Eggenberger *et al.*, 2015). These efforts could be particularly effective in older adults with subthreshold depression, as motivation and adherence may interfere less with implementation of the intervention when depressive symptoms are less severe.

Results from the Szymkowicz *et al.* (2022) study suggest clinical and demographic considerations should be made in any efforts to improve cognitive resilience in LLD. The highest-performing group in the study was more highly educated than the groups with cognitive deficits, suggesting that cognitive reserve may have been a factor. This is consistent with other evidence that educational attainment, a proxy for cognitive reserve, protects against depression-related cognitive deficits in older adults (McLaren *et al.*, 2015). Clearly, intervention in late life cannot change educational attainment earlier in life, but these findings suggest older adults with lower levels of education may be particularly at risk for cognitive impairment in depression, and thus may benefit even more from prevention or intervention efforts.

The highest-performing group also had fewer vascular risk factors than the group with the worst executive, attention/working memory, and processing speed performance, supporting vascular health as an important contributor to cognitive resilience. The large body of literature on vascular depression shows that the combination of depressive illness and vascular burden results in disproportionate cognitive impairment, particularly in executive functioning, as well as greater functional decline compared to nonvascular depression (Alexopoulos, 2019). Thus, vascular risk is another modifiable factor that could be included in treatments to promote cognitive resilience in LLD.

As summarized in a recent systematic review (Bogoian and Dotson, 2022), the very limited literature in Black older adults with comorbid depression and vascular disease suggests possible racial disparities in vascular depression prevalence (e.g. Reinlieb *et al.*, 2014) and associated functional disability (e.g. Gonzalez and Tarraf, 2013). Though vascular depression was not directly addressed in the Szymkowicz *et al.* study, race differences in their cognitive phenotype groups were consistent with the emerging results in the literature: The highest-performing group had the lowest vascular risk, while the most impaired group had the highest vascular risk as well as the lowest proportion of non-Hispanic White participants. Combined with well-established health disparities in vascular disease (Brothers *et al.*, 2019) and emerging evidence for race differences in vulnerability to vascular depression, these results underscore the need for studies on cognitive resilience in LLD that include racially diverse samples. This will allow for more generalizable results and can help to reduce health disparities in depression and in depression-related cognitive and functional impairment.

Borrowing from the cognitive resilience literature, another important future direction is to study high-risk depressed older adults who maintain their cognitive functioning. This can be done, for example, by identifying depressed older adults with intact cognitive functioning despite imaging evidence of vascular disease or neurodegeneration and determining how they differ from their cognitively impaired counterparts in demographic, clinical, and lifestyle factors. A focus on understanding people with LLD who show cognitive resilience despite underlying brain changes is in line with an increasing focus on positive neuropsychology and positive psychiatry.

A positive neuropsychiatry approach can be applied to a variety of mental health conditions to identify individuals who show cognitive resilience, determine the factors contributing to their resilience, and use that knowledge to develop interventions that can prevent and treat cognitive impairment related to psychiatric conditions. To do so, traditional patient versus control group comparisons must be complemented by data-driven techniques, such as those used in the Szymkowicz *et al.* study, that parse the cognitive heterogeneity within patient groups.

Applying data-driven techniques to longitudinal data could also be valuable, and this approach could be integrated with methods such as multilevel modeling to examine covariation in depressive symptoms and cognitive functioning to further characterize cognitive resilience in LLD. Recent studies in this journal demonstrate the potential utility of these methods (Hill *et al.*, 2020; Tu *et al.*, 2020). One study used a group-based trajectory model to identify different longitudinal trajectories of cognitive function (Tu *et al.*, 2020). The analyses revealed slow decline, rapid decline, and stable trajectories in a cohort of older adults, with the majority of the sample (81.5%) characterized by the stable trajectory. Modifiable factors such as leisure activity and cardiovascular disease impacted cognitive trajectories, suggesting potential targets for prevention

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and intervention efforts. Another study examined concurrent and lagged associations between different types of memory self-report and depressive symptoms in older adults (Hill *et al.*, 2020). The analyses revealed distinct associations between types of memory self-report (frequency of memory problems, perceived 1-year decline, and perceived 10-year decline) and depressive symptoms and showed that depressive symptoms predicted future report of memory decline, but self-reported memory decline did not predict future depressive symptoms. These approaches could be used to identify longitudinal cognitive trajectories and moderating factors in LLD and to determine the temporal relationships among depression, cognitive functioning, and lifestyle interventions.

Cognitive impairment in LLD exacts a tremendous toll on the individual, their family, and society. The increased functional disability, medical burden, dementia risk, and mortality risk (Perini *et al.*, 2019) associated with cognitive impairment in depression could be reduced with effective prevention and intervention efforts that target cognitive impairment in addition to mood symptoms. By using a positive neuropsychiatry approach in an inclusive manner that ensures representative samples are studied and the most vulnerable individuals are prioritized, future studies can reduce the burden of LLD and reduce health disparities in many of the negative outcomes associated with LLD.

Conflict of interest

VMD is owner of CerebroFit, LLC.

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