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Amyloid-Associated Depression—or Not?

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In the current issue of *Biological Psychiatry*, Mackin *et al*. (1) throw new light on the relationship between amyloid-β (Aβ) and depression in older individuals without dementia. But they may also compel us to throw some of our previous assumptions about this emerging field out the window. Early evidence for a link between late-life depression (LLD) and elevated Aβ pathogenesis came from postmortem studies of patients with dementia revealing an association between Aβ plaques and a history of major depression (2). The advent of positron emission tomography (PET) enabled the study of clinicopathologic associations in vivo and provided further support for Aβ pathogenesis as a possible mechanism underlying the connection between LLD and Alzheimer's disease (AD). Elevated cortical Aβ deposition in older individuals with current or lifetime major depression has been observed in most PET studies (3,4). Longitudinal cohort studies using PET imaging have also reported positive associations between Aβ pathology and subsyndromal depressive symptoms in cognitively normal older adults (5,6). Of note, also in this issue of *Biological Psychiatry*, Xu *et al*. (7) corroborate these findings in older adults without dementia and use causal mediation analyses to explore the mediation effects of AD pathologies on cognition. These authors thus provide important new evidence that the influence of minimal depressive symptoms on cognition is partially mediated by Aβ pathology and that the causal relationship between depression and Aβ might be bidirectional.

Against this complex and uncertain backdrop, Mackin *et al*. (1) will not provide any simplification or certitude, as they reveal the wholly counterintuitive possibility that LLD may actually be associated with reduced cortical Aβ burden. The authors evaluated the role of cortical Aβ deposition as a factor contributing to memory dysfunction and increased risk of dementia associated with LLD. They compared older adults with major depression (LLD) from the ADNI-D (Alzheimer's Disease Neuroimaging Initiative Depression Project) study and nondepressed cognitively unimpaired participants matched on age, sex, and *APOE* ε4 genotype from the regular ADNI database. They observed that 33% of LLD participants met the ADNI criteria for mild cognitive impairment (MCI). Compared with nondepressed individuals, the LLD group exhibited less global Aβ accumulation and a lower proportion of Aβ positivity. Similar results were found in secondary analyses restricting comparisons to the cognitively unimpaired LLD participants as well as when comparing the LLD group with a nondepressed group that included participants with MCI. The authors concluded that contrary to expectation, the LLD group showed less Aβ deposition than the nondepressed

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group, and Aβ deposition was not associated with depression history characteristics. Global Aβ was associated with worse memory performance, but this relationship did not differ between the LLD and nondepressed groups. They interpreted these results as suggesting that memory deficits and accelerated cognitive decline reported in previous studies of LLD are not due to greater cortical Aβ accumulation.

The findings of Mackin *et al.* (1) are thus counter to their own hypothesis but also at odds with a growing body of research that suggests a positive association between Aβ and depression or depressive symptoms (2–6). The study is most ambitious in attempting to compare participants in entirely separate cohorts—test groups from ADNI-D and comparison samples from the ADNI study. The former participants were recruited at two psychiatry department geriatric depression centers, whereas the latter were recruited at ADNI sites. The potential for sampling bias is thus not insignificant, as acknowledged by the authors. They point to the fact that individuals with LLD and concurrent MCI due to AD may have two distinct (and additive) contributors to cognitive dysfunction, making them more likely to receive a dementia diagnosis and to be excluded from the study. Excluding these individuals—who may have the greatest Aβ burden—from the LLD group may tend to lower mean Aβ levels and positivity rates in this group. A second source of sampling bias pertains to the separate recruitment pathways for ADNI-D and ADNI participants. ADNI study sites are almost entirely those that conduct AD clinical trials—many linked to memory clinics—and even the cognitively normal participants may be enrolled from among individuals seeking to participate in AD research based on family history and subjective cognitive concerns and are thus at higher risk of having early AD pathogenesis. In the initial iteration of ADNI, cognitively normal participants were eligible who did not meet criteria for MCI. The majority of the nondepressed participants analyzed by Mackin *et al.* (1) were enrolled in ADNI-2, which introduced new and intermediate diagnostic groups, including one for significant memory concern. The participants with significant memory concerns were included by Mackin *et al.* (1) with the cognitively normal group. Previous analyses of ADNI-2 diagnostic categories have suggested that the significant memory concern group appears similar to the normal control subjects in Aβ PET uptake (8). However, the possibility that both groups contain a higher Aβ burden than the population at large cannot be excluded.

Mackin *et al.* (1) painstakingly attempted to control for such biases in every way imaginable. They matched for *APOE* ε4 status between the LLD and nondepressed groups and conducted 3 separate analyses. For the primary analysis, they presented the one least likely to have yielded the counterintuitive result (and thus likely selected post hoc)—i.e., including only the cognitively normal participants in the nondepressed ADNI comparison group. The first of 2 sensitivity analyses included MCI participants in the nondepressed ADNI comparison group (matching the proportion of participants with MCI in each group) and—not surprisingly—yielded even more robust Aβ binding in the nondepressed group. The second restricted the sample to a subset of cognitively normal participants in each group and yielded numerically similar results to the primary analysis, which were significant for Aβ positivity but not for Aβ binding levels—perhaps due to reduced power with the smaller sample size.

If these efforts to control potential sampling bias are sufficient, we are left with the perplexing result stated in the title that LLD is associated with reduced cortical Aβ burden. As noted by Mackin *et al.* (1), this result suggests that other non–Aβ-mediated pathways are likely associated with risk for accelerated cognitive decline and dementia reported in LLD. These may include the direct impact of depressed mood on cognition and functional status, as well as indirect effects such as cortical atrophy associated with depressive symptoms. The results of this study may even implicate mechanisms of LLD that reduce Aβ deposition. In particular, the authors speculate that reduced cerebral blood flow or hypometabolism in LLD may limit Aβ uptake in brain regions implicated in depression, such as the anterior cingulate and orbitofrontal cortex. Such regions are indeed among those that yield the largest group differences in this study; however, the overall pattern is also consistent with the known spatiotemporal pattern of Aβ deposition in AD, with multiple studies indicating that neocortical deposition is an early phenomenon and that cortical accumulation appears earliest in the medial frontal and cingulate regions (9). Finally, to the list of non–Aβ-mediated pathways associated with risk for cognitive decline and dementia reported in LLD we should add—cerebrovascular disease. An accumulating body of research suggests that LLD is associated with an increased risk for AD but at least as great a risk for vascular dementia (10). The results of Mackin *et al.* (1) might be explained in part if a disproportionate number of individuals in the LLD group had cerebrovascular disease associated with incipient cognitive decline.

These results should remind us of the tremendous heterogeneity of depression syndromes that may occur late in life. Why should we expect them all to have a similar relationship with AD pathogenesis? If LLD is associated with an increased risk for both vascular dementia and AD (10), then we can expect considerable variability of both Aβ burden and cerebrovascular disease within LLD samples. Moreover, the authors note that the majority of their LLD participants had early onset, with long histories of depression, whereas late onset of depression may be more strongly linked to Aβ burden. Finally, late onset of depression is frequently subsyndromal, and PET studies have more consistently linked subsyndromal depression with increased Aβ burden (5–7).

With regard to syndromal LLD (major depression), Mackin *et al.* (1) have provided us with a thoroughly analyzed and provocative result that expands this already complicated field and that will require further study. It is easy to suggest that additional studies to remove sampling biases be conducted. However, these would presumably require population-based samples and perhaps be unfeasible. On the other hand, longitudinal analyses of convenience samples could compare the rates of cognitive decline and Aβ accumulation between patients with LLD and nondepressed participants. When followed over the course of years, the LLD group may (or may not) experience accelerated cognitive decline relative to nondepressed participants in association with (or without) greater Aβ accumulation. On the heels of the present results, none of these outcomes would seem far-fetched.

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