Biological Psychiatry

Late-Life Depression, Cortisol, and the Hippocampus: On the Need to Consider Depressive, Hippocampal, and Pharmacological Complexities

To the Editor:

We read with great interest the systematic review and meta-analysis carried out by Geerlings and Gerritsen (1) regarding hypothalamic-pituitary-adrenal (HPA) axis regulation and hippocampal atrophy in late-life depression (LLD). Examining 2702 LLD patients and 11,165 control subjects from 35 studies, the authors notably found that, relative to control subjects, LLD patients had significantly smaller hippocampi. The authors observed, however, that effect sizes were larger for case-control studies, studies with lower quality, and studies with small sample sizes and were almost absent in cohort studies and studies with larger sample sizes. Suggestive evidence that higher levels of cortisol were associated with smaller hippocampal volumes was additionally found. While Geerlings and Gerritsen (1) mentioned several clinical and methodological issues that may account for the often-inconsistent findings related to HPA axis regulation and hippocampal atrophy in LLD, we think that three important problems affecting this area of research have been overlooked by the authors. These problems lie in the neglect of 1) depression subtypes, 2) hippocampal structural and functional complexity, and 3) medication control.

The lack of consideration for depression subtypes in research on HPA axis regulation and hippocampal atrophy in LLD is of great concern given that some depression subtypes have been associated with opposite autonomic, immune, and endocrine profiles. The cases of depression with melancholic features and depression with atypical features, two prevalent depression subtypes (2–4), well illustrate this state of affairs. Indeed, whereas melancholic depression has been associated with insomnia, aphagia, sympathetic hyperactivity, decreased immune function, and hypercortisolism, atypical depression has been associated with hypersomnia, hyperphagia, sympathetic hypoactivity, increased immune function, and hypocortisolism (5,6). Such differences directly implicate the HPA axis and are likely to bear on the status of variables such as hippocampal volume. Not considering depression subtypes can therefore lead to misleading conclusions. We recommend that stronger efforts be deployed for depression subtypes to be taken into account in the study of HPA axis regulation and hippocampal atrophy in LLD. Interdependently, we note that LLD research on variables such as hippocampal volume would be facilitated by a deeper understanding of 1) the articulation of hypercortisolism and hypocortisolism (7) and 2) the relationships between currently described subtypes of depression, including melancholic and atypical depressions (2,8,9).

A second problem that tends to be neglected in research on HPA axis regulation and hippocampal atrophy in LLD pertains to the structural and functional complexity of the hippocampus. In effect, the hippocampus does not constitute a monolithic entity. While the dorsal-posterior hippocampus has been associated with "cold" cognitive functions (e.g., spatial memory) and found to work in close connection with the prefrontal cortex, the ventral-anterior hippocampus has been associated with "hot" affective functions (e.g., stress and emotion) and found to work in close connection with the amygdala and the hypothalamus (10). Because depression has been etiologically linked to unresolvable stress and appears to be rooted in an affective imbalance between positive/rewarding and negative/punishing life experiences, such subdivisions are directly relevant to the study of depressive processes and states. A related, challenging issue lies in the compensatory phenomena that may be at stake in the economy of hippocampal anatomy and physiology. As an illustration, in the classic study of navigation-related structural change in the hippocampi of London taxi drivers (11), the posterior hippocampal region of taxi drivers was found to be larger relative to those of control subjects, whereas the anterior hippocampal region was found to be larger in control subjects than in taxi drivers. Such results were suggestive of local redistributive plasticity within the hippocampus as a function of life experiences. We recommend that the posterior and anterior subdivisions of the hippocampus be distinguished in future analyses and that more research be dedicated to within-hippocampus anatomical and physiological compensatory changes.

Lastly, we draw researchers' attention to the need to better control for administered (antidepressant) medication (e.g., in terms of type, posology, and long-term effects on the nervous, immune, and endocrine systems) in research on HPA axis regulation and hippocampal atrophy in LLD. Indeed, there is for instance evidence that antidepressants affect HPA axis regulation by altering cellular corticosteroid receptor concentration (12). Controlling for medication is methodologically challenging (e.g., self-reports of past treatments are susceptible to retrospective memory biases). However, mixing results from medicalized patients with results from unmedicalized patients is clearly problematic. In a similar vein, not distinguishing patients with long-term medication intake from patients with short-term medication intake may lead to spurious conclusions.

Geerlings and Gerritsen (1) pointed out important limitations of current research on HPA axis regulation and hippocampal atrophy in LLD. In addition to the issues raised by these authors, we invite researchers to more systematically consider depression subtypes, hippocampal complexity, and medication control in this area of research.

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