

Depression and the Hippocampus: Cause or Effect?

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Research examining the relationship between major depressive disorder (MDD) and hippocampal volume has long wrestled with the chicken and egg question. From the time the first report was published finding smaller hippocampal volumes in patients with MDD compared with healthy control subjects (1), there have been hundreds of studies in the literature, with the majority, but not all, finding smaller hippocampal volumes in MDD (2). The direction of a potential causal arrow, however, remains unresolved. Studies supporting a role for episodes of MDD leading to smaller hippocampal volumes have found that longer cumulative duration of lifetime depression, total number of recurrent episodes, and earlier age of onset of depression are associated with hippocampal volume loss (2,3). On the other hand, evidence also supports the causality arrow pointing in the opposite direction. Studies supporting the role of hippocampal structural impairment in the etiology of depression have found that a smaller hippocampus predicts worse clinical outcome, and genetic influences on brain structures, including the hippocampus, have been identified in twin studies (4).

One explanation for the relation between MDD and smaller hippocampal volumes is the neurotoxicity hypothesis (5), which suggests that prolonged exposure to glucocorticoids increases neuronal susceptibility to insults, thereby increasing the rate of damage from toxic challenges or ordinary attrition. According to this hypothesis, the reduction in hippocampal volumes is a cumulative process from many years of depression, posttraumatic stress disorder, or chronic stress. In addition to abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, other biological abnormalities have been recently shown to contribute to hippocampal volume loss: stress-induced reduction in neurotrophic factors, in particular brain-derived neurotrophic factor (BDNF), and stress-induced reduction in neurogenesis. In preclinical studies, several forms of stress reduce BDNF-mediated signaling in hippocampus, whereas chronic treatment with antidepressants increases BDNF signaling (6). Similar changes are observed in postmortem hippocampi of humans with depression, as well as in serum BDNF concentration, although this remains controversial. Another important source of plasticity is the induction or downregulation of adult hippocampal neurogenesis, by which neural progenitors of the hippocampal subgranular zone divide to form new neurons that differentiate and integrate into the dentate gyrus (7). These additional mechanisms may be additive or synergistic with glucocorticoid neurotoxicity and there appear to be important developmental windows in these effects (8). At the time the neurotoxicity hypothesis was proposed, the effects of stress on BDNF and neurogenesis had not been described and there persists some tendency in the literature to oversimplify the connection between stress-induced neurotoxicity and hippocampal volume loss. An alternative explanation for the relationship is the vulnerability hypothesis, which suggests, in contrast to the neurotoxicity hypothesis, that

reduced adult hippocampal volume is not due to cumulative exposure to MDD, posttraumatic stress disorder, or chronic stress, but rather that reduced hippocampal volume is a pre-existing risk factor for stress-related disorders induced by genetics and early exposure to stress (9).

The report by Gerritsen *et al.* (10) in this issue of *Biological Psychiatry* investigated the role of dysregulated HPA axis function in the association between depression and smaller hippocampal volumes. The report is remarkable for several reasons. It used the largest sample ($n = 636$) to date to study both hippocampal and entorhinal cortex volumes in depression. The sample consisted of well-characterized late-life depression participants, subcategorized into those with early-onset depression (<50 years) (EOD) versus late-onset depression (>50 years) (LOD). The sample was also divided into those with current depression (defined as having been depressed within the past year), remitted depression, and never depressed. The extension to examining structural differences in both the hippocampus and entorhinal cortex is novel, having only rarely been examined together in investigations of depression. Most importantly, given their findings in late-life depression, the study reveals that the relationship between MDD and hippocampal volumes is even more complicated than previous studies have indicated. The study found that one or more episodes of depression were associated with smaller hippocampal volumes but not entorhinal cortex volumes. Early-onset depression was associated with smaller hippocampal volumes but not entorhinal cortex volumes, whereas LOD was associated with smaller entorhinal cortex volumes but not smaller hippocampus volumes. Smaller hippocampal volume was not associated with HPA abnormalities.

The finding that participants with one or more episodes of depression and those with EOD had smaller hippocampal volumes is consistent with the large number of studies that have identified hippocampal volume abnormalities in MDD, particularly in participants with greater numbers of depressive episodes, as would be expected in older people with EOD who would have experienced multiple depressive episodes. The finding that the LOD group had smaller entorhinal cortex volumes is fascinating because this region is among the first to show volume loss with preclinical Alzheimer's disease (AD) (11). The amyloid hypothesis states that accumulation of brain amyloid initiates a cascade of downstream events, ultimately resulting in cell death and brain atrophy. Cognitively normal individuals have an age-related increase in risk of abnormal amyloid binding with 19% of subjects having abnormal amyloid at age 60 to 69, 25% at age 70 to 79, and 30% at age 80 to 89 (12). Given the mean age of the sample (62 ± 9 years), approximately 20% could be expected to have elevated amyloid binding, likely indicating preclinical Alzheimer's disease (12). Thus, in some participants, the smaller entorhinal cortex volumes in the current study could be the result of amyloid-induced neurotoxicity in addition to or instead of MDD-associated volume loss (Figure 1).

Further, in older patients with depression, some studies have found an increased risk for AD and there has been substantial debate in the field about the possibility that depression is a risk factor for AD. Almost all of these studies have been cross-sectional, however. Recently, there have been two prospective studies with large sample sizes that found MDD to be a significant risk factor for subsequent AD (13,14). In those studies, participants were followed over a decade with both depressive episodes and dementia inci-

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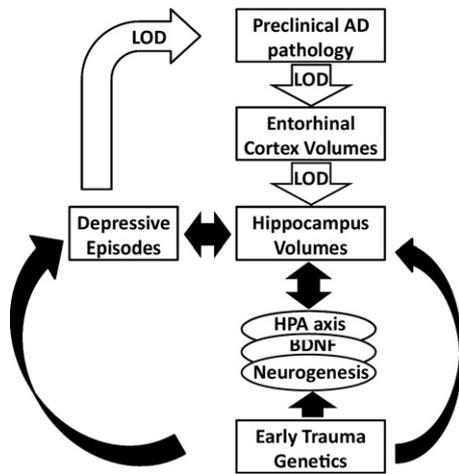


Figure 1. Converging predictors of hippocampal volume in late-life depression. The neurotoxicity hypothesis, consisting of abnormalities in hypothalamic-pituitary-adrenal axis, brain-derived neurotrophic factor, and neurogenesis predicts hippocampal volume and interacts with early-life trauma and genetics. The latter also have independent effects on hippocampal volume and depressive episodes. Together, these influences (shown as black arrows) account for much of the cumulative effect of early-onset depression. In addition, in late-onset depression (open arrows), in some cases operating through preclinical Alzheimer’s disease pathology, there are early decreases in entorhinal cortex volume; later in the course of illness, hippocampal volumes are also affected. AD, Alzheimer’s disease; BDNF, brain-derived neurotrophic factor; HPA, hypothalamic-pituitary-adrenal; LOD, late-onset depression.

dence determined, allowing identification of a causal relationship. The study by Gerritsen *et al.* (10) likely includes some proportion of participants who had entorhinal cortex volume loss by virtue of having preclinical AD, in addition to a history of or current depression. Incipient and mild AD is known to elevate cortisol levels, resulting from impairment in the hippocampal negative feedback loop that is normally inhibitory (5). This could help account for the abnormally elevated cortisol levels found in the LOD only, whereas in the overall sample of depressed patients, there was no difference in cortisol levels or in relationship with hippocampal volumes. It should be noted that the majority of patients with LOD do not have preclinical AD pathology or smaller entorhinal cortex volumes. Often, these patients may have vascular risk factors and/or comorbid medical illness, and frequent findings include greater burden of white matter pathology.

The overall finding of lack of a relationship between HPA axis activity and hippocampal volumes in MDD is, as the authors point out, limited by the cross-sectional design of the study. In general, HPA abnormalities are not thought to persist between depressive episodes. Given that many of the currently depressed participants were defined only as having an episode of depression up to 12 months previously and were not in an acute depressive episode, it is not clear that elevated cortisol levels would still have been present, nor would they be expected in the remitted depression subgroup. As the authors point out, there were compromises made in the

design of the study to gather a large sample size. Thus, in a future prospective study, it would be important to determine HPA axis abnormalities occurring concurrently with the depressive episodes to be able to best relate the cumulative occurrence and severity of HPA abnormality with hippocampal volume loss. The study raises the intriguing possibility that in a future study examining both hippocampal and entorhinal cortex volumes prospectively, the direction of causality between these volumes, depressive episodes, and HPA axis function could be determined. Particularly exciting would be a prospective study combining volumetric and molecular imaging for amyloid, with the promise of further teasing apart the complex relationship with preclinical AD.

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