Biological Psychiatry: Celebrating 50 Years

# Commentary

# Parsing the Hippocampus in Depression: Chronic Stress, Hippocampal Volume, and Major Depressive Disorder

Yvette I. Sheline, Conor Liston, and Bruce S. McEwen

Identifying biomarkers of major depressive disorder (MDD) has long been a goal of translational neuroscience. One such marker, hippocampal volume, has had an extensive and sometimes controversial history since it was first described (1). Most studies have found decreased hippocampal volume in patients with MDD, but there have also been a number of negative studies. These brain volumetry studies grew out of basic science work that first described the shrinkage of hippocampal CA3 dendrites by chronic stress mediated by glucocorticoids and excitatory amino acids (2) and then explored various rodent stress paradigms to show that chronic stress had equivalent deleterious hippocampal effects. With increasingly sophisticated methods it has been determined that stress effects were cumulative, involving effects on dendritic spines and synaptic signaling and extended to the medial prefrontal cortex (3). Further work clarified the roles of vulnerability and resilience and showed that stress-induced changes could be reversed. Additional basic mechanisms involved in hippocampal integrity, including neurogenesis, a role for brain-derived neurotrophic factor and other trophic factors and, most recently, functionality of microcircuits, have been discovered in rodent studies. Understanding the fundamental biology of stress effects on physiology is critical to understanding MDD and especially to developing new treatment paradigms; understanding the meaning of hippocampal and medial prefrontal cortex structural changes is important. In this issue of *Biological Psychiatry*, Belleau *et al.* (4) review findings related to stress and structural changes in MDD. The authors propose an overarching model based on numerous previous studies, discuss the pros and cons of the model, and include other potential contributing factors to depressive etiology. In this review, however, it is not clear whether stress and MDD are posited as the primary cause of volume reductions or vice versa. They suggest that although structural changes can result from stress, the development of MDD may be independent. They also discuss the many contrasting studies that demonstrate hippocampal volume loss associated with MDD, in which greater volume loss was associated with more recurrent MDD episodes, longer illness duration, and treatment resistance.

As a biomarker, hippocampal volume has been used to track disease severity, familial and environmental influences, and associaton with comorbid illnesses. In addition to their focus on structural volume loss as a cause or as an effect in recurrent MDD, Belleau *et al.* (4) also discuss the thesis that the exacerbation of stress-induced structural damage by other pathological processes may be necessary to induce further MDD episodes. They cite evidence that other stress-upregulated pathological processes, including inflammation, genetic vulnerability, hypothalamic-pituitary-adrenal axis dysregulation, and oxidative stress, potentially contribute to additional episodes with a lower dose of stress required. One such factor, the cytokine interleukin-6, has shown an inverse correlation with hippocampal gray matter volumes (5) in healthy adults, suggesting inflammation as a contributing factor in hippocampal gray matter reduction. The stress sensitization model, described by Post in 1992 (Am J Psychiatry 149;999–1010), has had an important influence in multiple neuropsychiatric diseases, in particular in affective illness. Studies have shown that individuals with early-life stress had a greater risk of developing a major depressive episode under lesser amounts of stress and also of developing recurrent, persistent, treatment-resistant MDD. The sensitization model may also explain why lesser levels of stress are required to trigger inflammatory pathways, increase glutamate, decrease gamma-aminobutyric acid, and reduce serotonin levels with each successive major depressive episode, and it may help explain the higher rates of cardiovascular illness, diabetes, and other systemic disorders in depression. It is an attractive frame for describing what is currently known about depression that does not commit to a particular etiological mechanism but rather postulates that there will be a stress-mediated augmentation of whatever mechanism or combination of mechanisms are responsible. Belleau *et al.* (4) suggest that future studies identify at-risk samples living in highly stressful environments to determine which stress-related neurotoxic processes affecting hippocampal and medial prefrontal cortex structures lead to MDD onset and what the temporal relationship is among these processes, structural volume loss, and MDD progression.

A related article in this issue of *Biological Psychiatry* by Roddy *et al.* (6) examines hippocampal substructure volumes in 80 patients with a range of MDD durations and 83 healthy control subjects. This study provides a clear focus on MDD as the driving force behind hippocampal volume loss and may explain some of the heterogeneity and discrepancies in hippocampal volumetry determinations in the literature. The study is innovative in creating several different definitions of hippocampal volume, from more restrictive to more extensive. Roddy *et al.* (6) used high-resolution magnetic resonance imaging to delineate patterns of volume reduction in the CA1 to CA4, dentate gyrus, subiculum, presubiculum, parasubiculum,

SEE CORRESPONDING ARTICLES ON PAGES 443 AND 487

 
https://doi.org/10.1016/j.biopsych.2019.01.011
Biological Psychiatry March 15, 2019; 85:436–438 www.sobp.org/journal
ISSN: 0006-3223

parahippocampus, fibria, and hippocampal tail. In a priori determined regions, three different composite measures were generated from computed substructure volumes: the hippocampus proper (HP), composed only of cornu ammonis regions; the hippocampal formation, also known as the "classic" hippocampal formation, which added the dentate gyrus, subiculum, and tail to HP; and an expansive definition, hippocampus extended, which added the parahippocampus, presubiculum, fimbria, and parasubiculum. Theses measures were used to compare patterns of reduction in patients with MDD and control subjects and in patients with first-episode MDD and those with multiple depressive episodes.

The hypothesis in this study is that the degree of hippocampal volume reduction in MDD would depend on the definition of the hippocampus used, with more restrictive definitions showing greater volume loss. While exact definitions of substructures vary widely across studies and parcellation methods also have varying degrees of anatomical fidelity, many of these issues have been addressed with the new FreeSurfer 6.0 software used by Roddy *et al.* (6). This subfield methodology in the Alzheimer's Disease Neuroimaging Initiative database has been shown to have higher sensitivity to detect subtle anatomical volume loss than whole hippocampal volumes (7). In combination with different subfield measures, Roddy *et al.* (6) identified an interesting effect of greater sensitivity of more restrictive subfield definitions. For example, Roddy *et al.* (6) found that hippocampal volumes were reduced even in patients with first-episode MDD compared with control subjects, but only if a restrictive definition of HP was used (see Figure 1 for a schematic representation of progressive hippocampal volume loss with recurrent depressive episodes). When including all patients with MDD, including those with recurrent illness, both the HP and hippocampal formation definitions showed significant reductions compared with control subjects. Finally, including just recurrent depression (but not first-episode patients) revealed a more extensive pattern of volume reduction, which, the authors hypothesized, reflected evolving hippocampal deterioration with increasing duration of depression. Comparing the extent of hippocampal volume loss demonstrated a progressive pattern of volume loss, with first-episode patients having the least (but still significantly smaller than control subjects), followed by the combined group of all MDD and finally with recurrent MDD having the smallest volumes. Across all hippocampal definitions and all patient groups, hippocampal volume loss was greater on the left, in keeping with many previous studies.

Roddy *et al.* (6) did not find a correlation between duration of depression and total hippocampal volume, perhaps reflecting the greater heterogeneity and lower sensitivity of total hippocampal volume measures. They did, however, find a significant correlation between depression duration and volume loss in the CA1 subfield, their most sensitive volumetric indicator. Roddy *et al.* (6) argue that the initial presentation of volume loss in left CA1, correlating with illness duration, may represent an illness marker that, with subsequent extension of volume loss into adjacent regions after repeated depressive episodes, suggests a potential disease process. In effect, they argue for a progressive effect of major depression chronicity on the extent of hippocampal volume loss. Roddy *et al.* (6) also reported an interesting post hoc analysis in which combining

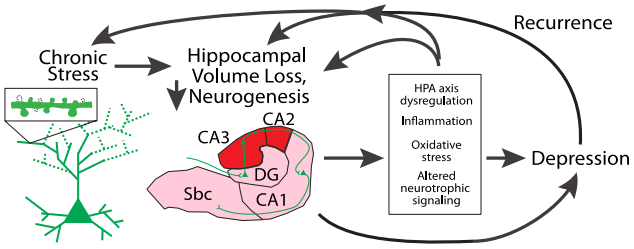


**Figure 1.** Chronic stress causes hippocampal volume loss through effects on hippocampal dendritic atrophy, postsynaptic dendritic spine loss, and neurogenesis (not pictured). Roddy *et al.* (6) show that the CA2 (red), CA3 (red), and CA4 (not pictured) subfields are most sensitive to this effect, with volume loss evident even in patients with first-episode depression. With repeated depressive episodes, the dentate gyrus (DG), CA1, and subiculum (Sbc) also exhibit volume loss (pink), encompassing the entire trisynaptic circuit (green neurons). Belleau *et al.* (4) review other factors that may interact with hippocampal volume loss to trigger depressive episodes, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, inflammation, oxidative stress, and altered neurotrophic signaling. These factors may also interact with each other (e.g., HPA dysfunction exacerbating inflammation and vice versa, and altering neurotrophin signaling). With repeated depressive episodes causing progressive hippocampal atrophy, relatively minor stressors may be sufficient to trigger recurrent depressive episodes.

cornu ammonis regions with the dentate gyrus yielded a volume measure that resulted in the greatest hippocampal volume difference between groups. As the authors point out, this dentate gyrus/cornu ammonis measure corresponds to the classic trisynaptic circuit, which is important in memory and pattern completion. Their analysis is reminiscent of a rodent study (8) comparing hippocampal subregion changes from inhibition of dentate gyrus neurogenesis versus exposure to chronic uncontrollable stress, showing separate subfield-dependent effects. Here it is important to note that reduced neurogenesis is a likely contributor to major depression and hippocampal volume loss.

In summary, Roddy *et al.* (6) used cross-sectional data in a manner that is compelling but not definitive. As they point out, in future studies it will be critical to have longitudinal data to effectively demonstrate a cumulative dose effect of depression on hippocampal volume loss. A limitation of their study is that it did not examine antidepressant treatment, an intervention that may mitigate against volume loss (9). A functional indicator for this protection was delineated in a rodent hippocampal slice study (10) that examined the effects of both chronic social defeat stress and antidepressants on hippocampal signaling. This study used a voltage-sensitive dye and found that signal throughput from perforant path to dentate gyrus to CA3 area to CA1 (i.e., the trisynaptic circuit) was decreased by chronic social defeat and that antidepressants improved signal throughput. Thus, ongoing work in rodent models using stress manipulations and pharmacological interventions to analyze responses at the circuit level can provide translatable insights to human depression.

## Acknowledgments and Disclosures

This work was supported by National Institute of Mental Health Grant Nos. U01MH109991, R01MH098260, and R01MH110939 (to YIS) and by National Institute on Aging Grant No. R01AG041502 (to YIS).

The authors report no biomedical financial interests or potential conflicts of interest.

## Article Information

From the Center for Neuromodulation in Depression and Stress (YIS), Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania; Departments of Psychiatry and Neuroscience (CL), Weill Cornell Medical College; and Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology (BSM), the Rockefeller University, New York, New York.

Address correspondence to Yvette I. Sheline, M.D., Center for Neuromodulation in Depression and Stress, Department of Psychiatry, University of Pennsylvania, 3700 Hamilton Walk, Richards D307, Philadelphia, PA 19104; E-mail: sheline@pennmedicine.upenn.edu.

Received Jan 10, 2019; accepted Jan 10, 2019.

## References

1. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW (1996): Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 93:3908–3913.
2. Magarinos AM, McEwen BS (1995): Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: Involvement of glucocorticoid secretion and excitatory amino acid receptors. Neuroscience 69:89–98.
3. Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, *et al.* (2006): Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci 26:7870–7874.
4. Belleau EL, Treadway MT, Pizzagalli DA (2019): The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology. Biol Psychiatry 85:443–453.
5. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR (2008): Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. Biol Psychiatry 64:484–490.
6. Roddy DW, Farrell C, Doolin K, Roman E, Tozzi L, Frodl T, *et al.* (2019): The hippocampus in depression: More than the sum of its parts? Advanced hippocampal substructure segmentation in depression. Biol Psychiatry 85:487–497.
7. Mueller SG, Yushkevich PA, Das S, Wang L, Van Leemput K, Iglesias JE, *et al.* (2018): Systematic comparison of different techniques to measure hippocampal subfield volumes in ADNI2. Neuroimage Clin 17:1006–1018.
8. Schoenfeld TJ, McCausland HC, Morris HD, Padmanaban V, Cameron HA (2017): Stress and loss of adult neurogenesis differentially reduce hippocampal volume. Biol Psychiatry 82: 914–923.
9. Sheline YI, Gado MH, Kraemer HC (2003): Untreated depression and hippocampal volume loss. Am J Psychiatry 160:1516–1518.
10. Stepan J, Hladky F, Uribe A, Holsboer F, Schmidt MV, Eder M (2015): High-speed imaging reveals opposing effects of chronic stress and antidepressants on neuronal activity propagation through the hippocampal trisynaptic circuit. Front Neural Circuits 9:70.