Commentary

Biological Psychiatry

Childhood Adversity and the Brain: Harnessing the Power of Neuroplasticity

Richard J. Davidson

In the current issue of *Biological Psychiatry*, Gehred *et al.* (1) showcase unique new data and a novel window on the long-term impact of childhood adversity on structural changes in the brain. This report uses data from a by now well-known birth cohort in Dunedin, New Zealand, creatively harnessed over many decades by Moffitt and Caspi. It is a testament to these scholars that they have continuously added to the measurement armamentarium of this project as new relevant measures and technologies have been developed. When the Dunedin study was first launched, neuroimaging did not exist. With the newly added neuroimaging measures along with the measurement of different aspects of development as the sample matured, this birth cohort offers a goldmine of rich data that have so effectively been explored over the years by Moffitt and Caspi and their colleagues. Gehred *et al.* (1) report that both prospectively ascertained and retrospective measures of childhood adversity were associated with smaller total cortical surface area, average cortical thickness, and smaller subcortical gray matter volume in a birth cohort of 861 participants. The imaging data were acquired when the participants were 45 years of age, with 94% of the original sample participating. Gehred *et al.* (1) also reported that associations with prospectively ascertained measures of adversity were consistently stronger than those with retrospectively reported adversity. Finally, the findings revealed widely distributed effects throughout the brain with virtually no regional specificity.

In this commentary I further discuss two striking findings from this study: first, that prospective measures of adversity are more strongly associated with the structural variations in the brain than the retrospective measures, and second, that the observed variations in the brain were widespread and not localized. Following this, I consider the implications of these findings for interventions that might reduce the deleterious impact of adverse events. Finally, I call for a parallel longitudinal investigation of positive protector factors that may reflect the neural embedding of early-life enrichment. Throughout I offer some recommendations and questions for future research.

One of the key novel findings from Gehred *et al.* (1) is that the prospective measures of adversity were more consistently associated with smaller cortical surface area and volume and smaller subcortical gray matter volume than were the retrospectively assessed measures. The prospective measures were derived from records gathered during the ages of 3 to 15 years and were obtained from notes from interviewers, pediatricians, nurses, and other examiners. The retrospective measures were obtained from structured interviews conducted when the participants were 38 years of age. Their data reveal that widespread brain surface area and volume reductions were still apparent even for participants who were exposed to early adversity and who reported relatively little early adversity as young adults. This is a striking finding with both theoretical and practical import. The findings suggest that it is the adversity that occurs in the early years of life that is critically important regarding brain structure and that a reinterpretation or reappraisal of these early-life events in young adulthood has little bearing on the neural scarring produced by these early insults. It will be of interest in future analyses to explore the extent to which the structural changes in the brain are mediators of long-term effects of adversity on psychopathology.

It is curious that other research has reported that it is the retrospective subjective reports of child maltreatment that best predict the subsequent development of psychopathology. The presence of clear objective indicators of maltreatment in the absence of retrospective subjective reports is associated with minimal psychopathology (2). How to reconcile these divergent interpretations is not clear. The differences may in part stem from the different ways in which the retrospective subjective measures were derived in each study. In Gehred *et al.* (1), the retrospective measure was derived from a structured interview at a single age. In Danese and Widom (2), the retrospective measure was derived from an extensive battery of self-report and interview-based measures. In the future it will be informative to examine the extent to which the diffuse presence of smaller cortical surface area and volume mediates the relationship between prospective measures of early adversity and subsequent psychopathology. It is also critical to evaluate the nature of the retrospective assessment measures and determine how different types of measures influence the observed associations.

The findings were quite striking in revealing associations between 1) prospective measures of adversity and 2) surface area and volume of widespread areas of the cortex and across multiple subcortical locations. Other neuroimaging methods that emphasize connectivity, including diffusion-weighted imaging to examine white matter connectivity and resting-state functional connectivity to measure functional connectivity among different brain circuits, are methods that may reveal more specificity because they focus on connectivity rather than on area or volume differences within regions. Such measures have revealed more localized effects of childhood adversity, with several findings suggesting effects on both functional and structural connectivity with the prefrontal cortex (3,4). Whether the failure to detect other more diffuse effects in these studies is a power issue or whether connectivity measures may reveal more localized effects of adversity on the brain is an issue that remains to be resolved.

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One of the studies cited above from our group (4) reveals that measures of anxiety and depression in the mother in the third trimester of pregnancy predict prefrontal white matter connectivity in the infant at 1 month of age. Such findings raise the possibility that adversity experienced by the mothers during pregnancy might contribute to the findings reported by Gehred *et al.* (1). Other research suggests that prenatal adversity increases sensitivity to deleterious postnatal influences (5). Commencing longitudinal investigations before birth is warranted because this is a period during which important influences on neurodevelopment are established.

While the authors are quite careful and clear in explaining that the association between childhood adversity and midlife brain structure does not establish the casual role of such adversity in producing the decreased cortical surface area and thickness and the decreased subcortical gray matter volume, it nevertheless raises the possibility that adversity "gets under the skin" and leads to these presumably deleterious alterations in brain structure. Does the absence of specific localized effects have implications for treatment? And does the diffuse pattern of structural variation lead to a transdiagnostic vulnerability to a broad spectrum of psychopathology? Of course, these questions will motivate future research. Reviews of basic and translational research indicate that the same mechanisms of neuroplasticity that enable adversity to alter structural brain features can be harnessed to promote resilience through appropriate forms of experience and training (6). Recent evidence indicates that systematic mental training for skills that promote increased mindfulness, meta-awareness, prosocial behavior, and perspective taking lead to widespread structural changes in different circuits of the brain (7) and may represent a form of transdiagnostic intervention that can potentially be studied as an antidote to the adverse effects of early adversity.

While some evidence suggests that severe early adversity such as the extreme emotional deprivation of Romanian orphanages of the Ceaușescu era are associated with diffuse alterations in brain structure that do not appear to normalize after environmental enrichment (8), it is possible that early exposure to loving, healthy social interactions in the form of positive secure attachment can result in a form of "affective reserve" that acts preventatively to decrease vulnerability to neuropsychiatric disorders later in life (9). We currently lack longitudinal evidence that potentially bears on this conjecture. It will be of great interest to see longitudinal datasets such as from the Dunedin study and other similar efforts to conduct analyses focused on early protective factors and to explore the degree to which such early advantage might similarly be neurally embedded as development unfolds. And while features of early adversity may reflect the intergenerational transmission of trauma, future research might usefully focus on the intergenerational transmission of well-being and through such analyses gain insight into the factors that might promote resilience and the neural and biological mechanisms that mediate such early beneficial influences.

Most importantly, this new work underscores the utility of longitudinal investigation and clearly highlights the critical importance of obtaining observational measures of early environmental influences because such measures reveal different patterns of association with later measures of brain structure.

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Article Information

From the Center for Healthy Minds, University of Wisconsin-Madison, Madison, Wisconsin.

Address correspondence to Richard J. Davidson, Ph.D., at rjdavids@wisc.edu.

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