How Does Adversity “Get Under the Skin” to Lead to the Development of Antisocial Behavior?

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Childhood adversity is considered to be the single greatest preventable cause of psychiatric disorders, accounting for 45% of the population-level risk for childhood-onset disorders and 29% of the risk for adult-onset disorders (1). Understanding how adverse experiences become biologically embedded in the brain and body to trigger psychopathology is therefore a critical issue for researchers, clinicians, interventionists, and policymakers. The study published by Mackey et al. (2) in this issue of Biological Psychiatry offers important new insights in this respect and provides novel data on the neural basis of impulsivity in adolescence.

The study used voxel-based morphometry to investigate relationships between brain structure and performance on a temporal discounting task assessing waiting impulsivity, in a large and well-characterized sample of typically developing adolescents (N = 1830). Adolescents who showed greater temporal discounting of future outcomes—i.e., those who were more likely to select the immediate reward, even if the delayed reward was substantially larger in value (for example, $20 today rather than $25 in a week’s time)—were found to have lower gray matter volume in the ventromedial prefrontal cortex, dorsal anterior cingulate cortex, and bilateral insula, and higher volume in the ventral striatum, than their less impulsive peers. This pattern of results fits with what we know about the respective functions of these regions from neuropsychological and functional neuroimaging studies in humans, as well as findings from comparative research showing that these brain regions are involved in temporal discounting in rodents and primates (3).

In our view, however, Mackey et al.’s most novel and important finding relates to their use of mediation analyses to test whether alterations in brain structure mediate the link between adversity and antisocial behavior. Intriguingly, they found that the effects of adversity on antisocial behavior were partly mediated by structural changes in brain regions implicated in impulsivity. Specifically, the ratio between the volumes of cortical and subcortical regions was found to mediate the effects of adversity (i.e., lower cortical–subcortical volume ratios were observed in those exposed to significant childhood adversity). As the authors note, these results are consistent with a developmental imbalance model whereby cortical—and particularly prefrontal—regulatory mechanisms are insufficiently developed at the same time that subcortical, and particularly striatal, functions are enhanced (4), potentially leading to excessive reward-seeking behavior. The authors also found that cortical volumes significantly mediated the relationship between adversity and antisocial behavior, whereas this was not the case for subcortical volumes considered alone. As lower cortical–subcortical volume ratio might be a general marker of brain immaturity, an interesting question for future research is whether exposure to adversity disrupts and delays the development of the brain, and particularly the cortex.

It should be noted that a recent study by Kamkar et al. (5) provided complementary findings regarding the effects of adversity on reward processing in the brain. Kamkar et al. found that exposure to childhood adversity was linked to more impulsive behavior on a temporal discounting task, as well as enhanced reward-related learning in a reinforcement learning task, in children between 9 and 12 years of age (5). Using functional magnetic resonance imaging, the authors were able to show that increased ventral striatal sensitivity to rewards partly mediated the relationship between adversity and reward-related learning. Although this study had a much smaller sample (N = 40) and used functional magnetic resonance imaging rather than structural magnetic resonance imaging methods, it provides an interesting parallel to the study by Mackey et al. by revealing functional mechanisms that potentially mediate the effects of adversity on reward-seeking behavior.

Along with the many strengths of the study, several caveats should be considered when interpreting Mackey et al.’s findings. First, and most importantly, the study used a cross-sectional design, which is not optimal for testing the effects of mediation. Demonstrating that the ratio of cortical–subcortical volumes changes over time in response to adversity and that such alterations mediate the effects of adversity on antisocial behavior within a longitudinal study will be important, albeit logistically, technically, and ethically challenging. Second, it should be noted that although temporal discounting paradigms provide objective measures of impulsivity, these tasks only tap one aspect of impulsivity—i.e., waiting impulsivity (3). Future research should therefore investigate whether other forms of impulsivity, such as nonplanning and motor impulsivity, are related to early-life adversity and whether they partially mediate the association between adversity and antisocial behavior. This is an important issue, because these three measures of impulsivity have partially distinct etiologies and neural substrates (3), and impulsivity is a core feature of multiple psychiatric and neurological disorders (e.g., attention-deficit/hyperactivity disorder, conduct disorder, Parkinson disease, and frontotemporal dementia). It may therefore represent a transdiagnostic marker of vulnerability that could be explicitly targeted via pharmacological or nonpharmacological treatment or even in preventive interventions. Third, the brain regions that appear to be affected by adversity are not just involved in waiting impulsivity but are also involved in reward-related behavior.
also involved in interoception, or awareness of the physiological state of the body [6], so the effects of structural changes in these regions are unlikely to be limited to impulsivity. Fourth, the use of gray matter volume as an index of brain structure in cortical regions is potentially problematic, because this measure is influenced by multiple morphological features, such as cortical thickness, surface area, and cortical folding, which have distinct developmental trajectories and genetic determinants (7). Future studies should therefore investigate these morphometric measures separately to improve our understanding of the neuroanatomical basis of impulsivity and its relationship with childhood adversity. Fifth, the degree of variation in the adversity measure was somewhat limited given the relatively affluent nature of the IMAGEN sample, and further work is needed using more deprived samples in which extreme forms of adversity are represented, such as looked-after or formerly institutionalized children. The same was true for the antisocial behavior measure—although the range on this measure was quite large, relatively few participants had high levels of antisocial behaviour, and even fewer would have met formal diagnostic criteria for conduct disorder or oppositional defiant disorder. There was also no information about whether the antisocial behavior had resulted in functional impairment, which might be an important factor that differentiates between normative experimentation and problematic antisocial behavior. Sixth, it is unclear whether adversity-induced alterations in brain structure should be interpreted within a stress-induced damage or an adaptive calibration framework (8). Do the structural changes observed in adolescents exposed to high levels of adversity reflect stress-induced damage or adaptation of brain circuits to a more uncertain world, whereby their decisions about future events are calibrated according to the contingencies present in their environment (8)? In a neighborhood or family environment in which other people’s behavior is unreliable, unpredictable, or impulsive, it may be advantageous to adopt a more present-oriented mindset—to live in the moment, because everyone else in your immediate environment does. While this present-oriented mindset may be adaptive in such a chaotic environment, it may lead to problems in adapting to adult life. Finally, while using continuous measures of both life events and antisocial behaviors was a logical decision in the study, given the absence of cutoff points on these measures, this implicitly assumes that different negative life events (changing schools vs. the death of a family member) can be treated as equivalent and that the effects sum together or are cumulative, whereas more complex relationships between different life events are likely, and the developmental timing of such events may be critical. As the authors correctly note, children are not passive recipients of such life experiences, but may elicit positive or negative treatment from their caregivers or peers as a result of their own behaviors. To give a concrete example, highly impulsive children and adults with attention-deficit/hyperactivity disorder are more likely to have a serious or life-threatening accident than their peers (10).

In summary, the study by Mackey et al. extends our understanding of the neural bases of impulsivity in adolescence in several important ways, and the findings are likely to be robust and replicable given the large sample size and objective measure of temporal discounting used. Although limited by the use of a cross-sectional design, the observation that structural changes in brain regions linked to impulsivity, such as the ventromedial prefrontal cortex, insula, and ventral striatum, mediate the relationship between exposure to adversity and antisocial behavior is interesting and represents an important first step in delineating the neural mechanisms that mediate the effects of adversity on psychopathology. Adversity is a risk factor for multiple classes of mental disorders (1), and future research should investigate other forms of psychopathology, such as mood or anxiety disorders, and key psychological constructs implicated in those phenotypes, such as emotion regulation, to examine whether mediation via changes in brain structure or function can also be demonstrated in those cases. A further important direction for future research will be to test whether alterations in brain structure or function mediate the associations between negative environmental exposures and psychopathological outcomes in the context of longitudinal studies.

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