Race-Related Disparities in Childhood Adversity, Trauma, and Stress-Related Psychopathology

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Childhood adversity, maltreatment, and stress are all significant risk factors for the development of psychopathology. These risk factors frequently interact, and this is especially the case for the risk to develop stress-related psychiatric illnesses and comorbid substance use. This issue of the *Journal* brings together informative papers that address risk factors for the development of psychopathology by examining issues of causality, associations between racial disparities related to childhood adversity and brain structure, interactions between genetic risk and social support, and imaging predictors of trauma outcomes. The research presented includes 1) results from a meta-analysis of childhood maltreatment studies that estimates the magnitude of the causal effect of maltreatment on the development of psychopathology; 2) an important study on childhood brain development that is focused on understanding how differences in childhood adversity due to racial disparities relate to brain structure; 3) an examination, drawing on unique samples of medical interns and recently widowed individuals, of interactions between polygenic risk scores for depression and perceived social support in relation to the development of stress-related depressive symptoms; 4) an attempt to replicate findings from an earlier report that described neuroimaging predictors of trauma-related outcomes in adults; and 5) results from a meta-analysis that compares the relative efficacy of different treatments for PTSD with comorbid alcohol or substance use disorders.

A Meta-Analysis of Studies Attempting to Elucidate the Causal Role of Childhood Maltreatment on the Development of Psychopathology

There is no question that early-life adversity, particularly in the form of childhood maltreatment, is associated with the broad risk to develop psychiatric disorders. The extent to which childhood maltreatment plays a causal role in the development of psychiatric disorders, however, is more difficult to determine. This is the case because numerous other risk factors for the development of psychopathology (e.g., genetic, socioeconomic, and demographic) are also often associated with childhood maltreatment, and in observational studies it is difficult to disentangle the effects of these interrelated factors. Baldwin et al. (1) attempt to clarify the causal and selective contribution of childhood maltreatment to the later development of psychopathology by performing a meta-analysis on studies of childhood maltreatment that have used quasi-experimental designs. Unlike prospectively designed experiments, quasi-experimental designs use existing data from observational studies in which subjects are not randomized and by various means attempt to isolate factors of interest and/or control for potential confounds (2). Baldwin et al. included quasi-experimental studies that used family-based designs to account for potential family-related confounds, longitudinal studies examining the time course of the relation between maltreatment and psychopathology while controlling for other individual factors, natural experiments in which large groups of individuals are affected (i.e., children raised in Romanian orphanages), and propensity score designs, which allow for comparing between-group differences while matching individuals in the comparison groups on potentially confounding factors (3). Thirty-four studies with data from a total of 54,646 individuals who were less than 18 years of age and had experienced abuse, neglect, institutional deprivation, or other forms of victimization were identified and used in the meta-analysis. Overall, the findings revealed a small but significant effect of maltreatment being "causally" linked to the development of a wide range of psychopathology. It is notable that the magnitude of this effect was considerably less than that reported from studies that did not use quasiexperimental designs, suggesting the importance of contributory, interrelated factors to the association between maltreatment and psychopathology. Additionally, compared with other types of adversity, the strongest associations with the development of psychopathology were seen for emotional

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abuse and institutional neglect. However, it should be noted that this result is based on only a handful of studies, raising some caution regarding the veracity of this finding. In their editorial (4), Dr. Meike Bartels from Vrije Universiteit Amsterdam and Dr. Christel Middledorp from the University of Queensland discuss the findings in more detail and point out the importance of distinguishing associational findings from causal findings in relation to the effects of childhood maltreatment, and the importance of identifying the other maltreatment-associated factors that contribute to the development of psychopathology.

The Effects of Racial Disparities in Childhood Adversity on Brain Structure

Due to the long-term impacts of structural racism, Black Americans have endured, and continue to face, many significant societal disadvantages. As a consequence, Black American children are on average exposed to greater levels of childhood adversity than their White American counterparts. Additionally, numerous studies have linked childhood adversity to alterations in brain structure and function, including the neural systems that are involved in mediating responses to threat. Dumornay and coauthors (5) use the large Adolescent Brain and Cognitive Development (ABCD) data set to examine the relation between race-related disparities in adversity occurring during childhood with differences in brain structure. Data from 9–10-year olds (Black Americans, N=1,866; White Americans, N=7,516) were used for analysis in this study, which included structural MRIs to assess gray matter volume, demographic data, measures of neighborhood disadvantage, levels of family conflict, material hardship, and trauma history. Consistent with the larger United States population, the data from the ABCD sample revealed marked disadvantages for Black American children as reflected in significantly lower levels of parental educational attainment, employment, and income; higher levels of neighborhood disadvantage, family conflict, and financial hardship; and greater levels of trauma. Of the 14 brain regions of interest selected for analysis, 12 of these (e.g., amygdala, hippocampus, frontal pole, rostral anterior cingulate, and lateral orbitofrontal cortex) were found to have significantly less gray matter volume in Black American children compared with White American children. Across the entire sample, significant relations were observed between measures of childhood adversity and gray matter volumes in most of the regions selected for analyses, which included orbitofrontal cortical regions, insular cortex, and the amygdala. It is important to note that in the next set of analyses the researchers found that, when controlling for measures of adversity, the effects attributed to racial differences on reductions in gray matter volume were significantly weakened in some brain regions. This appeared to be the case for gray matter volume reductions in the caudal anterior cingulate and the lateral orbitofrontal cortex and points to the importance of childhood adversity in prominently contributing to these effects. These findings provide compelling evidence that challenges previous work that directly attributed structural brain differences to race per se. In their editorial (6), Drs. Deanna Barch and Joan Luby from Washington University in St. Louis discuss the findings from this study in relation to the importance of developing an even more complete understanding of the how social determinants of health impact brain development. They suggest that the magnitude of the effects of the social determinants of health on brain structure presented in this study may have been underestimated. Furthermore, they emphasize that it is important to not misinterpret the findings from this paper in any way as to support race as contributing to the structural brain differences found between Black and White children in the ABCD study.

Stress-Related Depression: Interactions Between the Polygenic Risk to Develop Depression and Social Support

Stress is a risk factor for the development of depression, and social support can be an important modulating factor. Loss of social support can be a stressor in and of itself, increasing the likelihood of depression, whereas effective social support can buffer the negative impacts of stress. Cleary et al. (7) investigate the relations among stress, perceived social support, and the development of depression with a particular emphasis on understanding the interaction between the polygenic risk to develop stress-related depression and changes in social support. Data from two samples of individuals who were experiencing substantial stressors were used for the analyses. One sample consisted of 1,011 physician interns assessed during their first year of training, a period that is quite stressful, and the other sample included 435 recently widowed individuals. As expected, both groups of individuals demonstrated increases in depression scores associated with the stress of internship or loss of a spouse. It is interesting that the internship group reported a decrease in social support over the 1-year internship period whereas the widowed group demonstrated an increase in social support after the loss of a spouse. Analyses of both samples revealed a significant interaction between polygenic risk scores for depression and changes in perceived social support. Individuals with higher polygenic risk scores were most sensitive to different levels of social support. In both samples the researchers found that higher depression polygenic risk scores were associated with a greater likelihood of developing depression when social support was decreased, but when social support was increased higher polygenic risk scores were associated with a decreased likelihood of developing depression. Thus, it appears that individuals with higher depression polygenic risk scores are more sensitive to both the negative and positive impacts of social support. This finding is not intuitive as it might be expected that higher levels of social support would not have much impact on individuals that have a greater genetic loading for depression. In clinical terms, individuals with high genetic risk may be the

individuals that are most sensitive to social support during stressful periods, with the possibility that these individuals would also show considerable benefit from therapeutic interventions aimed at increasing social support. In their editorial (8), Dr. Daniel Belsky from Columbia University and Dr. Benjamin Domingue from Stanford University discuss the significance of the findings from this paper and more generally address methodologic and statistical issues that are important when studying psychopathology-related gene by environment interactions.

Data Addressing the Reliability of Neuroimaging Predictors of Trauma-Related Outcomes

Ben-Zion and colleagues (9) present data that examine the possibility of using brain-based biotypes as characterized with neuroimaging parameters to predict clinical outcomes in recently traumatized individuals. This paper follows-up, and attempts to replicate, findings from a 2021 study by Stevens et al. (10) in which it was reported that neuroimaging-based biotypes could be identified with machine learning techniques that were predictive of the later development of PTSD and anxiety symptoms. To accomplish this, Ben-Zion et al. use a similar data set in what the authors term a "conceptual nonexact replication" and use similar analytic strategies in collaboration with Stevens and colleagues. In the Stevens et al. study, fMRI was performed using three tasks (i.e., threat-related, inhibitory control, and reward) in individuals on average 18 days after their traumatic experience. The findings characterized three imaging clusters that were replicated across two study cohorts, with the "reactive/disinhibited" cluster being associated with threat- and reward-related brain regions, and also being the most predictive of PTSD symptoms and longer-term anxiety.

In the Ben-Zion et al. study, data from 130 acutely traumatized individuals collected in Israel were analyzed, with 88% of this group having been involved in a motor vehicle accident. fMRI was performed within 1 month of the trauma using different paradigms from those used by Stevens et al. These were aimed at assessing neural responses associated with threat and reward but did not include an inhibitory control task. With this strategy, Ben-Zion et al. identified different neuroimaging clusters or biotypes, some of which shared features with those characterized by Stevens et al. However, unlike the Stevens et al. findings, these clusters did not predict clinical outcomes. While the current study by Ben-Zion et al. was similar in design to the Stevens et al. study and attempted to replicate the analytic methods previously used, it was by no means an exact replication, with important differences that could account for the divergent findings. For example, the current study excluded individuals with prior PTSD diagnoses, whereas this was not the case in the Stevens et al. study. Also, while attempting to assess brain reactivity in relation to the same psychological/cognitive constructs, different imaging tasks were used in the two studies, and in the current study there was not a task assessing response inhibition. Also, the demographics, gender, and trauma types of the samples markedly differed between the two studies. Despite these potentially important differences, the authors argue that useful biomarkers should be evident and reliable across different patient populations that have experienced acute trauma. Taken together, these two studies point to both the potential difficulties, and additional work needed to be done, to understand how the field can effectively use brain-based neurotypes to improve diagnostic acumen, predict illness course, and aid in treatment selection. Drs. Murray Stein and Jessica Bomyea from the University of California at San Diego contribute an editorial (11) in which they laud the collaborative efforts of these two research groups in their efforts to work together to address the question of replicability. They also provide an in-depth discussion that considers the potential reasons for the lack of replicability between these two studies, while at the same time emphasizing the importance of the ongoing quest to identify reliable and generalizable biotypes that are predictive of the development of psychopathology.

Comparing Treatments for PTSD With Comorbid Alcohol or Other Substance Use Disorders: A Meta-analysis Using Individual Patient Data

PTSD is commonly comorbid with alcohol use disorder and other substance use disorders. Hien et al. (12) use individual patient data from 36 randomized clinical trials to compare the efficacy of different treatments for these comorbidities. The authors point out that there are many treatments, especially different psychotherapies, that are used to treat patients with PTSD and substance use disorders but little data regarding their relative efficacy, especially in relation to the comorbidity of these disorders. In this report, the authors use a method termed "Virtual Clinical Trial" that enables the comparison of different treatments using meta-analytic data sets. This is accomplished using integrative data analysis methods, which bring together different datasets into one analysis and propensity score weighting that helps deal with different confounds and baselines found in the different datasets. Across the 36 studies, data from 4,046 patients were included from individuals that met criteria for PTSD or subthreshold PTSD plus alcohol use disorder or other substance use disorders. Different treatment classifications were coded for the analyses: trauma-focused therapy, integrated PTSD and alcohol or other drug treatment therapy, medications for PTSD, medications for substance use disorders, behavioral treatment by itself for substance use disorder, other pharmacotherapy, and nonmanualized community-based treatment considered to be treatment as usual. In relation to PTSD symptoms, the treatment as usual group demonstrated a medium effect size and most of the comparator treatments were found to be significantly better than treatment as usual. The combination of trauma-focused therapy and alcohol and other drug use pharmacotherapy appeared to be the most efficacious with a large effect size. For efficacy in treating the severity of alcohol use-related

symptoms, treatment as usual was found to have a small effect size whereas a large effect size was found for trauma-focused therapy combined with alcohol-related pharmacotherapy or other pharmacotherapy. For symptoms associated with other comorbid substance use problems, none of the treatments were significantly better than treatment as usual, which was found to have a moderate effect size. In summary, the analyses revealed that when compared with treatment as usual, the strongest effects on PTSD symptoms comorbid with alcohol misuse symptoms were found for the trauma-focused therapies combined with medications for alcohol use disorder.

Conclusions

This issue of the *Journal* helps to refine our understanding of the impact of childhood adversity, trauma, stress, and social support on the development of psychopathology while also, relevant to the treatment of stress-related psychopathology, seeks to clarify the relative efficacy of treatments for PTSD comorbid with alcohol or other substance use disorders. Major findings within this issue are that 1) despite reports of stronger associations between childhood maltreatment and psychopathology, the causal role of childhood maltreatment appears to be relatively small; 2) reductions in gray matter volume in Black compared to White American children can, in part, be attributed to racial disparities in adversity occurring during childhood; 3) individuals with stress-related depressive symptoms and high depression polygenic scores appear to have heightened sensitivity to both the negative and positive impacts of social support; 4) an attempt to replicate previous findings of neural biotypes predicting clinical outcomes in recently traumatized adults failed; and 5) the most effective treatment approach for PTSD comorbid with alcohol misuse appears to be the combination of trauma-focused therapy with medications for alcohol use disorder.

While all of the papers in this issue of the *Journal* make valuable contributions, I consider the findings from Dumornay et al. (5) to be critically important and the most immediately relevant as they serve to underscore the care that must be taken regarding the interpretation of findings that point to Black-White differences in biological factors related to risk and the expression of psychopathology. This paper indicates that it is race-related disparities in childhood adversity, and not race per se, that are important contributors to observed differences in brain structure that are associated with the risk to develop psychopathology. These findings speak to the need for Psychiatry as a field to be outspoken about the detrimental psychological impacts of race-related disparities in childhood adversity, to call out the fact that these disparities stem from structural racism, and to vigorously support rectifying efforts by pursuing antiracist policy changes.

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