Commentary

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Childhood Maltreatment Alters Normative Changes in Whole-Brain Resting-State Connectivity

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One in four children experiences childhood maltreatment before reaching adulthood (1). Maltreatment refers to abuse, which can be physical, sexual, or emotional in nature, or neglect, which captures inadequate access to basic childhood needs and/or appropriate supervision. Childhood maltreatment increases risk for psychopathology and impairments in cognitive functioning (2), which in turn shape mental health and educational outcomes across the life course (3). Critically, the effects of childhood maltreatment on adult outcomes are consistently found to be independent of adult circumstances, suggesting that the short-term impacts of abuse and neglect set the stage for long-term outcomes. Maltreatment may exert persistent effects on socioemotional and cognitive outcomes because the developing brain is sensitive to environmental experiences (4), particularly during periods of rapid developmental change (e.g., adolescence). Thus, alterations in neural function have been proposed as key mechanisms through which maltreatment shapes maladaptive outcomes across the life course.

Childhood maltreatment is thought to affect several neural systems (5) that mature throughout adolescence. Most of this work has examined neural activation in, or connectivity between, isolated regions of interest during task-based functional magnetic resonance imaging (fMRI). For example, studies have reported maltreatment effects on 1) corticolimbic circuitry (e.g., the amygdala, medial prefrontal cortex, and hippocampus), which supports salience detection and emotion processing; 2) the frontoparietal network (e.g., the inferior frontal gyrus and superior parietal sulcus), which supports executive function, cognitive control, and language development; and 3) the frontostriatal network (e.g., the striatum and orbitofrontal cortex), which supports reward processing. However, maltreatment effects on neural function during task-based fMRI are inconsistent: some associations have been replicated (e.g., the association between maltreatment and heightened amygdala reactivity to threatening stimuli), whereas others have been more mixed (e.g., it remains unclear whether maltreatment accelerates or delays normative changes in corticolimbic connectivity) (5). Such directional inconsistencies in maltreatment—neural function associations may be due, in part, to the wide variety in fMRI task designs and definitions of neural regions examined, as well as reliance on cross-sectional data in nonrepresentative samples. Novel methods that support replication across studies are needed to identify a generalizable understanding of how childhood maltreatment sculpts neural function.

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Rakesh *et al.* (6) address many of these limitations by examining the effects of childhood maltreatment in a community-based sample of 130 16-year-old adolescents with significant variability in maltreatment severity. Using resting-state fMRI data collected at two time points spaced approximately 2 years apart, the authors investigate changes in resting-state functional connectivity (rs-FC) within and between 7 resting-state networks comprising 210 cortical and 36 subcortical regions. The 7 networks included 6 task-positive networks commonly examined in task-based fMRI studies (i.e., frontoparietal, dorsal attention, corticolimbic, salience, somatomotor, and visual) as well as the default mode network (DMN), which is more active when the brain is at rest. Growing evidence suggests that individual differences in resting-state network connectivity are replicable across time and predict task-relevant connectivity and behavioral performance (7). Thus, whole-brain rs-FC approaches circumvent many of the replication challenges (e.g., due to differences in task design) in the task-based fMRI research. Moreover, an examination of how childhood maltreatment sculpts network-level rs-FC is consistent with the growing knowledge that neural function supports complex human behaviors at a systems level rather than within single regions of interest (8).

First, Rakesh *et al.* (6) pair maltreatment analyses with an examination of how rs-FC within and between networks changes across adolescence in the entire sample. From a developmental psychopathology perspective (3), this is important because our understanding of how adversity alters neural function is predicated on knowledge of how the brain normatively develops over time. Charting average developmental changes in rs-FC across participants, Rakesh *et al.* (6) report age-related decreases in DMN between-network connectivity (e.g., DMN–salience and DMN–frontoparietal) and report increases in within-network connectivity (e.g., salience and somatomotor) and increases between task-positive networks (e.g., salience–somatomotor, dorsal attention–salience, and dorsal attention–limbic). These results are consistent with previous research (7) suggesting that rs-FC becomes increasingly segregated with development (i.e., there are decreases in DMN between-network connectivity and increases in within-network connectivity). Moreover, decreases in DMN between-network connectivity were magnified in girls, highlighting plausible neurodevelopmental immaturity among males who, on average, progress through puberty at older ages.

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Maltreatment, however, attenuated DMN between-network segregation: childhood maltreatment at 16 years of age was associated with increases in DMN connectivity with the frontoparietal, salience, and dorsal attention networks from 16 to 19 years of age, as well as increases in task-positive between-network connectivity (e.g., frontoparietal–dorsal attention and frontoparietal–salience). Sex moderation analyses revealed that such increases were more pronounced in males compared with females. With imaging at two time points, Rakesh *et al.* (6) were able to investigate theories of adversity-associated "developmental delay" (i.e., greater network integration indexed by stronger DMN between-network rs-FC and weaker within-network rs-FC) versus adversity-associated "accelerated maturation" (i.e., maltreatment hastens normative rs-FC development of greater network segregation across time). Relative to the developmental patterns observed in the entire sample, maltreatment-associated patterns of DMN between-network connectivity supported the notion of neurodevelopmental delay rather than acceleration. In contrast, maltreatment-associated patterns with task-positive between-network connectivity indicated acceleration rather than delay. These results suggest that rather than a global characterization of accelerated maturation versus developmental delay, maltreatment and other forms of childhood adversity may sculpt neurodevelopment in a network-specific manner. As evidenced by a recent systematic review (5), few studies examine network topology beyond a single circuit (e.g., corticolimbic). Rakesh *et al.* (6) suggest that network-based perspectives are needed to understand how adversity sculpts the developing brain globally.

Rakesh *et al.* (6) provide preliminary evidence that greater increases in average rs-FC mediated the association between childhood maltreatment and depression symptoms. Although it is tempting to generalize neural patterns (e.g., changes in within- or between-network rs-FC across development) as maladaptive, more research is needed to contextualize brain function in behavior. If the brain is sensitive to environmental experiences and adapts in response to internal and external demands, do we have enough evidence to label neural patterns as "adaptive" or "maladaptive"? Although depressive symptoms are impairing, patterns of risk and resilience are complex and multidimensional: behavioral symptoms represent only one component of global functioning. Functional outcomes (e.g., interpersonal capabilities and economic stability) are shaped by numerous processes including physical and mental health, identity formation, and cognition. In addition, childhood adversities such as maltreatment operate in conjunction with protective factors at multiple levels of ecological influence (e.g., self-control, strong community social ties, and family cohesion), all of which have been shown to moderate the effects of maltreatment on youth outcomes (9). Future work should move beyond variable-centered approaches that examine how neural function mediates the effect of isolated adversities on isolated behavioral outcomes, to person-centered approaches that integrate the spectrum of environmental exposures and developmental outcomes. For example, it would be informative to characterize rs-FC network patterns in youth exposed to maltreatment who demonstrate maladaptive functioning across multiple domains versus youth exposed to maltreatment and promotive factors (e.g., social support) who thrive. This type of paradigm shift toward examining the "whole child" will require interdisciplinary collaboration between neuroscientists, developmental psychopathologists, and even sociologists with expertise in the broader community context (10).

Rakesh *et al.* (6) lay the groundwork for replication and extension of their findings in other datasets by using a freely available image processing pipeline (i.e., fMRI Prep), standardized parcellation atlas (with sensitivity analyses showing similar results using another parcellation scheme), and well-validated and widely used behavioral measures. Even more laudable is the use of a population-based study of adolescents. To understand how maltreatment and other forms of childhood adversities sculpt network-level rs-FC, scientists need to understand how within- and between-network connectivity develops normatively in population-based samples that include youth from a variety of sociodemographic backgrounds. In a field dominated by convenience sampling, the study sample used by Rakesh *et al.* (6) is a first step toward achieving this goal. A school-based recruitment strategy with a well-defined sampling frame resulted in significant variability in area-level disadvantage that did not differ from the catchment area (i.e., metropolitan Melbourne, Australia). This type of thoughtful sampling wherein all individuals in the sampling frame were given the opportunity to participate, as opposed to families with unique access (e.g., to research institutes), is precisely what the field needs to promote replication and generalizability (10). Fortuitously, the ages of data collection in the Rakesh *et al.* (6) study parallel data collection in the newly released ABCD study, a longitudinal population-based study of >11,000 9- to 10-year-old youths in the United States who will undergo neuroimaging every 2 years until early adulthood. Thus, the adversity-associated changes in rs-FC networks observed in the current study can be examined in the ABCD participants to determine generalizability.

Childhood maltreatment is common, affects functional outcomes across the life course, and sculpts the development of neurobiological systems. Rakesh *et al.* (6) provide a novel perspective for how childhood maltreatment shapes rs-FC across adolescence, demonstrating that a developmental longitudinal approach helps us understand adversity-associated deviations from normative brain development.

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