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An Interactive Developmental Neuroscience Perspective on Adolescent Resilience to Familial Depression

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Decades of empirical and theoretical work have been directed toward identifying risk factors in the intergenerational transmission of depression. Receiving considerably less attention in the field is the study of attributes that might constitute protection from major depressive disorder (MDD) among offspring of parents with depression. This disinterest persists despite research showing that roughly 40% of such offspring never go on to develop the disorder. Thus, resiliency to depression, whether a foundational trait or the outcome of several interactive factors across development, may reflect processes that can be identified, targeted, and enhanced in prevention and intervention efforts.

In this issue of *JAMA Psychiatry*, Fischer et al¹ address this topic through functional brain connectivity, contributing interesting results and testable hypotheses for future studies. The study used a prospective design and followed the daughters of mothers with recurrent depression from age 12 to 18.5 years to identify resilient daughters (who had an absence of MDD) and converted daughters (who developed MDD). Approximately 6 years after the baseline assessment, the researchers assessed seed-based functional connectivity patterns in 3 major networks supporting cognitive and affective processing in the offspring. The primary results across networks and seeds suggest that resilient daughters exhibited a host of connectomic differences relative to daughters in a low-risk control group and those at high risk who had converted to MDD. Compared with the low-risk control group, the outcomes of the resilient group and the converted group were substantially different. This is the first study to demonstrate that relatively normative functional connectivity within and across key networks (as well as different connectivity of unknown relevance) may serve a protective role for the development of MDD in the female offspring of mothers with MDD. If replicated, these findings provide a potential prevention mechanism for intervention (ie, the modulation of functional connectivity patterns).

The definition of resilience is complicated and dynamic, particularly when viewed through the moving lens of adolescence.² As such, it will be necessary to determine whether these patterns of functional connectivity can be detected at an earlier age. An important question also becomes apparent: can resilience be represented as a static or preordained brain mechanism present at enrollment (foundational resilience), or is it a process that evolves over the course of adolescence, perhaps looking quite different over time (interactive

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resilience)?³ For example, recent work by our group⁴ suggests that individuals with internalizing disorders exhibit disrupted patterns of network connectivity throughout development that interact with the age of the person at the time of assessment. Specifically, children and preadolescent youth with a history of internalizing psychopathologies exhibited dys-functionally elevated cross-network connectivity patterns relative to healthy controls, and yet this cross-network pattern was reversed in late adolescence and adulthood. Thus, these data, along with the work of others, highlight the importance of understanding not only differences in functional connectivity between daughters who are resilient to MDD or those who convert to it, but also stages of development and the clinical, cognitive, and affective processes that may be supported by or correlate with these connectivity differences.

Indeed, theoretical models of interactive resilience promote the idea of cross-contextual mediation and moderation in which the environment influences resilience processes at the neurobiological level, or the biological context influences the effects of supportive processes at the environmental level.⁵ Fischer et al¹ propose an experience-dependent plasticity effect on brain networks based on their post hoc demonstration of a positive association between positive life events and amygdala-ventromedial prefrontal cortex connectivity in older adolescent females (with a mean age of 18.5 years) who are resilient to MDD (per Figure 1D in Fischer et al). To confirm this hypothesis, a follow-up study could include multiple assessments of life events and brain connectomics across the developmental span to specify the emergence and directional nature of this relationship. This type of design would also allow us to determine if connectomics are malleable in a treatment-relevant fashion, and if positive features in the environment have the potential to contribute to adaptive changes in neurobiological systems—questions that remain vital for the development of prevention goals.

Longitudinal, multiple repeated assessments of the complex interactions between brain and environment that shape resilient outcomes can increase clarity in illustrating resilience and whether it is foundational or interactive. There are several important design considerations for studies that build on the work of Fischer and colleagues.¹ First, the age of off-spring at the time of study enrollment continues to be a perplexing decision. We recommend an earlier age of enrollment to evaluate the dynamic, interactive development of resilience over time, although this also requires substantial and perhaps different funding models. This design can result in the inclusion of youth with more severe psychopathology who better represent the full range of risk. Moreover, earlier enrollment presents greater opportunities for detection and intervention and thus has greater potential clinical benefits (eg, the opportunity to identify earlier and intervene earlier). Second, we recommend enhancing the level of granularity in measurement of parental psychopathology (eg, severity, timing, and duration of exposure to parental depression) and caregiver characteristics (eg, presence of the offspring's father, quality of parental relationships) to better understand if there are sensitive periods when neurobiological variables interact with environmental characteristics to promote resilience. Third, we encourage the use of strategies such as multisite studies to include ethnically and socioeconomically diverse samples, given the important role of familial resources in resilience. Fourth, within a model of interactive resilience, it is also possible to actively facilitate primary or secondary resilience for at-risk adolescent females. For example, a future study might include a facilitated resilience arm using a prevention

program that aims at enhancing adaptive emotion regulation skills or rumination modulation.^{6,7} This type of approach would substantially increase our understanding of the interactive development of brain connectomics associated with resilience in a standardized longitudinal model. Finally, we recommend providing a standardized treatment for daughters who convert to illness, as this will reduce variance in modeling secondary resilience (eg, prevention of relapse) by removing heterogeneity associated with differing effects of various types of treatment.

In summary, the work of Fischer and colleagues¹ provides an important foundation for studying neurobiological factors, such as functional connectivity, that may reflect resilience for daughters of depressed mothers. The shifting of focus to an interactive resilience-based model of psychopathology among the offspring of depressed parents is timely and exciting. This type of work ultimately increases our understanding of promotive factors that can be strengthened, existing techniques that facilitate resilience, and the ways in which these techniques might be improved and more widely disseminated.

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