Commentary

Connecting With Resilience

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When it comes to mental health, we tend to focus more on what can go wrong and how than on what goes right and why. The intriguing question posed by Ohashi *et al.* (1) in this issue of *Biological Psychiatry* is what neurobiological systems might confer resilience, allowing some who experience early maltreatment to avoid subsequent mental ill health. Their focus is white matter integrity, and they use graph theory to describe the structural connectivity and, by inference, information flow among brain systems.

First, Ohashi *et al.* (1) identify brain markers of maltreatment that appear to be present irrespective of mental health outcome. These findings dovetail with previous reports of structural and functional brain differences among maltreated individuals with no history of clinically significant mental health problems (2,3). Intriguingly, this suggests that resilience may be embodied in distinct compensatory brain systems. This is an important observation and is consistent with the notion that disease and recovery may be distinct and separable (4). Thus, if resilience markers can coexist with maltreatment markers, then resilience may be a distinct entity that is more than, say, the undoing of maltreatment's effects. Ohashi *et al.* (1) make clear the clinical implications when they conclude that "…efforts to treat maltreated individuals with psychopathology do not have to focus on reversing maltreatment-related alterations, but may instead foster specific nodal changes that bring the circuitry of these individuals more into line with the circuitry of resilient individuals."

In actuality, the individuals Ohashi *et al.* (1) identified as resilient did suffer less maltreatment than the individuals they identified as being susceptible to psychopathology—an unfortunate confound that muddies the search for resilience markers. Consequently, the authors reclassified the maltreated participants as those who were asymptomatic with regard to mental health and those who were symptomatic, which avoided the confound with level of maltreatment. By contrasting these two groups, Ohashi *et al.* (1) identified measures of reduced connectivity as the key compensatory systems of resilience. Specifically, they found that multivariate connectivity measures of the right amygdala—an a priori region of interest based on previous studies of maltreatment—were significantly lower in asymptomatic participants relative to symptomatic participants. Univariate analyses revealed that both nodal efficiency and degree centrality of the right amygdala were reduced in asymptomatic participants when compared with symptomatic participants. Interestingly, asymptomatic participants also differed from control participants regarding right amygdala connectivity—with asymptomatic participants exhibiting significantly lower nodal efficiency, degree centrality, and closeness. To test for potential differences in centrality across all nodes, the authors subsequently used both elastic net and random forest regression approaches. Notably, these two methodological approaches produced largely overlapping results, with each approach identifying differences in the same five nodes: the right amygdala, the left frontal inferior pars triangularis, the right middle cingulum, the right paracentral lobule, and the left supplemental motor area. In addition to these five nodes, random forest regression identified differences in four more nodes, including the left and right olfactory cortex—cortical regions that include the subgenual anterior cingulate, share robust anatomical connections with the amygdala, and have been repeatedly implicated in the pathophysiology of mood disorders (5).

The graph theoretical analysis tools used here offer an exciting approach to describing whole-brain connectivity. Whereas the resolution of human neuroimaging is too coarse for many neuroscience questions, the graph theoretical analysis tools might be argued to be somewhat ideal for exploiting one of the particular strengths of neuroimaging, namely its whole-brain survey of brain structure and function. That said, caution in the interpretation of these graph theory measures is warranted. There are quite a few inferential steps in going from assessing measures such as nodal efficiency and degree centrality on diffusion-weighted magnetic resonance images to concluding that resilient individuals have a brain circuitry that has a diminished ability to propagate information and hence ultimately serves to quieten their "self-castigating voices." The interpretations offered by Ohashi *et al.* (1) are intriguing and plausible but post hoc, necessitating more research to confirm that these particular graph theory measures do indeed translate to these functional and psychological consequences. As always, replication is essential. The choice to conduct a cross-validation—in which the data are split into model training and model test sets but using variables that were initially defined by the entire dataset—leads to concerns with overfitting (6). Ohashi *et al.* (1) tackle this concern, but the ultimate test will be with a new independent dataset.

Caveats aside, the search to understand resilience so that maltreated individuals who are resilient and maltreated individuals who are not resilient can be identified earlier is, of course, of utmost importance. Ohashi *et al.* (1) focused on cerebral white matter. If other brain and biological measures that have been linked to resilience [e.g., gray matter volume (7), resting-state functional connectivity (8), and epigenetic modification (9)] were incorporated into a multimodal model, we might achieve even better classification accuracy. Beyond brain measures, understanding what social supports and environmental factors bolster resilience, and determining if they do so by modifying these very same brain markers of resilience, would lead to a more comprehensive understanding of the phenomenon. Indeed, the availability of social supports

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has been found to moderate risk for depressive symptoms among maltreated youths (10); investigating the brain pathways that underlie such moderation effects may prove valuable for further understanding resilience. Ohashi *et al.*'s (1) results also leave open for others to explore the etiology of these brain resilience factors. Were the resilient individuals the lucky few endowed with the optimal neurobiology to tackle their maltreatment? Or were there intrapersonal factors that responded to the maltreatment or interpersonal factors that bolstered the maltreated individuals that led to the development of a resilient brain? Longitudinal, prospective studies may shed light on these questions. Moreover, beyond resilience, it would be interesting to determine what might lead to someone's thriving—that is, not just presenting with the absence of mental health problems, but doing especially well in life achievement measures. Large prospective longitudinal cohorts that more fully capture population variability may facilitate the study of such individuals.

As with most valuable studies, Ohashi *et al.*'s (1) findings raise numerous new questions. What is the mechanism by which aspects of right amygdala centrality are reduced in resilient individuals? As mentioned above, is it a response to the adversity or a preexisting good fortune? Might these mechanisms be central to evidence-based treatments for early adversity and trauma (e.g., exposure-based cognitive behavioral therapy) that have been shown, on average, to reduce levels of psychopathology as well as amygdalar reactivity? To what extent is resilience an umbrella term for numerous compensatory processes? Reduced connectivity of the amygdala, which is a focus here, may not be the key system in other domains requiring resilience, such as the ability to avoid relapse in drug users or in those who overcome a family or genetic predisposition to other types of poor mental health. Even if so, and the key brain systems are different, do the connectivity processes here offer insight into a generalizable compensatory response? Might it be that blunted communication for brain systems central to a disorder is a general characteristic of resilience, and thus might we expect the recovering addict to show reduced connectivity for systems relevant to addiction processes, such as the ventral striatal or insula? Or will the neurobiology of resilience turn out to be every bit as varied and complex and intriguing as the neurobiology of illness?

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Article Information

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