Commentary

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Restoring Weight and Brain Function: Intrinsic Neural Activity and Connectivity Alterations as State Markers of Adolescent Anorexia Nervosa

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Psychiatric neuroscience research has long faced the challenge of distinguishing state from trait markers of illness. This distinction is particularly important in the case of anorexia nervosa (AN), a debilitating disorder characterized by severe dietary restriction that can have profound and starvation-related effects on the central nervous system. These effects are difficult to disentangle from potentially preexisting neurobiological differences. Decades of research have shown that acute phases of AN are associated with widespread alterations in brain structure and function (1,2), but little research to date has helped to clarify which of these alterations represent long-lasting sequelae or "scars" of the illness; which represent traits that predispose individuals to develop AN and persist even after symptom remission and weight restoration; and which represent temporary markers of the actively symptomatic and weight-reduced state. Several studies have begun to tackle these questions by comparing individuals who have fully remitted from AN to healthy control individuals. However, few studies have used longitudinal designs to identify neurobiological alterations that are present in the acute phase of AN but that resolve with normalized eating and weight.

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging,* Seidel *et al.* (3) addressed this gap by studying the brain function of adolescent patients with AN using resting-state functional magnetic resonance imaging (fMRI). Importantly, this was one of the first and largest examinations of longitudinal neural changes in this population. The authors compared 89 healthy control individuals to 87 acutely underweight female adolescent patients with AN before and after short-term weight restoration in treatment (weight gain of at least 12% of their body mass index [BMI] from the initial assessment). To control for any potential influence of differences in food intake immediately before scanning, all participants completed resting-state fMRI after an overnight fast. Four different resting-state fMRI metrics were calculated: regional homogeneity (ReHo), degree centrality, voxel-mirrored homotopic connectivity (VMHC), and fractional amplitude of low-frequency oscillations. These metrics characterize spontaneous neural activity and can help clarify the organization and synchrony within neural circuits. Before weight restoration, patients with AN showed different neural activity patterns than healthy control individuals throughout the brain and across all 4 metrics. After weight restoration, many of these differences were no longer detectable, particularly in VMHC and ReHo. Surprisingly, the degree of posttreatment weight gain was associated with changes only in ReHo and VMHC, and only in 1 brain region, the insula. Substantial evidence suggests that this region, which is integral in processing internal body state information, plays a crucial role in AN (6). Seidel *et al.*'s (3) findings suggest that weight gain may be pivotal to reversing some functional alterations involving this area. However, outside of the insula, the normalization of intrinsic neural activity may be related to the restoration of energy reserves with normalized eating, rather than increases in BMI. Overall, these fMRI findings importantly confirm what smaller functional imaging studies [e.g., (4)] and large-scale structural imaging studies (5) in adolescents previously suggested: Several brain-based alterations detected in acute AN seem to normalize after weight restoration with treatment.

The major and distinguishing strengths of Seidel *et al.*'s work (3) are the sample size and the longitudinal design. Studies that scan large groups of individuals with AN before and after treatment are particularly rare. In addition, the patient group was compared with closely matched control individuals, and analyses carefully considered potential covariates like age and motion artifacts. Such repeated-measures, case-control designs are crucial to disentangling the effects of weight loss and insufficient energy intake from the neurobiological factors that contribute to AN psychopathology. The study also used both frequentist and Bayesian approaches to increase confidence that claims about the absence of differences between weight-restored patients and healthy comparison subjects were appropriately qualified. Overall, the work of Seidel *et al.* (3) exemplifies how longitudinal neuroimaging designs can inform our understanding of both the pathophysiology of AN and changes associated with treatment.

Despite these strengths, it is difficult to interpret the functional significance of resting-state alterations without clear connections to behavioral or clinical measures (7). Seidel *et al.* (3) examined associations between resting-state fMRI metrics and several self-report measures of symptom severity, but changes in cognitive eating disorder symptoms were unrelated to changes in any resting-state fMRI metrics in any brain region. In addition, although the various metrics of resting-state fMRI that Seidel *et al.* tested can offer powerful insights into the organization of brain circuits, the results themselves showed mixed directionality. Depending on the region, patients with AN showed both lower and higher values of ReHo, degree centrality, VMHC, and fractional amplitude of low-frequency oscillations before treatment compared with healthy control individuals. It is not clear whether altered pretreatment activation and connectivity patterns were indicative of deficits or compensatory processes. Relative to task-based fMRI, resting-state fMRI protocols offer the advantage of

SEE CORRESPONDING ARTICLE ON PAGE 447

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minimizing participant burden. However, additional behavioral measures could enhance interpretability and help clarify how changes in resting-state fMRI metrics contribute to the pathophysiology of AN.

The findings of Seidel *et al.* (3) also raise new questions and highlight additional directions for future research. First, like Seidel *et al.*, most repeated-scan studies of AN have focused on adolescent samples in pivotal stages of neurodevelopment and neural plasticity. Future large and longitudinal studies are needed to determine whether adult patients' brains change with weight restoration in the same ways that adolescent patients' brains do. Second, long-term weight maintenance after short-term weight restoration can be one of the most challenging parts of recovery in AN (8), and it is unknown whether the normalization of brain structure and/or function after acute weight restoration predicts long-term maintenance of restored weight and full remission from AN. For example, in some brain regions, posttreatment hyperactivation or hypoactivation relative to controls, rather than activation that is equivalent to that of controls, could be needed to promote full recovery. Third, Seidel *et al.*'s results highlight questions about the time course of physiological and psychological changes in AN remission. The fact that widespread neural change after roughly 3 months of treatment was unrelated to cognitive symptom reduction, or, in most cases, the degree of weight gain, suggests that some brain metrics may be highly sensitive to realimentation. Future work could investigate whether this early neurobiological normalization after increased energy intake facilitates patients' abilities to engage with therapeutic interventions that target cognitive symptoms (10). Fourth, Seidel *et al.* found that not all resting-state metrics normalized among acutely weight-restored individuals. Just as other cognitive, behavioral, and biological measures may take up to a year or longer to normalize after maintaining weight restoration [e.g., body composition (9)], some neural alterations may take longer to resolve. Research that helps delineate the time course of neural change would further inform our understanding of the trajectory of recovery in AN. Information about the importance and beneficial brain-based effects of sustaining restored weight for specific amounts of time could be useful to clinicians and powerfully motivating to patients. Moreover, additional neuroimaging research that comprehensively characterizes alterations that persist after short-term weight restoration may help to identify important neural targets for relapse-prevention efforts.

In sum, Seidel *et al.*'s work (3) addresses important gaps in the literature by examining longitudinal changes in neural activity in AN after treatment. The authors show that many resting-state differences that distinguish adolescent patients with AN at the start of treatment from healthy control individuals are no longer detectable after partial weight restoration. We hope these important findings inspire future investigations that link changes in brain structure and function to changes in cognition, subjective experience, weight, and behavior in AN.

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