Experience, Perception, and Depression

Two articles in this issue of the *Journal* seem at first to anchor opposite ends of the depression research spectrum. One article uses reported symptoms and childhood history to examine the course of depression in almost 27,000 people while the other examines functional MRI data from a sample of 27. However, these articles do converge when it comes to the interaction of experience with our interpretation of experience in the genesis and maintenance of depression.

Nanni et al. (1) investigate the effect of childhood maltreatment on the course of depression using data from 16 large observational studies and 10 clinical trials. In the observational studies, which included community and clinical samples of people with depression, a recalled history of childhood maltreatment was associated with a twofold greater risk of chronic or recurrent depression. In the clinical trials, a recalled history of childhood maltreatment was associated with a 1.4-fold greater risk of poor response to depression treatment, including antidepressants or specific psychotherapies.

Observing this consistent association between a recalled history of childhood maltreatment and the outcome of depression, we might wonder about the direction of causality. One view focuses on the effect of experience, concluding that childhood maltreatment increases the long-term risk of depression. An alternative view focuses on the interpretation of experience, concluding that more severe or recurrent depression increases the likelihood that traumatic childhood experiences will be recalled.

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The studies in the meta-analysis by Nanni et al. (1) cannot clearly distinguish these two possibilities. Alternative research designs can, however, help clarify the direction of causality. In support of the hypothesis that childhood maltreatment causes subsequent depression, two prospective studies (2, 3) demonstrated an association between documented maltreatment and subsequent depression. In addition, two twin studies (4, 5) indicated that childhood maltreatment has a specific effect on the risk of adult depression beyond any genetic or shared familial effects. However, we also have evidence that childhood maltreatment is not often reported (6) and that recall is influenced by mood state (7). This evidence suggests a recursive relationship: childhood maltreatment increases the risk for adult depression, which may then increase the likelihood that childhood maltreatment will be recalled. Expressed in more general terms, negative experiences increase the risk of depression, but depression can also increase the recall of negative experiences.

The experimental research described by Robinson et al. in this issue (8) is relevant to the effect of mood on the interpretation of negative and positive events. The authors used a reversal-learning task to assess sensitivity to both positive experiences (reward) and negative experiences (punishment) in people with and without a current diagnosis of major depressive disorder. As indicated by task performance, depression was associated with impaired response to reward but not with heightened sensitivity to punishment or negative reinforcement. This diminished behavioral response to reward was

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accompanied by an attenuated hemodynamic response (as measured by functional MRI) in the anteroventral striatum.

As Nanni et al. (1) point out, the association between childhood maltreatment and poorer prognosis of depression does not necessarily imply that treatment for depression is less valuable or necessary. Whether or not a history of childhood trauma argues for or against the benefit of depression treatment can only be answered with data comparing treatment with no treatment (or placebo or inactive treatment). This distinction is most clearly illustrated by research on the severity of depression and the outcome of antidepressant treatment (9). Not surprisingly, severity of depression predicts poorer long-term outcome, and more severe depression at treatment onset predicts poorer treatment outcome. However, pretreatment severity also predicts greater effectiveness of antidepressant treatment when compared with placebo. There is no conflict between these two findings. An individual characteristic can predict poor outcomes with treatment and even poorer outcomes without treatment, resulting in more robust net benefits of treatment.

At this time, it is unclear whether a history of childhood maltreatment will affect the selection of a specific depression therapy. In one study of outpatients with chronic depression, a history of childhood trauma predicted more favorable response to a specific psychotherapy (cognitive behavioral analysis system of psychotherapy) than to nefazodone (10). This finding has not been replicated, and it is not clear whether it might generalize to other medications or other types of psychotherapy. We have no evidence suggesting that a history of childhood trauma is useful in selecting from among different types of psychotherapy or different antidepressants (11).

The findings of Robinson et al. (8) do raise interesting questions about the aims and content of psychotherapy for depression. Established psychotherapies for depression typically include a mix of interventions that reduce the depressogenic impact of negative experiences (whether remote or immediate) and augment the antidepressant effect of positive experiences. If the cognitive biases of depression reside more in a diminished response to a positive experience or reward and less in an exaggerated response to a negative experience or punishment, this might have implications for developing more narrowly targeted psychotherapy. It is interesting to consider the findings of Robinson et al. alongside the clinical finding that behavioral activation (a depression-specific psychotherapy focused almost exclusively on increasing exposure to positive events) may be more effective in the treatment of severe depression than is the less specific cognitive therapy approach (12).

When considering the clinical implications of these two lines of research, however, we must remember that greater clarity about the etiology or pathophysiology of depression may not directly translate into more effective or more specific therapy. The findings of Nanni et al. (1) on the etiologic role of childhood trauma might suggest that the most effective psychotherapy would focus on reducing the enduring effects of that traumatic experience. But the findings of Robinson et al. (8) might suggest the opposite approach, focusing instead on increasing exposure to and the impact of positive experiences. Etiology or pathophysiology cannot settle questions of therapy, but they can suggest specific hypotheses to guide the development and testing of theoretically informed treatments.

Taken together, these two articles illustrate the combination of epidemiologic, clinical, and preclinical research that is needed to advance our treatment of depression. The available treatments for depression are, on average, only modestly effective. And our ability to improve those odds by matching patients with treatments is, at this time, quite poor. Scientific progress in developing more effective treatments and in matching treatments to individuals will require a clearer understanding of specific etiologic factors and pathophysiologic processes. Epidemiologic studies of 27,000 people and imaging studies of 27 people can both contribute to that understanding.

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