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Experience, Perception, and Depression

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Two articles in this issue of the journal seem at first to anchor opposite ends of the depression research spectrum. One used reported symptoms and childhood history to examine course of depression in almost 27,000 people while the other considered functional MRI data from a sample of 27. But these articles do converge on questions regarding the interaction of experience with our interpretation of experience in the genesis and maintenance of depression.

Danese et al. examined data from 16 large observational studies and 10 treatment trials regarding the influence of childhood maltreatment on the course of depression. In observational studies, including both community and clinical samples of people with depression, a recalled history of childhood maltreatment was associated with a two-fold greater risk of depression being chronic or recurrent. In clinical trials, a recalled history of childhood maltreatment was associated with a 1.4-fold greater risk of poor response to depression treatment – including treatment with a range of antidepressants or specific psychotherapies.

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

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

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

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

As Danese et al. point out, the association between childhood maltreatment and poorer prognosis of depression does not necessarily imply that treatment for depression is less valuable or less necessary. Whether or not a history of childhood trauma argues for or against the benefit of depression can only be answered with data comparing treatment to no treatment (or to some placebo or inactive treatment). This distinction is most clearly illustrated by research regarding severity of depression and outcomes of antidepressant treatment (7). Not surprisingly, severity of depression predicts poorer long-term outcome. And more severe depression at time of starting treatment consistently predicts a poorer treatment outcome. But pre-treatment severity of depression also predicts a greater benefit of antidepressant treatment compared to placebo. There is no conflict between these two findings. An individual characteristic can predict poor outcomes with treatment and even poorer outcomes without treatment, with a net result that the benefit of treatment is more robust.

At this time, it is also unclear whether a history of childhood maltreatment has implications for selection of a specific depression therapy. Among 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 (8). This finding has not been replicated, and it is not clear if 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 antidepressant medications (9).

The findings of Robinson et al. do raise interesting questions regarding the aims and content of psychotherapy for depression. Established psychotherapies for depression typically include a mix of interventions to 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 lie more in a diminished response to positive experience or reward and less in an exaggerated response to negative experience or punishment, this might have implications for development of 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 (10).

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

Taken together, these two articles also illustrate the combination of epidemiologic, clinical, and pre-clinical research needed to advance treatment of depression. Our 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 the development of more effective treatments and in the matching of treatments to individuals will require a clearer understanding of specific etiologic factors and pathophysiologic processes. Epidemiologic studies of 27,000 and imaging studies of 27 can both contribute to that understanding.

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