Commentary

Keep the Change: Embracing Variability as a Path to Richer Theoretical Models of Borderline Personality Disorder

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In a comedy sketch for *MADtv*, Bob Newhart, playing a psychiatrist, offers a client definitive treatment for claustrophobia: "It'll take three minutes and involve two words," he says. The client nervously agrees to the plan. Newhart prepares to begin the session, briefly hears about the clinical problem, then shouts "STOP IT!"

The scene is funny for its shock value, flying in the face of the years of hard work many have committed to traditional talk treatments. However, the joke also appeals to a well-founded fear that our theories and treatments for serious mental illness may lack important levels of understanding. Relief is now coming from efforts in biological psychiatry to describe and test mechanistic models that fully engage and integrate data from patient histories, behavior, and neural signals. This approach pushes beyond patient versus healthy control subject comparisons, asking what patients have in common across diagnostic lines, and how development and recovery occur.

Borderline personality disorder (BPD) has lagged behind other psychopathologies in biologically grounded mechanistic models and well-powered research studies. BPD is prevalent (ranging from 2% to 6% in the United States); patients with BPD are highly distressed by their symptoms, are high utilizers of health care, and have an elevated risk of suicide (1,2). There is no medication for BPD that has been approved by the U.S. Food and Drug Administration, and the evidence-based psychotherapies have been difficult to scale for the large numbers who need them (2). Despite the clear need for specific treatment targets, we remain murky on the pathways in development that lead to BPD, the branch points for BPD versus other psychopathology, and the circuit and computational bases of the disorder. Many people with BPD do experience significant and sustained remission and recovery (3), and yet we know little about the factors that promote/impede recovery. This knowledge gap is starting to be filled by researchers testing clearly articulated models of pathology. We have a strong history of psychology and epidemiology in BPD; new studies using biological approaches can engage these data to draft and test clinically relevant, empirically sound frameworks.

In this issue of *Biological Psychiatry*, Bilek *et al.* (4) take this approach, linking levels of analysis to test a model of social dysregulation in BPD. Healthy control subjects have a strong amygdala response to looking at negative (e.g., fearful, angry) faces, and this response rapidly decreases as they continue to look at the faces. People with BPD are known to have high amygdala activity at rest (5). Bilek *et al.* (4) report that consistent with previous work, amygdala activity in BPD does not decrease as negative faces are repeated over time. They offer a well-powered replication of this habituation deficit, confirming this interesting finding. They then extend the previous work by testing how this neural mechanism fits into a model of the life history of BPD. Early-life trauma (especially neglect) is perhaps the best-described risk factor for BPD; Bilek *et al.* (4) test the link between adverse childhood experiences and decreased amygdala habituation. Across all participants they found that the adverse childhood experience score, and not a dimensional BPD scale score, explained the observed variance in amygdala habituation.

This study extends our thinking about aberrant learning in BPD into questions of its developmental origins and the specificity of deficits in relation to BPD, in particular versus trauma-associated disorders in general. Future work might extend this dimensional approach by considering assessments of current posttraumatic and affective symptoms. Also, in BPD, as in many other settings, a reduction in clinical symptom count does not correlate directly with a return to meaningful function (3). Our patients measure treatment effects by their ability to have satisfying day-to-day lives with occupations and relationships. Bilek *et al.* have gone further than most by including a group with remitted BPD in their sample. We would do well to follow their lead in this area. Models that test the biological substrates associated with symptom improvement and functional recovery will help us to pinpoint targets for therapeutic intervention.

Models of BPD should also focus on the variability of clinical symptoms and how that high-frequency change may be recapitulated and supported by candidate mechanisms. Bilek *et al.* (4) point out that affective lability is a core symptom of BPD. Indeed, clinical studies have defined changeable mood as the most sensitive single-item assessment for BPD (6). Frequent changes in the intensity of other BPD symptoms (e.g., trust and impulsivity) have also been well described in the clinical literature, especially in the wake of interpersonal stressors (2). The habituation task considers change in mean amygdala signal over several task blocks and, interestingly, finds less change in patients with BPD than in healthy control subjects. This dissociation between the clinical variability that is a defining feature of BPD and the aberrant stability of laboratory measures of learning in BPD has also been observed in other settings. We have identified blunted response to volatile versus stable reinforcement schedules for both social and nonsocial cues (7). Computational modeling of interactive

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social data has also revealed rigidity in BPD responses to shifting social cues (8). Hula *et al.* (8) modeled social behavior in a multiround trust game in terms of hierarchical organization of learning. Their results suggest that people with BPD have aberrant prior expectations of partner behavior. This finding offers a clue to how early adversity may be linked to aberrant neural signals. People with early adversity have learned in childhood to expect the environment to be unpredictable. Given this expectation, they may be less likely to change when the environment changes. In interpersonal interactions, this prior expectation means that people with BPD have a blunted response to social volatility when it occurs. They persist with stable behavior despite environmental cues that would lead others to change their behavior. In social settings, this could lead to interpersonal ruptures, as a social partner's repeated bids to communicate problems may not be detected, and opportunities to adjust behavior are missed. This framing of BPD in terms of rigid response to environmental change coheres with Bilek *et al.*'s finding of rigid response to repeated negative faces (4) but complicates the traditional clinical model.

Future studies should work out both the details of aberrant learning in BPD and the ways that aberrant learning may fit into the mechanisms the develop and maintain clinical symptoms. To identify the level(s) of disruption in learning, experiments can test the relative contributions of prior expectations for volatility (our hypothesized disruption), prediction error amplitude and precision, and interaction of these parameters with high arousal in response to negative social cues. Getting to meaningful answers will depend on continued attention to variability, including responses to changing cue valence and reward probability, and the frequency and amplitude of changes in clinical symptoms. One good example of this approach in BPD in a recent neurofeedback trial is the measurement of variance in mood, rather than mean, as a primary outcome measure. Zaehringer *et al.* (9) collected hourly mood surveys with ecologic momentary assessment and defined variance between surveys as a real-world measure of affective lability. We can also attend to variance in neural signals—for example, the temporal dynamics of the amygdala signal. Previous work testing habituation in a small BPD sample suggests that the between-group difference is actually greater with more time: Denny *et al.* (10) found sensitization to negative faces in a multiday paradigm. Efforts to measure variability with greater temporal resolution over longer periods of time and in both laboratory and naturalistic settings will be important going forward.

We are poised to significantly improve our understanding and treatment of mental illness by committing to the clear articulation of testable models that connect clinical observations to experimental results through data-informed theoretical frameworks. Future work in the biological underpinnings of BPD and related disorders will do well to follow the lead of Bilek *et al.* (4) in building experiments to test predictions that link life experiences through brain function to symptoms. Furthermore, focus on adverse childhood experiences and on the variability of symptoms and biomarkers is relevant beyond BPD, especially in posttraumatic stress disorder and bipolar disorder. As we build and elaborate models of BPD and other psychopathology, it will be particularly important to consider the role of variability in experimental measures and how it may relate to the core problem of symptom fluctuation.

Article Information

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