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Commentary

When Brains Get Left Behind: Borderline Personality and Social Rejection Inscribed in the Rostromedial Frontal Cortex

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"Who among us…" doesn't mind rejection? Feeling social rejection or exclusion is painful and distressing, especially when it is dispatched by someone we depend on. In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Fertuck *et al.* (1) suggest that the psychological significance of social rejection can be situated in the wider context of Maslow's Theory of the Hierarchy of Needs (2). This enduring psychological model posits 4 fundamental social needs that motivate the range of human behavior: belonging, self-esteem, control, and meaningful existence. Social exclusion is seen as a direct threat to these needs, often leading to the subjective experience of rejection distress. In moderation, this distress can be considered adaptive, as it signals to those important others that the social bond needs affirmation or repair. Indeed, overt expressions of distress and behavioral consequences in response to ruptures of the social bond are readily observed in most highly social mammals [dog lovers see (3)]. When humans experience this response in an unstable manner, however, as noted below, considerable hazardous behavior can ensue, in ways that can be hard to predict and even harder to mitigate, and this is one of our greatest concerns as clinicians.

We have learned in the modern era of cognitive neuroscience that responses to social rejection relate to the brain's sensitive detection that things are not right, that what we have received from our environment has not matched our goals. Thus, regions in the medial frontal cortex relating to social rejection light up (as revealed during functional magnetic resonance imaging) as they do when we make errors, have expectations violated, or feel somatic pain (4,5). Luckily, much of the time (surely not always) the brakes get applied automatically; the brain's tendency for operating homeostasis kicks in, allowing us to subvocalize "I can deal with this," and we (or our observers) experience that as emotion regulation. Unfortunately for some of us, the experience of rejection has a destabilizing, chaos-generating effect, and this can lead to trouble for both ourselves and those around us. And if rejection-related trouble is a regular feature of one's psychological functioning, that individual may receive a psychiatric diagnosis of borderline personality disorder (BPD). As Fertuck *et al.* (1) note, for persons with BPD, this can often lead to high-risk urges and behaviors, including self-harm, suicide attempts, and completed suicide (7). These responses to rejection are a hallmark of BPD as much as any other clinical feature, and yet we have had only a foggy idea about how this happens in the brain.

Until now. Fertuck *et al.* (1) describe how social rejection is inscribed in the brains of individuals with BPD and perhaps why this is so destabilizing for cognition, affect, and behavior. Using a popular experimental computer task called Cyberball, where visual characters toss a ball back and forth, a brain can be scanned while its owner experiences inclusion or exclusion from the game. Previous work has established that this experience of exclusion is associated with neural activation in medial frontal cortical regions that overlap substantially with those that mediate the processing of errors, violations of rules or expectations, and somatic pain (4–6). In the present study, Fertuck *et al.* refined the task and image analytic procedures to obviate a few unresolved issues in the BPD clinical research literature using this task, such as the interpretive ambiguity introduced with block design analyses comparing exclusion versus inclusion, and the lack of conditions with graded degrees of exclusion that might reveal how brain-regional blood oxygen level–dependent activation varies with parametric changes in this key task-related parameter. They studied unmedicated, clinically stable adult females with BPD, each lacking clinical features such as a history of psychotic disorders, current major depressive episode, current substance use disorder, or a suicide attempt within the last 6 months, which represent important comorbid conditions or potentially confounding factors that might limit the interpretability of the findings. The investigators compared their brain responses with functional magnetic resonance imaging during Cyberball viewing to a matched participant group lacking BPD or other psychiatric disorders. All participants were told that they would play a computerized ball-tossing game over a network with 2 other players (introduced to participants with the presence of 2 adult male confederates), while their actual play was against a covert computer program. Self-reported rejection distress associated with each condition (measured with the self-report need-threat scale, derived from the Maslow model) was entered into the regression model as a predictor of blood oxygen level–dependent signal change in each voxel, along with task event regressors, and task event–related signal change was evaluated within and between groups, including as modulated by the degree of rejection distress. The investigators found that neural responses to exclusion were not significantly different between groups; however, as self-reported rejection distress increased, the rostro-medial prefrontal cortex (rmPFC) response to exclusion events decreased in the BPD group yet did not decrease in control subjects. Among those with BPD, stronger decreases in the rmPFC

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response with rejection distress was associated with higher trait rejection expectation (measured with the Rejection Sensitivity Questionnaire). Aside from brain responses to these provocations, self-reported rejection distress was higher in the BPD group than the comparison group with every degree of rejection and was comparable between groups only in the condition with the highest level of subject inclusion.

As the authors have noted elsewhere, the rmPFC is part of the so-called default mode network, a large-scale, distributed network primarily located in midline neocortical structures (8). The default mode network is involved in varied psychological phenomena such as internally directed, self-referential, autobiographical, and theory of mind processes, and it is also curiously active when our minds are wandering, something akin to the free-association process elicited in classical psychoanalysis. The default mode network is engaged especially with information processing focused on the relationship between self and others and on episodic past and future events. Thus, it makes sense that this brain region would be activated with social rejection or exclusion, and as a common feature of many medial frontal cortical sectors in humans, to signal to other frontal regions that effort should be brought online or adjusted to resolve the mismatch and the subjective distress that goes along with it. The apparent inability of persons with BPD to sustain rmPFC activation in the face of heightened rejection distress suggests a locus of brain disturbance that may induce a cascade of adverse changes in cognition, affect, and finally overt behavior. In other words, this may be a candidate flashpoint in the brain for the hazardous behavior that serves as the most serious outcome in this condition. Future work to follow on these findings should include further cognitive neuroscience investigation to characterize the downstream effects of failing rmPFC activity on the brain circuits responsible for the generation and regulation of cognition, affect, and behavior. This in turn may suggest a discrete neural target for potentially varied interventions to bolster the patient's neural and psychological tolerance for rejection distress. These interventions could be biomedical (pharmaceuticals, device-based treatments) or psychosocial in nature. Attendant to one of the few genuine, time-tested rules in mental health, they will probably be best integrated in a multidisciplinary suite of diverse interventions (9) to best advance the field toward improved, optimized clinical outcomes for patients.

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Article Information

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