

The Social Brain, Stress, and Psychopathology

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Social discrimination can have pervasive effects on human health and performance. This notion is a major thread binding together findings in social psychology, health psychology, and epidemiology. From a psychiatric perspective, it may also be critical for a more



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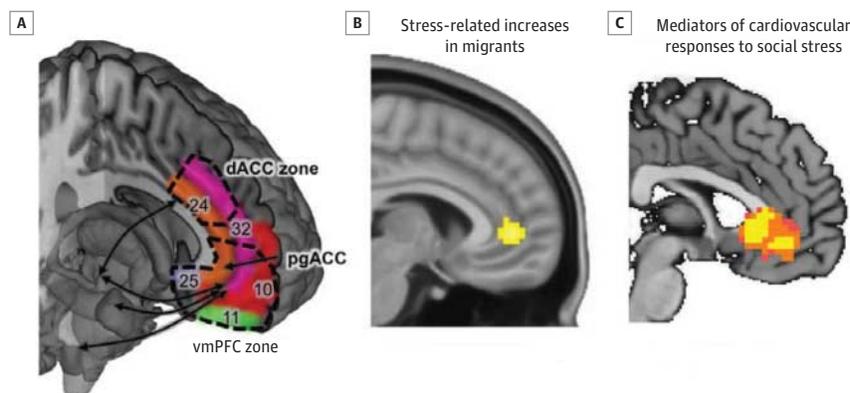
complete etiological picture of psychopathology. Social influences can be subtle but powerful. For example, priming racial identity can influence physiological measures of threat and performance on benchmark tests like the Scholastic Aptitude Test.^{1,2} As emphasized in the article by Akdeniz et al,³ ethnic minority immigrants are at greater risk than their native counterparts for schizophrenia,⁴ and this risk may extend to other mental and physical health disorders.⁵ To fully understand, prevent, and treat schizophrenia and other brain disorders, we need to understand the relationships between social context, stress, and brain health that cut across diverse psychiatric and neurological conditions.

Perennial questions in the study of virtually every major disorder are what confers risk for illness and how can those risks be minimized. Even in disorders that are highly heritable such as schizophrenia, there is a long history of research on social and environmental factors,⁶ and the relationship between genetic risk and schizophrenia onset may be highly dependent on the social and physical environment. However, research has now shifted away from early theories about parenting styles and toward biological explanations.

As demonstrated by Akdeniz and colleagues, social and biological explanations are not an either/or proposition. Akdeniz and colleagues used functional magnetic resonance imaging to probe social stress-related activity in native German individuals and immigrants by asking them to perform a math task under social-evaluative threat—observation by authority figures coupled with negative feedback about performance. Immigrants showed stronger stress responses than their German counterparts in the pregenual anterior cingulate cortex, a part of the ventromedial prefrontal cortex (vmPFC) implicated in the generation and regulation of social threat and other emotional states. The vmPFC comprises several subregions (**Figure**) that regulate brainstem governors of physiological responses to threat.^{7,8} Thus, the brain findings suggest a link between migrant status—a demographic variable typically studied in sociological contexts—and biological responsibility to social threat.

Studies of demographic variables are inherently observational, and inevitably questions arise. Is it really immigrant status that is driving the effects? Is it really social stress responses that are different in immigrants, or perhaps differences in basic task performance or the neurovascular responses that give rise to functional magnetic resonance imaging signals? One of the unique aspects of the study by Akdeniz and colleagues is that it provides several informative controls. They controlled for experimental comfort and related psychological context effects by comparing Turkish immigrants tested by Ger-

Figure. Regions in the Ventromedial Prefrontal Cortex and Stress-Related Activation



A, The pregenual anterior cingulate cortex (pgACC) is part of a functional ventromedial prefrontal cortex (vmPFC) zone that encompasses multiple cytoarchitectonic areas (colored and marked with Brodmann area numbers). The vmPFC is a core part of the default-mode network, whose activity is high at rest and is reduced during the performance of many cognitive tasks but

increases above baseline in response to evaluative threat, self-referential processing, and other emotional challenges. dACC indicates dorsal anterior cingulate cortex. B, Relative activity increases with evaluative stress in migrants in the study by Akdeniz et al.³ C, Activity mediating the effects of evaluative stress on cardiovascular responses is shown.⁷

man experimenters and German natives tested by Turkish experimenters. The vmPFC stress effect was largest in the immigrants even when the participant-experimenter ethnicity match was equated. In addition, they used several control tasks, including basic performance of a challenging cognitive task, and found immigrant vs native differences only in the social stress challenge.

A broader implication of the study is that increased acute threat responsivity at the brain level—particularly in vmPFC-subcortical threat appraisal circuits—may constitute a form of load on the organism.⁹ That load may accumulate over time to affect the integrity of brain-body regulatory systems and increase risk for multiple types of brain disorders. Indeed, the vmPFC has been the focus of intense interest across multiple psychiatric disorders, including depression, anxiety disorders and posttraumatic stress, and substance use disorders.¹⁰ For stress researchers, it is visceromotor cortex; for decision-making researchers, it is a focal point for the computation of value; for memory researchers, it is central to autobiographical memory and prospective thought; for social neuroscientists, it is central to the notion of self (eg, see the article by Roy et al¹¹). One way of integrating these ideas is that the vmPFC may be central for the representation of schemas or situations, which are representations of the self-in-context that can engage a variety of emotional responses.¹¹ A bias in vmPFC-subcortical circuits to perceive many situations as threatening may underlie multiple forms of psychopathology and confer risk for other, often comorbid diseases as well.

How the relevant brain systems should be probed is an active area of interest and debate. Many kinds of affective challenges are now routinely used to study psychopathology in the magnetic resonance imaging environment¹²—from viewing emotional facial expressions and standardized images or sounds to more ecological stressors such as that used by Akdeniz and colleagues—and it is an open question that will be the most useful for characterizing resilience vs disability and disease risk. That the stressor is social in this case may be crucial, as social threats in particular may involve the vmPFC in both the generation and regulation of negative emotional responses. Whereas subcortical circuits (eg, amygdala-brainstem pathways) are in many cases sufficient for basic affective responses and affective learning, the vmPFC may be required to add

emotional “color” to everyday interactions in meaning-imbued social contexts.¹¹ Hence, tasks that require appraisals of abstract events (eg, being judged unfavorably by an expert) may be particularly informative as probes of persistent threat appraisals to situations that are common in modern life.

By showing that migrants show increased stress responsivity, the study by Akdeniz and colleagues lays a foundation for linking migrant status and brain-body stress responses to psychopathology in larger population-based studies. The mediators of the increased disease risk conferred by migrant status are unknown and understudied, and the keys may lie either within the brain itself or in systems that involve brain-body interactions. For example, migrants show elevated levels of physiological markers linked to inflammation and metabolic dysregulation.^{5,13} Stress-linked inflammation, compounded over years, might contribute to poor vascular and brain health and ultimately to increased risk for schizophrenia, neurodegeneration, and other brain health disorders. Research linking emotion- and stress-related brain responses to inflammation and disease is just beginning to emerge, but the results are suggestive. In the study by Akdeniz and colleagues, perceived discrimination was linked to greater vmPFC activity and greater coupling between the vmPFC and the dorsal anterior cingulate cortex, an area linked to prothreat responses across many paradigms. In a recent study of emotion and inflammation,¹⁴ increased dorsal anterior cingulate cortex activity during emotion was linked to increased levels of the proinflammatory cytokine interleukin 6, which mediated a relationship with physiological measures of cardiovascular disease risk.

A final open question concerns how to intervene to mitigate disease risk. If social threat appraisals are an important factor, this may be good news; physiological stress responses that depend strongly on psychological construals may be more amenable to psychological interventions than their more hard-wired affective counterparts. In the study by Akdeniz and colleagues, perceived discrimination mediated the effects of immigrant status on vmPFC responses to stress. Therapeutic approaches that attempt to modify perceptions psychologically may be an important complement to pharmacological interventions, and perhaps there are combined psychological and pharmacological treatments that work better than either type of approach alone.

ARTICLE INFORMATION

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Published Online: April 16, 2014.
doi:10.1001/jamapsychiatry.2014.288.

Conflict of Interest Disclosures: None reported.

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