Biological Psychiatry: Celebrating 50 Years

The Uncinate Fasciculus in Anxiety Disorders: A Potential Treatment Target?

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Anxiety disorders, the most prevalent class of pediatric mental disorders, are viewed as conditions of abnormal threat processing. The circuitry engaged by threats in a range of mammalian species encompasses the amygdala and its connections to the ventral prefrontal cortex, insula, and hippocampus. Thus, this circuitry can be targeted in translational research. Cross-species translational research is crucial for psychiatry given the inaccessibility of the human brain to many research techniques. While considerable research on mammals' threat responses study the function of gray matter regions, recent data suggest the importance of also examining white matter microstructure (1). This raises a particular set of questions about the role of white matter microstructure in anxiety and threat processing, which are ideally suited for cross-species research.

In this issue of *Biological Psychiatry*, Tromp *et al.* (2) conduct such work in rhesus macaques by examining the microstructure of the main fiber tract connecting the amygdala and the ventral prefrontal cortex: the uncinate fasciculus (UF). In 581 monkeys, the authors assessed the heritability of UF microstructure and its relationship to anxious temperament. Consistent with a previous study in humans (3), key findings occurred only in males. Specifically, Tromp *et al.* (2) found a negative association in males between anxious temperament and fractional anisotropy, a metric that is associated with directional coherence, axonal density, and axonal diameter (4). Moreover, the authors showed that environmental factors explain UF microstructure variability across monkeys. Overall, the work implicates aberrant UF microstructure in sex-specific mechanisms of juvenile anxiety, hints at relevance for personalized medicine, and raises questions concerning particular psychosocial factors that connect environmental experiences, the risk for anxiety, and white matter microstructure.

Aside from these intriguing findings, several aspects regarding the design and methods used in this study are particularly noteworthy. First, the authors take an unusual approach by extending their initial clinical findings (3) to animal research. In this concrete example, this led to findings that could be used to support invasive studies in monkeys to illuminate mechanisms producing brain–behavior relationships first observed in patients (e.g., UF fractional anisotropy). Notably, this research strategy contrasts with often-used approaches that begin by examining processes in animals to inform parallel studies in humans. When searching for clinical insights, advantages may follow from the approach used by Tromp *et al.* (2). Future research might compare the speed with which clinical breakthroughs follow from the two approaches. A second unique aspect of the work concerns the breadth of integration across different levels of scale (i.e., behavior, brain, and genes). The authors' work links UF microstructure to environments more than genes. This insight can guide future research on environmental factors, including studies identifying risk factors and novel targets for psychosocial interventions. Finally, the authors revealed some level of specificity for UF findings by failing to observe relationships between anxious temperament and the microstructure of other white matter tracts. In sum, this exciting work substantially extends existing knowledge regarding the pathophysiology of anxiety.

Like most novel discoveries, this study raises many questions to be pursued in future work. One set of questions concerns the nature of relations among UF microstructure, anxious temperament, and other associated behaviors. In children, early anxiety is a strong predictor of later-life mood disorders (5) and associated dysfunction in both reward-responding and frontoamygdala function (6). So far, mood–anxiety comorbidity confounds attempts to reliably dissociate their distinct neurobiological signatures. In this context, it is noteworthy that UF microstructure has been as strongly or even more strongly implicated in the pathophysiology of mood disorders compared with the pathophysiology of anxiety disorders. Thus, it seems possible that abnormal UF microstructure is specific for neither anxiety nor mood symptoms but relates to a common latent factor such as negative affectivity (7). This view is supported by studies linking aberrant UF microstructure to impaired emotion regulation (8) that is characteristic of anxiety and mood disorders. This raises questions about the range of behaviors across development related to the UF microstructure in the macaque, which might provide unique insights into the etiology of anxiety and mood disorders.

A second important question concerns the cellular mechanisms that underlie alterations measured with diffusion tensor imaging. As Tromp *et al.* (2) lay out, their main finding is with fractional anisotropy, which is influenced by variations in fiber organization, axonal density, and myelination. Of these factors, myelination appears particularly interesting because evidence documents its plastic response to experiences throughout the lifespan (1), and thus it naturally lends itself as a treatment target. However, little is known about the particular types of experiences that drive myelin plasticity. Tromp *et al.* (2) discuss several. For example, they propose that exposure therapy, the first-line treatment for anxiety disorders, might specifically target UF microstructure (Figure 1). From a neuroscience perspective, exposure therapy is thought to exert its effects through medial prefrontal inhibition of the amygdala's response to fear-provoking stimuli (9). During this process, myelination of axons in the UF that transmit inhibitory signals from the medial prefrontal cortex to the amygdala might increase. It might even be possible to facilitate such experience-

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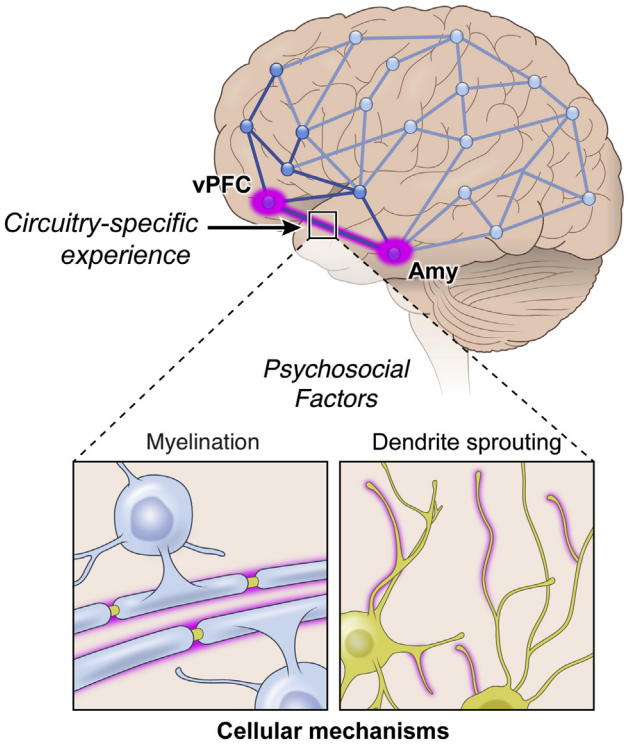

Figure 1. Understanding uncinate fasciculus plasticity from different levels of scale. Experiences that specifically engage frontoamygdalar circuitry are thought to change the microstructure of the uncinate fasciculus through changes in myelination but possibly also other cellular mechanisms, such as dendrite sprouting. This process is potentially moderated by psychosocial factors, such as aerobic exercise, healthy sleep patterns, or social stress. The brain is intrinsically organized in networks, and therefore alterations in the uncinate fasciculus microstructure are likely to affect larger emotion-regulation and decision-making networks. Amy, amygdala; vPFC, ventral prefrontal cortex.

triggered myelination through aerobic exercise and healthy sleep patterns, which appear to enhance the plastic potential of myelin throughout the brain (Figure 1). If proven correct, this could not only guide the development of psychosocial treatments but also indicate a new target for pharmacological interventions in anxiety disorders.

To leverage myelin plasticity as a target for psychosocial interventions in youth, however, it will be essential to determine how experience-evoked myelination interacts with developmental myelination; a long-lasting process that in the case of the UF continues until the third decade of life (10). In addition, it will be important to elucidate whether experiences only increase or also decrease myelination. Finally, because the brain is organized in functional networks, alterations in the myelination of specific tracts such as the UF might affect not only the interaction between two gray matter regions such as the amygdala and the medial prefrontal cortex. It can be expected that they also impact more extensive networks (Figure 1), and this might influence a multitude of neuropsychological processes and symptom dimensions. To adequately address these questions, future studies must integrate different sources of information, such as diffusion tensor imaging results, sequences sensitive to myelin, and assessments of brain function in a longitudinal design.

In closing, Tromp *et al.* (2) provide an example for the application of diffusion tensor imaging in elucidating the brain-based mechanisms of anxiety, and they call for a better integration between neuroimaging and psychosocial research to better characterize environmental factors that influence individual differences in brain circuits. Finally, the study allows for the opportunity to highlight several aspects of white matter plasticity in the context of psychiatry and neuroscience, which will hopefully benefit future research in this new area.

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Article Information

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