Neuroimaging of Externalizing Behaviors and Borderline Traits

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Research in externalizing disorders and borderline personality disorders (BPD) is at its start. A common pathway for these disorders is expressed in developmental models that focus on impulsive traits. These impulsive traits may develop into ordinary personality traits, to severe derangement, or abnormality of function (i.e., BPD and externalizing disorders) under influence by both internal factors (i.e., poor emotional regulation skills, lower IQ) and external factors (i.e., family dynamics, early-life adversity, peer influences, and socialization) (1). So far BPD research has mainly focused on the psychological aspects of the disorder. Several studies reported that an early-life trauma (e.g., childhood abuse or maternal separation), genes, neurobiological alterations, or a combination of these may play a crucial role in the development of BPD (2,3). Nevertheless, pathogenetic mechanisms are still under debate, and previous studies had many methodologic shortcomings.

What we know is that there are functional neurobiological disturbances in BPD (2,4), and a number of BPD neuroimaging studies have reported reductions and functional abnormalities in regions involved in the regulation of stress responses, emotion, and affect, including the hippocampus, the orbitofrontal cortex, and the amygdala (5). Interestingly damage to the orbitofrontal cortex also leads to externalizing behavior (6), with pronounced impairments seen when injury occurs during childhood (7). Moreover, functional magnetic resonance imaging studies in attention-deficit/hyperactivity disorder showed that functional connectivity in affective networks is altered in patients with that disorder compared with healthy control subjects (8).

Unfortunately, previous studies included small samples and were cross-sectional. There is also the question of whether the studies used appropriate methods of detection of psychiatric comorbidity and took into account heterogeneity of treatment methods used. Because of these limitations, the underlying biological explanation of early signs of personality disorders such as externalizing behaviors and borderline traits are far from clear.

Recently, several attempts have been made to bridge the gap between childhood and adult psychiatric disorders, for example, between overlapping characteristics of externalizing disorders and BPD. Although there are shortcomings with previous studies in the area of early biological signs of BPD, one of the most interesting studies has recently been carried out by Maier-Hein *et al.* (9), who investigated 20 adolescent patients with a DSM-IV-defined diagnosis of BPD, 20 patients with mixed psychiatric diagnoses who did not fulfill more than one of the nine DSM-IV diagnostic criteria of BPD, and 20 healthy controls with no current psychiatric disorder (9). They aimed to find diffusion abnormalities in limbic frontal fiber bundles like the fornix, cingulum, and uncinate fasciculus that are involved in emotion regulation using diffusion tensor imaging. Tractography can be used to explore specific fiber bundles in the brain. Using this technique, lower fractional anisotropy, which is a measure of diffusivity along the fiber tracts relative to perpendicular directions, was revealed in the fornix in BPD compared with both control groups. In addition, authors tested whether there were also abnormalities in diffusion measures in other white matter brain tracts using a so-called tract-based whole-brain analysis implemented in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fsl4.0/tbss/index). In this tract-based whole-brain analysis, BPD patients showed no significant reduction in fractional anisotropy compared with patients with mixed psychiatric disorders, except for one isolated region within the right superior fronto-occipital fasciculus. An increased radial diffusivity (diffusivity perpendicular to the main diffusion direction) was found bilaterally in parts of the inferior fronto-occipital fasciculus with projections to the orbitofrontal cortex, the internal capsule, the superior longitudinal fasciculus, and the superior fronto-occipital fasciculus when comparing BPD patients with mixed psychiatric disorders.

In summary, differences in the fornix and the inferior and superior fronto-occipital fasciculi suggest a widespread alteration within the brain of patients with BPD compared with control subjects (9). This study is to be complimented for including a clinical control group. Unfortunately, the fornix and uncinate fasciculus was not represented well in their tract-based whole-brain analysis in contrast to other diffusion tensor imaging studies using a higher number of gradient directions, so it is not possible to repeat this finding with the whole-brain method. Thus far, the relevance of diffusion changes in brain fiber tracts is unclear, and basic experimental work in this area is required. Despite these limitations, the approach of starting at early stages of the disease is a step forward, and longitudinal designs to track individuals from adolescence or even childhood to adulthood might be promising in the future.

In the second study, Ameis *et al.* used a large longitudinal sample of 297 children and adolescents from the National Institutes of Health Magnetic Resonance Imaging Study of Normal Brain Development to examine the relationship between cortical thickness and cortico-amygdalar networks and externalizing behaviors (10). Participants were recruited at six study centers across the United States. Cognitive, neuropsychological, and behavioral testing and magnetic resonance imaging (MRI) brain scanning were performed at 2-year intervals for up to three research study visits. Thus, 517 MRI scans and Childhood Behavior Checklist (CBCL) scores were obtained. Externalizing behaviors were characterized at each study visit using the CBCL. Structural magnetic resonance images were acquired on 1.5-Tesla scanners, and MRI data were analyzed at the Montreal Neurological Institute (10).

Significant negative correlations between CBCL externalizing scores and cortical thickness were found in the left posteromedial orbitofrontal cortex, right retrosplenial cingulate, and the right medial temporal cortex. These negative correlations remained

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significant after correction for attention problems. Thus, this large study in healthy children could identify that cortical thickness in orbitofrontal, cingulate, and medial temporal cortices is associated with externalizing behaviors in healthy children. The orbitofrontal cortex, retrosplenial cingulate, and medial temporal cortex are brain regions important for decision making and behavioral regulation, and thus these findings are line with core features of externalizing problems (10).

Moreover, significant differences in relationships between amygdala volume and orbitofrontal cortical thickness in children with lower versus higher externalizing behaviors were found. Children with lower externalizing behaviors exhibited positive correlations between amygdala volume and left orbitofrontal cortical thickness, whereas this association was not present in children expressing higher rates of externalizing behaviors, indicating that the development of amygdala-orbitofrontal connections may have been disturbed in children with high externalizing behaviors (10).

Using a general population sample is an advantage of this study. However, this sample did not include children with externalizing disorders, and therefore, the results cannot be generalized to clinical populations. More important, CBCL provides parents' understanding of presenting problems rather than a clinical diagnosis. These cross-sectional data show interesting findings, however, and it will be promising to analyze the longitudinal data of this study.

An advantage of looking at earlier developmental stages is the ability to overcome confounders such as medication or comorbidity, which become increasingly relevant in adolescence and adulthood. Although investigations of biological abnormalities at early or even prestages of externalizing and personality disorders may be promising, it is difficult to generalize these findings to the adult disease population. Therefore, there is a need to follow up on externalizing disorders and personality disorders from childhood or adolescence to adulthood. Promising methods for such longitudinal studies are neuroimaging and neurophysiologic techniques, as well as the use of blood markers associated with the stress hormone system and inflammatory system. Ideally, internal factors such as emotional regulation skills and external factors such as early life adversity and peer influences should also be explored, and environment × gene interactions should be examined. These future studies might result in a better understanding of the complex neurobiological background of these disorders.

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