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Commentary

Neuroimaging candidate endophenotypes of social anxiety disorder

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Social anxiety disorder (SAD) is one of the main adolescent-onset mental health disorders with a serious social economic burden [3]. While the pathogenesis of SAD remains unknown, finding a biological marker of SAD is crucial for clinical diagnosis and treatment.

Endophenotype, a kind of measurable subclinical biological trait that is related to the nature of disease, can be a bridge between the clinical disorder and genetic vulnerabilities. Endophenotypes need to follow 4 criteria [5] including the association with the disorder(*criterion 1*), state-independence(*criterion 2*), heritability (*criterion 3*), and co-segregation with the patient within a family(ie, the endophenotype is more prevalent in patients compared with their healthy relatives) (*criterion 4*). Besides, endophenotypes should be more prevalent in nonaffected family members than in the general population. Endophenotypes might not just be associated with one disease, so one needs to compare with other disorders to find an ideal endophenotype.

Most previous neuroimaging studies of SAD is focused on *criterion 1* which have shown association between neuroimaging findings and clinical phenotypes of SAD. For example, connective changes between the amygdala and prefrontal cortex are significantly associated with SAD [6]. However, correlation analysis provides limited information on mechanisms of SAD, which restrict their clinical relevance. The stability and hereditability of image features have seldom been studied in high risk populations. For example, children at high risk for social anxiety showed changes in intrinsic connectivity of default-mode networks [4]. Though these studies provide some evidences related to *criterion 2* and *criterion 3*, the complex interaction between brain maturation and pathophysiology of SAD remains unclear.

Bas-Hoogendam and colleagues conducted the first neuroimaging family study on SAD (the Leiden Family Lab study on Social Anxiety Disorder, LFLSAD), which included 132 individuals from 9 families. Structural features including subcortical grey matter volume, cortical thickness and white matter tracts were studied, and they found candidate endophenotypes that met *criterion 3* and *criterion 4* [1,7]. Grey matter characteristics of frontal, parietal and temporal ROIs co-segregated social anxiety within families. Increased fractional anisotropyin the left and right superior longitudinal fasciculus also showed similar potential to be endophenotypes.

In a study recently published in *EBioMedicine* [2], Bas-Hoogendam and colleagues analysed 109 resting-state fMRI data from the LFLSAD. According to other research, they selected 6 networks of interest, including default mode, dorsal attention, executive control, frontoparietal, limbic and salience networks, and found that social anxiety co-segregated with intrinsic functional connectivity (iFC) within the dorsal attention network and frontoparietal network. Co-segregation of the iFC with social anxiety means this potential endophenotype is associated with the level of social anxiety symptoms within families. The iFC of multiple voxels within correlated clusters is at least moderately heritable, because the narrow-sense heritability (h^2) is higher than 0.20. They provided potential functional image endophenotypes that met both *criterion 3* and *criterion 4*. This functional connection change might provide a target of intervention in high-risk individuals.

Using data from the LFLSAD, they have found grey matter structural, white matter tracts microstructural, and functional candidate endophenotypes subsequently. But the inner association amongst them is not clear. This work highlights the potential of finding endophenotypes that meet all SAD criteria. However, there is still much work to be done. One is verifying that candidate endophenotypes are associated with the disease by comparing patients with healthy volunteers. Another is proving the stability by longitudinal studies on individuals with SAD. This family study design can encourage patients to visit the lab together, and it might be easier for patients to finish follow-up visits, as individuals with SAD will avoid making contact with others. But SAD is a disease of polygenic inheritance, which is controlled by complex genetic mechanism and environmental effects. With this in mind, inclusion of only 9 families in this study might not be enough. Individuals from the same family share not only similar genetic material but also environmental factors. Future studies could combine a family design and an individual design to more effectively study imaging endophenotypes of SAD.

Contributors

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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