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Commentary

Gray matter matters: The structure of the socially-anxious brain

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Social anxiety disorder (SAD) is a serious, disabling and prevalent anxiety disorder, with a chronic course and a complex pathophysiology [1]. Treatment for the disorder is often only moderately effective, so insight in the neurobiological alterations underlying the condition is pivotal in order to improve therapeutic interventions in clinical practice [2]. In the last decade, several neuroimaging studies have explored differences in brain structure between patients with SAD and healthy control participants, for example by employing a mega-analytical approach on an international multi-center dataset of MRI data [3]. In addition, qualitative reviews and quantitative meta-analyses, based on the results of patient-control studies with relatively small sample sizes, have shed light on changes in gray matter volume in SAD [4,5]. These studies point at differences in brain structure in various subcortical (for example, putamen and thalamus) and cortical brain regions (including prefrontal areas, regions of the parietal cortex and temporal areas), but the results are, until now, heterogeneous, probably due to methodological differences with respect to the analyses, as well as to variations in clinical characteristics like psychiatric comorbidity and treatment (either by pharmacological drugs or cognitive behavioral therapy).

Given the diverse findings of studies on this matter, the recent research article published in *EBioMedicine* by Zhang et al. [6] entails a relevant addition to the field and has the potential to provide additional insights into the neurobiology of the disorder. The authors investigated gray matter characteristics between patients with SAD and an age- and gender-matched group of healthy controls (n = 32 in both groups) [6], extending previous studies in two ways. First, the sample included SAD patients without comorbidity who were treatment-naive, so variations in brain structure due to comorbidity and treatment were most likely excluded. Second, the authors used the software package FreeSurfer to investigate two distinct characteristics of gray matter at the whole-brain level: cortical thickness (CT) and cortical surface area (CSA). Distinguishing between these parameters is important, given their divergent developmental trajectories and distinct genetic underpinnings – which is relevant given the genetic background of SAD [7]. For example, an endophenotype study involving families genetically enriched for SAD revealed widespread alterations in cortical gray matter characteristics which were associated with the level of social anxiety symptoms, but did not find overlap in regions showing changes in CT and CSA [8]. So, investigating CT and CSA separately most likely leads to better insights in the underlying neurobiological alterations, in comparison to examining just gray matter volume alone.

Interestingly, the results of the study indicated changes in CT and CSA in mainly the same brain area: patients with SAD had thinner (so lower CT) but more expanded (larger CSA) cortical gray matter in the bilateral prefrontal cortex (PFC). In addition, patients had increased CSA in the left superior temporal gyrus (STG), without alterations in CT in this region [6]. These findings suggest that SAD is associated with cortical reorganization in regions functionally implicated in emotion processing and decision making (PFC), and processing social knowledge (STG). Furthermore, the authors reported an inverse relationship between CSA in the superior frontal gyrus (part of the PFC) and duration of SAD. However, due to the cross-sectional nature of the study and the fact that age of onset in SAD is often hard to assess retrospectively due to the generally gradual progressive course of the disorder during childhood and adolescence, a development based on an innate vulnerability to SAD [1,7], this finding needs to be interpreted with caution.

Despite these meaningful results concerning brain structure in SAD, which to a large extent coincide with reported functional alterations related to the disorder [4], several important questions are still unanswered, providing directions for future studies. First, given the high comorbidity rate in patients with SAD, it needs to be elucidated to what extent the findings of the present study [6], involving a unique sample of non-comorbid never-treated patients, apply to the more general group of SAD patients who often suffer from comorbid psychopathology like other anxiety disorders, depression and substance abuse. Furthermore, the analyses by Zhang et al. [6] did not reveal associations between characteristics of brain structure and symptoms, while several other studies have reported such symptom-brain correlations, as well as on changes in brain structure related to treatment [2,7]. Next, while the SAD-related alterations reported by Zhang et al. are restricted to two brain areas, other work in the field have revealed far more extended changes in brain structure [2,4,5,8]. These inconsistent findings stress the need for replication studies.

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Large-scale studies, for example within the framework of the ENIGMA (Enhancing NeuroImaging Genetics by Meta-Analysis) consortium, are of importance, as they have the potential to test the reproducibility and robustness of neuroimaging findings [9]. As outlined in a recent review paper, the ENIGMA-Anxiety working group, which has a subgroup devoted to unraveling the neurobiology of SAD, has much potential to address such questions [10].

Taken together, the findings of Zhang et al. [6] as well as those of other recent papers in this field indicate the importance of considering gray matter in understanding the neurobiology of SAD. Given the diverse findings to date, we are convinced that we have not heard the last of this, and future research involving large sample sizes is highly warranted [10].

Author declaration

Dr. Bas-Hoogendam has nothing to disclose.

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