EBioMedicine 36 (2018) 5–6

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Brain changes in social anxiety disorder run in the family

Andreas Frick [a,b,*], Kristoffer N.T. Månsson [a,c,b]

[a] Department of Psychology, Stockholm University, Stockholm, Sweden
[b] Department of Psychology, Uppsala University, Uppsala, Sweden
[c] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Social anxiety disorder (SAD) is a prevalent and costly psychiatric condition that causes great suffering for afflicted individuals [4]. Central for SAD is the fear of being evaluated, and social situations are either avoided or endured with great anxiety. The current treatment options leave a large proportion still suffering. Thus, proper understanding of the etiological processes leading to SAD is important for development of novel treatments and prevention strategies. An important contribution to this end is the first report of structural brain alterations suggested to be candidate endophenotypes for SAD by Bas-Hoogendam and colleagues in this issue of *EBioMedicine* [1,2]. The authors used data from the innovative multiplex, multigenerational Leiden Family Lab Study on Social Anxiety Disorder including 110 participants, consisting of those with SAD and unaffected family members from 8 families genetically enriched for SAD [2]. Heritability estimates of three measures of brain morphology were derived from anatomical T1-weighted magnetic resonance images. Moderate-to-high heritability of SAD-associated morphological changes was found in the volume of the globus pallidus, cortical thickness in frontal and temporal regions, as well as the cortical surface area of the fusiform gyrus.

Here, an endophenotype is an intermediate between SAD-related genes and the behavioral and cognitive symptoms. In other words, the findings suggest that genetic susceptibility for SAD is related to changes in brain morphology that in turn are associated with (increased risk of) SAD. Finding endophenotypes for SAD is important, because they may 1) cast light on genotypic variations associated with SAD and 2) identify treatment and prevention targets. It should be noted that the study design prevented the authors from assessing all the proposed criteria of endophenotypes. For one, they did not include healthy controls from the general population in their study, which precluded testing of the criterion that SAD-related changes in brain morphology are also evident in non-affected probands when compared to the general population. This is an unfortunate omission, because it prevents strong conclusions regarding brain morphology as a candidate endophenotype for SAD. Further studies are needed that address this and the other criteria of endophenotypes not tested by Bas-Hoogendam et al., i.e. that they are state-independent and present already before diagnosis.

As reviewed by Bas-Hoogendam et al. [1,2], more than a dozen studies have been published examining brain morphology alterations in SAD. Findings from these studies have been mixed and the structural brain alterations in SAD seem to be best described as diffuse and widespread [6]. The very few treatment studies that have included brain morphology as an outcome measure also cast light on the structural alterations associated with SAD. We recently found that symptom improvement was associated with long-lasting reductions in amygdala volume following cognitive-behavioral therapy ([8,9]), in line with attenuation of amygdala activity as a marker of successful treatment [7]. Although more studies are needed to determine the extent and location of treatment-related changes in brain morphology, the potential discrepancy between the widespread morphological alterations seen in SAD patients and the rather circumscribed changes associated with treatment may indicate that there indeed are state-independent morphological alterations supporting the endophenotype criteria.

There are unresolved questions that should be addressed by the field in future studies. First, the relation between structural brain changes and behavior is largely unknown, i.e. do specific morphological alterations underlie specific aspects of SAD-related cognitive and emotional dysfunction. Second and related to the first question, the link between SAD symptoms and anatomical alterations is still not well understood. Third, investigations including both functional and structural brain measures are rare in the literature. This is a critical question because morphological measurements derived from magnetic resonance imaging are macroscopic and capture a variety of cellular mechanisms, e.g. changes in blood flow [5]. Therefore, complementing structural imaging with other imaging techniques would be useful to tease apart SAD-related alterations in brain morphology from e.g. neural activity. Fourth, although the etiology of SAD is not fully understood, it seems clear that it involves an interaction between, genetic, biological, and environmental factors. To better understand how these factors contribute to SAD, a developmental perspective is needed, which unfortunately is largely lacking in the SAD literature, but see e.g. Buzzell et al. [3] for an exception. For example, it is still unknown if brain changes are present before or as a consequence of SAD. In this respect, the family design employed by Bas-Hoogendam (in press) could provide important contributions, especially if combined with a longitudinal design following children until adulthood to clarify the trajectory of heritable brain changes and their contribution to social anxiety and the relation to other established risk factors such as childhood maltreatment and the temperament behavioral inhibition [4].

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.08.048.
* Corresponding author at: Department of Psychology, Uppsala University, Box 1225, SE-751 42 Uppsala, Sweden.
E-mail address: andreas.frick@psyk.uu.se (A. Frick).

https://doi.org/10.1016/j.ebiom.2018.09.009

Disclosure

The authors declared no conflicts of interest.

References

[1] Bas-Hoogendam JM, van Steenbergen H, Tissier RLM, Houwing-Duistermaat JJ, Westenbreg PM, van der Wee NJA. Subcortical brain volumes, cortical thickness and cortical surface area in families genetically enriched for social anxiety disorder - a multiplex multigenerational neuroimaging study. EBioMedicine 2018;36:410–28.

[2] Bas-Hoogendam JM, Harrewijn A, Tissier RLM, et al. The leiden family lab study on social Aanxiety disorder: A multiplex, multigenerational family study on neurocognitive endophenotypes. Int J Methods Psychiatr Res 2018;28:e1616. https://doi.org/10.1002/mpr.1616.

[3] Buzzell GA, Troller-Renfree SV, Barker TV, Bowman LC, Chronis-Tuscano A, Henderson HA, et al. A neurobehavioral mechanism linking behaviorally inhibited temperament and later adolescent social anxiety. J Am Acad Child Adolesc Psychiatry 2017;56:1097–105. https://doi.org/10.1016/j.jaac.2017.10.007.

[4] Craske MG, Stein MB. Anxiety. Lancet 2016;388:3048–59. https://doi.org/10.1016/S0140-6736(16)30381-6.

[5] Franklin TR, Wang Z, Shin J, Jagannathan K, Suh JJ, Detre JA, et al. A VBM study demonstrating 'apparent' effects of a single dose of medication on T1-weighted MRIs. Brain Struct Funct 2013;218:97–104. https://doi.org/10.1007/s00429-012-0385-6.

[6] Frick A, Gingnell M, Marquand AF, Howner K, Fischer H, Kristiansson M, et al. Classifying social anxiety disorder using multivoxel pattern analyses of brain function and structure. Behav Brain Res 2014;259:330–5. https://doi.org/10.1016/j.bbr.2013.11.003.

[7] Gingnell M, Frick A, Engman J, Alaie I, Björkstrand J, Faria V, et al. Combining escitalopram and cognitive–behavioural therapy for social anxiety disorder: Randomised controlled fMRI trial. Br J Psychiatry 2016;209:229–35. https://doi.org/10.1192/bjp.bp.115.175794.

[8] Månsson KNT, Salami A, Carlbring P, Boraxbekk C-J, Andersson G, Furmark T. Structural but not functional neuroplasticity one year after effective cognitive behaviour therapy for social anxiety disorder. Behav Brain Res 2017;318:45–51. https://doi.org/10.1016/j.bbr.2016.11.018.

[9] Månsson KNT, Salami A, Frick A, Carlbring P, Andersson G, Furmark T, et al. Neuroplasticity in response to cognitive behavior therapy for social anxiety disorder. Transl Psychiatry 2016;6:e727. https://doi.org/10.1038/tp.2015.218.