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RESEARCH HIGHLIGHT

The social and winding road between inflammation and PTSD

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At some point, life may expose us to a traumatic event. The effects are highly variable, not simply depending on the intensity of the experience. Most people show resilience, while others—about 7–8% of the population (https://www.ptsd.va.gov/index.asp)—develop post-traumatic stress disorder (PTSD). PTSD is associated with disorders with an inflammatory component; moreover, elevated levels of pro-inflammatory markers are detected in blood of PTSD patients [1]. Whether inflammation increases PTSD risk, results from PTSD, or simply is a correlate, remains unclear [1].

In this issue of *Neuropsychopharmacology*, Carvalho et al. [2] explore the directionality of the association of inflammation with PTSD, by investigating genetic relationships between C-reactive protein (CRP, an inflammation marker), PTSD and traits related to trauma response/exposure, social support and socioeconomic status (SES). They show evidence of a positive correlation between inflammation and PTSD possibly driven by low SES.

To analyze the genetic architecture of these traits, they turn to recent statistical techniques leveraging GWAS-derived summary statistics. They first use linkage disequilibrium (LD) score regression (LDSR), a technique based on the notion—particularly valid for polygenic traits—that the more genetic variation an index variant tags (i.e., the higher its LD score), the higher the probability that this index variant will tag a causal variant of a trait, thus having a greater effect size in a GWAS. From the regression coefficients of the observed GWAS test statistics on the LD scores, it is possible to reliably estimate the heritability of a trait due to common genetic variants (SNP-based heritability). If a trait has a high SNP-based heritability, we can assume that its GWAS statistics will provide trustworthy information about its polygenic architecture. Using LDSR, the authors select 20 GWAS with appropriate characteristics for downstream analyses, i.e., related to polygenic effects rather than confounding factors, like cryptic relatedness and population stratification [2]. They employ another application of LDSR, cross-trait score regression, to estimate the genetic correlation among the traits investigated, i.e., the proportion of variance between traits associated with shared genetic factors. They detect high genetic correlation of PTSD with trauma response/exposure, social support, and SES [2], consistently with prior evidence: because PTSD GWAS was performed on patients with a majority of trauma-exposed controls [3], we should expect that genetic susceptibility to PTSD overlaps with the response to trauma. Moreover, Polimanti et al. [4] previously found that trauma-exposure traits are PTSD risk factors, and that SES can mediate the relationship between educational attainment (EA) and PTSD. There is also a weak positive genetic correlation between CRP and PTSD, and CRP levels correlate with trauma response/exposure, social support and SES [2].

The detection of genetic correlations does not allow understanding of any directionality. To infer these, Carvalho et al. use mendelian randomization (MR), a method for evaluating—not establishing—causality between a modifiable exposure and a specific trait, by analyzing the relationship between that trait and a genetic predictor of the exposure. They use an application of MR, the TwoSampleMR, which allows inference of causal relationships between phenotypes, again by GWAS statistics. As genetic tools, they select polygenic risk scores (PRS). By further exploring with PRS the genetic correlations detected in the LDSR, they first validate the genetic relationship of CRP with PTSD, and with traits related to trauma exposure, social support and SES; and the genetic relationship between PTSD and SES. Second, they study causal relationships in these validated associations. In each analysis, they verify that the results are not driven by SNPs associated with CRP and PTSD. They do not detect any specific directionality in the association between inflammation and PTSD, i.e., genetic susceptibility to high CRP level is associated with increased PTSD risk and vice versa. A bidirectional negative genetic association also emerges between SES ("household income") and high CRP levels.

Genetic risk for high CRP levels is also associated with social support and, importantly, genetic susceptibility to low SES ("household income", "deprivation index") shows a causal relationship with PTSD [2].

Therefore, intricate genetic relationships emerge, without a clear directionality, in the association between inflammation and PTSD (Fig. 1); this may mean that the relationship is not causal in either direction but accounted for by a third factor. The analyses described above identify traits related to social support and SES as candidates. To narrow down the search, the authors use multivariate MR to evaluate whether the effects of CRP, social support, and SES, on PTSD are independent of each other. They find that the genetic association between CRP and PTSD is independent from social support, while dependent from genetic factors associated with SES [2] (Fig. 1). Thus, genetic factors associated with low SES may mediate the genetic relationships not only between EA and PTSD [4], but also between social support, CRP, and PTSD [2].

These data build on recent findings showing that the genetic overlap across several psychiatric disorders and substance use traits is affected by genetic risk for low SES [5], indicating that genetic susceptibility to low SES may drive the association also between physical and mental health [2]. What does that mean? The interpretation depends on what "genetic susceptibility to low SES" is. This measure, constructed from genetic variants more frequent in individuals with low SES in one population, is associated with a limited proportion of the variance of SES in o-

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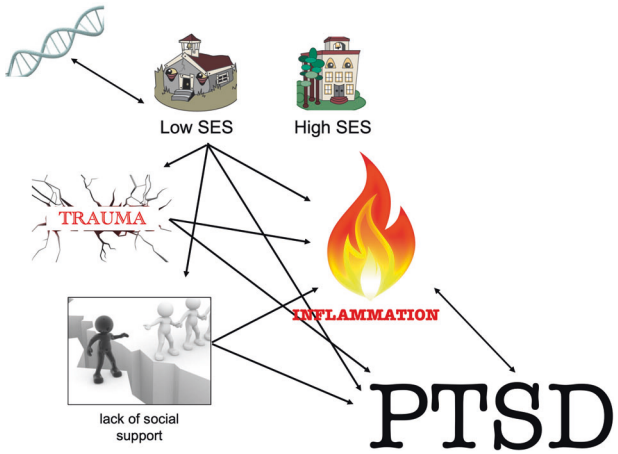

Fig. 1 The intricate genetic relationship between SES, trauma, social support, inflammation, and PTSD. Genetic factors associated with low SES may drive the genetic relationships between traits related to trauma and social support, CRP, and PTSD.

ther populations, so we can be certain that it is not the only determinant of SES. Genetic variants associated with low SES and then with inflammation and PTSD may have a causal role in affecting the individual experience, in particular impairing cognitive abilities, which are known to correlate with lower EA and lower income. According to this hypothesis, EA may underlie the genetic relationship between SES and PTSD. However, previous work of Polimanti suggests the opposite, that genetic factors linked with SES mediates the genetic relationship between EA and PTSD [4].

More conservatively, SES genetic factors are more frequent in those living in environments associated with low SES, increasing their probability of experiencing stressful settings (trauma, social factors), and their risk of developing inflammatory conditions and PTSD. In this scenario, the relationship between genetic risk for low SES, CRP, and PTSD is mediated by actual low SES, which is known to affect physical and mental health. Indeed, recent findings indicate that genetic risk for EA, linked with lower SES, is geographically clustered [6, 7], and thus related to a wide range of disadvantageous environmental variables, increasing risk for both physical and mental disorders. Because higher CRP is detected in many other disorders, including sleep disturbances [8], these data raise the question of whether some associations are epiphenomena of a common underlying condition linked to genetic and social correlates of low SES.

So, is the relationship between SES, social support, inflammation, and PTSD a result only of social stratification? This is a question the new work by Polimanti's team [2] cannot answer, being based on the study of genetic relationships, which does not exclude different mechanisms implying non-genetic components of these conditions. Moreover, social stratification may not be totally independent of genetic factors. For example, a driver in the geographical clustering of genetic correlates of SES was identified in the migration caused by low SES [6]: genetic variants may affect the tendency of individuals to migrate in response to stressful, dangerous situations. By influencing individuals to remain in stressful environments, the same genetic variants may affect the risk of experiencing low SES, inflammation, and PTSD.

This study indicates that integrating genetic and social science, and clarifying the mechanisms underlying the genetic associations with social stratification and SES, will benefit the understanding of the genetic and etiological basis of physical and mental health traits. Finally, improving the quality of life of those exposed to trauma living in low SES regions may be more effective in preventing PTSD than administering anti-inflammatory drugs.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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