Persistent child and adolescent anxiety predicts development of psychotic disorders via elevated inflammation

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Psychotic disorders (PDs) are a common group of conditions which include schizophrenia, schizoaffective disorder and brief psychotic episodes. These disorders have a varied and complex aetiology comprised of genetic and environmental risk factors. PDs such as schizophrenia often have a prodromal stage during adolescence and subsequent diagnosis hinges on symptoms presenting over the course of several years, but the manifestation of these symptoms is likely a consequence of brain changes in the years predating their onset. We may therefore find clues as to the antecedents of PDs by looking at late childhood and early adolescence. In this issue of *Biological Psychiatry,* Morales-Munoz *et al* (1) examine the prospective association between persistent child and adolescent anxiety, inflammation and adult psychosis, and their results hold important implications for novel therapeutic strategies for reducing psychosis risk by targeting childhood anxiety and/or inflammation.

PDs are often characterised by perceptual, cognitive and affective disturbances, commonly featuring hallucinations, delusions, disorganised cognition and mood. Anxiety is a prominent clinical feature of schizophrenia in particular, and there exists significant comorbidity between this diagnosis and anxiety disorders. Anxiety is often pronounced during the prodromal phase of schizophrenia(2), which manifests during adolescence, known to be vulnerable period of brain development and susceptibility to psychiatric disease. While anxiety could be a consequence of psychotic symptoms, some evidence suggests that heightened anxiety may actually precede the onset of psychosis (2). For example, burden of polygenic risk for schizophrenia is strongly associated with anxiety symptoms in adolescents (3). Meanwhile, recent genetic evidence strongly implicates the immune system in risk for developing schizophrenia (4) and these schizophrenia-associated immune pathways also impact profoundly upon anxiety and fear behaviour in

rodent models (5). Whether anxiety and dysregulated inflammation interact to influence risk for developing psychosis is however unknown.

Morales-Munoz *et al.* utilised data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort to test the association between persistent childhood and adolescent anxiety and adult psychosis. Anxiety was measured via parental report when children were 8, 10 and 13 years of age via the generalised anxiety dimension of the Development and Well-Being Assessment (DAWBA). Importantly, their measurement of anxiety during late childhood and early adolescence was unlikely to be confounded by early symptoms of prodromal psychosis since these typically emerge later in adolescence. Psychotic experiences (PEs) at 24 years of age were measured via the semi-structured Psychosis-like Symptom Interview and considered present if at least three positive symptom domains had presented within the prior 6 months; hallucinations, delusions and thought interference. The prevalence of Psychotic disorders (PDs) at age 24 were identified by individuals meeting diagnostic criteria for PDs, which are considered a more restricted phenotype characterised by recurrent PEs with detrimental impacts on social and occupational functioning. The authors ensured there was a clear timeframe between the last measure of anxiety (at 13 years of age) and subsequent adult psychosis (24 years of age). Mean levels of C-reactive protein, an acute phase protein that is released in response to circulating cytokine levels, were measured in blood samples drawn at ages 9 and 15 and included as a mediating factor. Cannabis use at age 15 was included as a confounder due to known associations with anxiety and PDs, and socioeconomic factors such as sex, ethnicity and maternal age were included as covariates.

Analyses identified three distinct childhood-anxiety trajectories across timepoints. The majority of the cohort (72%) demonstrated persistently low levels of anxiety, whereas 21% had persistent moderate levels of anxiety and 5.4% reported persistent high levels of anxiety. The latter classification was significantly and directly associated with presence of PEs and PDs at 24 years of age, with PDs showing the strongest association, likely due to PEs being a more heterogenous phenotype. Interestingly, whilst persistent high anxiety was also associated with depression and generalised anxiety at age 24, these relationships were weaker than that observed for PDs. No association between persistent high anxiety and hypomania, phobias or substance abuse disorders was found suggesting that persistent childhood and adolescent anxiety has a specific association with PDs and

to a lesser degree, mood disorders. Furthermore, mean CRP at ages 9 and 15 were found to mediate the prospective association between persistent high anxiety and adult PDs and PEs. These novel results highlight a potential causal role of early persistent anxiety in the development of psychosis and provide important evidence for a role of inflammation in disease aetiology.

It is difficult to determine whether persistent anxiety or inflammation emerged first but there are likely to be multiple mechanisms at play and probable reciprocal interactions between these factors. For example, persistent anxiety in childhood and adolescence may chronically activate the stress response, leading to persistent low-grade inflammation, the presence of which has been associated with a range of morbidities (6). Immune dysregulation may in turn disrupt homeostatic immune-mediated neurodevelopmental processes such as synaptic pruning (reviewed in 7). The complement system in particular has been strongly linked to schizophrenia via genetic evidence and its role in developmental synaptic pruning (4). Recent evidence suggests that expression of complement proteins in the human prefrontal cortex are usually dampened down during the peak of adolescent synaptic pruning (8), but chronic inflammation may lead to a failure of normal downregulation thereby promoting excessive pruning and the synapse loss thought to be central to schizophrenia. Genetic risk factors, such as complement *C4A* copy number status (4) may further exacerbate this process. Alternatively, genetic variants in immune loci may lead to dysregulated immune signaling from the offset, which subsequently alters the development and synaptic organisation of brain areas involved in anxiety, mood and emotion, over time contributing to distorted perception and development of positive symptomatology.

An important question in this emerging relationship between anxiety, inflammation and psychosis is the extent to which peripheral inflammation, such as that measured by Morales-Muñoz *et al,* accurately reflects or perhaps provokes brain inflammation. At least in the case of major depression, evidence shows strong correlations between plasma CRP and cytokine levels in cerebrospinal fluid (9). As a marker, CRP has broad clinical use but in future work, analysis of 'inflamed' high-anxiety subgroups could be expanded to provide more detailed information on immune markers beyond CRP, as there is currently little information on inflammatory markers associated with anxiety. In addition, since anxiety is an extremely prevalent diagnosis, more studies will be needed to further characterise

paediatric anxiety associated with elevated inflammation, including whether this constitutes a specific subtype of anxiety that is reliably and intimately tied to the developmental trajectory of psychosis versus other psychiatric disorders, such that it could be used for patient stratification.

The results of Morales-Muñoz *et al* suggest that identifying individuals with persistent-high anxiety in childhood and early adolescence in the presence of ongoing inflammation could be a strategy to predict future psychosis risk and thus prioritise for prophylactic therapy, whether it be anxiety or inflammation targeted. Interestingly, analysis of electronic health records (10) revealed a significantly decreased risk of psychosis in adults who received the anti-inflammatory antibiotic minocycline for at least 3 months during adolescence, suggesting that treatments aimed at reducing risk for psychosis may not need not be given for long durations to be beneficial. Similar analyses of psychosis prevalence in adults who received a course of anxiolytic medication during adolescence could also be informative in determining the relative contributions of inflammation and anxiety to psychosis. In conclusion, this study makes an important contribution to the literature in showing prospective associations between persistent child and adolescent anxiety, abnormal inflammatory processes and adult psychosis and adds further weight to the concept that anxiety may be an inherent part of the pathway to psychosis, rather than a separate entity.

Disclosures

Dr. Westacott reported no biomedical financial interests or potential conflicts of interest

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