More depressed patients than previously estimated could have increased activation of their immune system

May 30 2023

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New research from the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) at King's College London has used an assessment

of gene expression involved in the immune response to show that there could be more patients with major depressive disorder (MDD) with activated immune systems than research has previously estimated.

By identifying the molecular mechanisms involved in this association, the research could pave the way to better identify those patients with an immune component to their depression which would potentially help to provide more personalized approaches to treatment and management of MDD.

The research, published in *Translational Psychiatry* builds on previous findings that there is an activated immune response in many people with MDD.

However, most of the research in this area has focused on the levels of inflammation related proteins like C-reactive protein (CRP). Studies using CRP have found that about 21 to 27 % of people with depression have an activated immune response but CRP levels do not capture the complete picture of the immune response. This new study set out to observe broader immune related characteristics that are not captured by CRP levels.

168 participants were sourced from the Biomarkers in Depression Study (BIODEP). 128 of them had a confirmed diagnosis of MDD and they were then divided into three subgroups according to their levels of CRP in the blood.

Researchers analyzed the expression of 16 genes whose activation is involved in the immune response. Gene expression is the initial stage of the process by which the information present in our genes influences our features and behavior. The initial analysis found increased expression of immune-related genes in people with MDD compared to the those without a diagnosis of depression.

When comparing MDD patients who did and didn't have elevated levels of CRP in their blood, there were no differences in the expression of these 16 genes, suggesting this pattern of expression was independent of CRP levels and potentially underlying a different mechanism.

Importantly, researchers then conducted a secondary analysis on all those participants (both with and without a diagnosis of MDD) who had CRP values of less than 1, meaning that they are not considered to have any inflammation. The researchers found that participants with MDD and low levels of CRP still had significantly higher expression of immune genes compared to those without a depression diagnosis.

Professor Carmine Pariante, Professor of Biological Psychiatry at King's IoPPN and the study's senior author said, "Previous research into this field has had a significant focus on C-reactive protein (CRP) levels within people with MDD which is a known marker for inflammation but just part of the immune response."

"Our study has successfully broadened this focus and shown that there is an immune response in the genes of those with MDD that is independent of CRP levels and, crucially, even in those where inflammation is not captured by measuring CRP. This means that increased immune activation is present in many more depressed patients than originally thought."

"These important findings will allow us to identify the molecular pathways involved in depression and also help to more accurately identify those who have different types of immune responses which could pave the way for more personalized approaches to treatment."

Dr. Luca Sforzini, the study's first author from King's IoPPN said, "This evidence contributes to strengthen our knowledge on immune-related depression. Notably, people with depression and immune alterations are

less likely to respond to standard antidepressant medications and may benefit from specific interventions targeting the immune system."

"I am hopeful these findings will aid current and future research in better characterizing individuals with depression based on their immunobiological profiles, offering more effective clinical strategies to a large number of people who are not benefitting from current antidepressants."

The evidence of an immune related predisposition in people with depression irrespective of their levels of inflammation as routinely measured can extend our concept of immune related depression.

More information: Higher immune-related gene expression in major depression is independent of CRP levels: results from the BIODEP study, *Translational Psychiatry* (2023). DOI: 10.1038/s41398-023-02438-x

Provided by King's College London