

Inflammatory Depression or Depression with Inflammation?

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Abstract

Many patients with major depression have measurable inflammatory abnormalities, but the observation is not a stand-alone causal diagnosis. Inflammation may precede symptoms, accompany medical comorbidity, follow adverse health behaviors or act as a moderator of treatment response. The distinction between inflammatory depression and depression with inflammation determines whether a biomarker can guide therapy or merely describe additional risk.

A common marker, many sources

C-reactive protein rises in numerous inflammatory and metabolic states. Obesity, infection, autoimmune disease, poor sleep, tobacco exposure and other factors can produce elevated CRP independent of psychiatric diagnosis. Depression itself may influence activity, diet, stress and sleep, which in turn affect inflammation. Cross-sectional findings are therefore insufficient to establish direction of effect. Even when an inflammatory association is statistically significant at population level, the individual patient may have a different causal pathway.

Treatment as a test of causal claims

If a specific inflammatory pathway sustains depression in a subset, modifying that pathway might improve symptoms in that subset. Yet broad anti-inflammatory treatment has not established itself as a general antidepressant strategy. The infliximab trial in treatment-resistant depression found no overall benefit, while generating exploratory hypotheses about baseline inflammatory status. The correct response is not to discard neuroimmune psychiatry or to declare it proven. It is to define prespecified populations and clinically meaningful outcomes more carefully.

A better phenotype

Potentially informative features include systemic inflammatory disease, metabolic syndrome, anhedonia, fatigue, sleep disruption and objective biomarkers in repeated measures. None is uniquely diagnostic. A good model would predict which measures change before mood improves and whether a pathway-specific intervention performs better than appropriate comparator care. The distinction between modifiable risk, causal driver and marker of severity is more important than the rhetorical appeal of the subtype label.

The patient-level consequence

An elevated inflammatory marker deserves contextual medical interpretation, not automatic immune suppression. A normal marker does not render depression less real. Conversely, depression in a patient with inflammatory bowel disease, rheumatoid arthritis or another significant medical disorder may reflect both psychological and biological burdens. Integrated care can address these simultaneously without assuming one explains everything.

Conclusion

The useful research question is not whether inflammation and depression ever coexist—they do—but whether specific immune states define reproducible, treatment-relevant subgroups. Until then, causal certainty is premature.

Selected readings

- Raison et al., Infliximab and treatment-resistant depression
- Pollak et al., Autoimmune psychosis evidence framework