

24 — Inflammatory Depression or Depression with Inflammation?

Neuroimmune Psychiatry · Conceptual research article · No original clinical data presented

Abstract

The critical psychiatric question is whether inflammation is a causal driver of depression in a particular subgroup or an effect of the same exposures that produce depression. This paper advances a phenotype-specific position: some depressive presentations may be sustained by inflammatory biology, but the biomarker pattern that predicts benefit from an anti-inflammatory intervention has to be discovered rather than presumed.

Association does not answer which intervention would work

Inflammatory markers can rise because of infection, adiposity, smoking, impaired sleep, chronic pain or other illness. Each may also influence depressive symptoms through independent pathways. A case-control difference in C-reactive protein cannot by itself tell us whether reducing that protein or a related cytokine will improve mood. A more decisive design would specify an inflammatory phenotype before treatment and test whether a targeted intervention changes both the relevant pathway and clinically meaningful function. A response confined to one biologically characterized stratum could be far more informative than a small mean effect across all depression.

Oxalate-related inflammation deserves consideration only as a proposed initiator in a subset with documented oxalate physiology; it should not be inferred from a high inflammatory marker alone. The novel thesis would be advanced if oxalate-linked inflammation predicted a distinctive symptom course after controlling for other causes of inflammation and renal disease.

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.

A diagnostic label does not settle the direction of causation

Some patients with major depressive symptoms also have measurable inflammatory abnormalities. The observation has inspired proposals for an inflammatory subtype of depression, but the central unresolved question is whether immune activation contributes to the syndrome, accompanies it, results from associated behaviors, or reflects another illness. Chronic pain, obesity, sleep disturbance and physical inactivity can each influence inflammatory markers and depressive symptoms. Even if inflammatory signaling is truly involved, it may represent one pathway among several rather than a stand-alone diagnosis.

The distinction between a depressed patient who is inflamed and a patient whose depression is partly driven by inflammation has immediate scientific consequences. To support the latter, investigators should identify temporal precedence, specificity of the biological mediator, and evidence that modifying the pathway changes meaningful psychiatric outcomes. A treatment that reduces systemic inflammation and improves joint pain may improve mood secondarily, without directly altering the brain mechanism originally proposed. Functional improvement is valuable but does not resolve how it happened.

What immune mechanisms might contribute

Cytokine signaling can influence sleep, motivation and central neural processes. Immunometabolic shifts involving tryptophan and kynurenine metabolism provide plausible bridges, and alterations in glial regulation may matter in some conditions. Yet general inflammatory markers such as C-reactive protein do not reveal the exact neural signaling pathway in an individual. A common mistake is to move from elevated blood CRP to a claim of microglial activation to a specific psychiatric cause without demonstrating the intervening steps. Each transition is a research question, not a logical certainty.

The oxalate-psychiatry series raises a parallel possibility: in a person with proven oxalate-associated tissue inflammation, some mood or cognitive symptoms might be influenced by immune signaling. This is an interesting hypothesis because crystal-driven renal inflammation has specific experimental foundations. But it does not follow that individuals with depression who eat high-oxalate foods share that mechanism. Characterization of oxalate burden and a clinically meaningful inflammatory state must precede any specific interpretation.

Separating subgroups from statistical noise

A useful depression study could stratify participants according to prespecified inflammatory phenotypes, objectively evaluate relevant medical disorders, and track clinical outcomes over time. It should ask whether the inflammatory subgroup differs in symptom profile or treatment response after accounting for body composition, sleep, smoking, medication and chronic illness. Subgroup analyses become unreliable when investigators discover categories after inspecting many outcomes and then describe them as established biological types. Replication is essential.

A negative trial of an immune-targeting intervention in an unselected depressed population would not necessarily disprove every inflammatory subtype; it might indicate that the participants were not selected for the pathway. Conversely, a modest benefit in a subgroup would not establish a universal inflammatory cause. The purpose of terrain medicine here should be to refine the biological differential diagnosis, identifying when immune regulation matters and when other explanations fit better. The clinician still has to treat the psychiatric disorder appropriately while investigations proceed.

A subgroup result can be both promising and misleading

Suppose a small trial finds that patients with elevated inflammatory markers experience greater symptom improvement under a particular intervention. The result is interesting, but its interpretation depends on whether the subgroup was specified before randomization, how many outcomes were tested, and whether the effect is clinically meaningful. If investigators inspected many thresholds and retained only the favorable one, the apparent biological subtype may be a statistical accident. Replication should test the same definition and endpoint, not invent a new cutoff that again fits the available data.

The comparison condition matters as well. An anti-inflammatory intervention that reduces joint pain or improves sleep may indirectly lessen depressive symptoms. A trial focused only on a depression scale might misattribute that benefit to direct central immune modulation. Measuring pain, sleep and activity allows a more discriminating mediation analysis, although causal mediation itself requires assumptions. This is a recurring theme in terrain research: discovering that two domains improve together does not establish which one caused the other to change.

A disciplined place for the oxalate question

Patients with documented hyperoxaluria and chronic inflammatory illness could be studied as one defined subgroup, but the investigator should not assume they represent inflammatory depression generally. Oxalate chemistry, kidney function and inflammatory profiles would need to be measured together. If psychiatric symptoms improve independently of changes in renal pain, digestive symptoms and general disease activity, the oxalate-mediated hypothesis becomes more compelling. If improvements reflect relief of chronic physical illness, that remains a genuine clinical benefit, but a narrower causal claim. The goal is to identify which model predicts the observations most accurately.

The most revealing finding might be the absence of a unique biological subtype. If patients with elevated inflammation show outcomes similar to others after controlling for sleep, pain and disease severity, broad inflammatory labels may add little clinical value. Such a result would still support treating established inflammatory disease on its own merits, while challenging the claim that the biomarker identifies the psychiatric mechanism. Intellectual discipline requires accepting that a plausible shared pathway may be a poor diagnostic discriminator. Terrain medicine gains credibility when it reports that limitation openly rather than adding more unvalidated biomarkers.

The next experimental step should test whether a mechanistically selected intervention changes both the proposed immune pathway and a specific psychiatric outcome. If only physical symptoms improve, investigators should report that finding accurately rather than reclassifying the effect as central immune modulation. If mood improves independently of pain and sleep, the mechanistic interpretation becomes more interesting. Transparent endpoint selection and replication are what turn a plausible inflammatory story into medical evidence.

Conclusion

A sharper inflammatory-depression theory asks whose depression is maintained by which inflammatory process. A general claim about inflammation is too weak to change clinical reasoning.

Selected readings

- Raison et al., Infliximab and treatment-resistant depression: <https://doi.org/10.1001/2013.jamapsychiatry.4>
- Pollak et al., Autoimmune psychosis evidence framework: <https://pubmed.ncbi.nlm.nih.gov/31669058/>