Biological Psychiatry: Celebrating 50 Years

Did Spider-Man Work in the NESDA Cohort? In Immunopsychiatry, With Great Power Comes Great Responsibility

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It is difficult not to get excited about the burgeoning field of research studying the interaction between the brain, the mind, and the immune system. Indeed, as a psychiatrist, I particularly welcome the buzz around work that specifically focuses on psychiatric patients (that is, immunopsychiatry) because the immune system may deliver some exciting opportunities to improve the treatment of mental disorders at a time when many pharmaceutical companies have withdrawn from research and development in psychiatry.

Immunopsychiatry is certainly riding a wave, and it is recognized that the investigation of the relationship between the immune system and the brain is an essential aspect of mainstream psychiatry research and practice.

But, as Spider-Man's Uncle Ben is widely reported to have said, "With great power comes great responsibility." And the most important responsibility that we—scientists operating in this research area—have at the moment is to study relevant questions, deliver reliable findings, and, most importantly, maintain realistic expectations.

Immunopsychiatry should not become a victim of its own success; we should minimize the risk that the enormous amount of work conducted, not always with the strongest methodological approaches, could lead to lack of replication and eventually to disappointment in scientific, clinical, and public opinion.

With this in mind, I read with enthusiasm the article by Lamers *et al.* (1) on the longitudinal association between depression and inflammatory markers in the Netherlands Study of Depression and Anxiety (NESDA) in this issue of *Biological Psychiatry*. I like this paper for what it finds, but I like it even more for what it does not find. This paper takes its "great responsibility" seriously.

Many will know the large cohort that underpins the NESDA, which recruited more than 2900 persons with and without depressive and anxiety disorders from the community and from primary care and secondary care settings in three cities in the Netherlands between September 2004 and February 2007. At baseline, and in two follow-ups at 2 and 6 years, blood biomarkers of inflammation were analyzed.

So what do Lamers *et al.* (1) find in this paper?

First, and perhaps not surprisingly, they find both a cross-sectional and a longitudinal association between a diagnosis of depression and higher levels of inflammation, as measured by the widely used biomarker interleukin-6 (IL-6), at all the three time points: baseline, 2 years, and 6 years.

However, Lamers *et al.* (1) do not find a cross-sectional association between depression and an even more widely used biomarker, C-reactive protein (CRP). This is important because CRP is often the only biomarker of inflammation used in immunopsychiatry studies: it is easy to measure, widely available in most laboratories, and clinically relevant because it is elevated in patients with chronic low-grade inflammation due to metabolic or cardiovascular disorders. Moreover, CRP is a peripheral biomarker that reflects both peripheral and central inflammation (2).

The mismatch between IL-6 and CRP in this article is particularly interesting because CRP is an acute phase protein produced by the liver in response to IL-6, and thus CRP levels are generally considered to be highly correlated, both biologically and statistically, with levels of IL-6. However, the correlations in this study are relatively small (0.33–0.43 using Spearman's rho).

Lamers *et al.* (1) discuss this mismatch at length, but I would like to emphasize that the evidence supporting a role of IL-6 in depression is truly overwhelming. For example, blood messenger RNA levels of IL-6 and of other genes associated with IL-6 signaling are elevated in patients with depression, as shown in a separate study of the NESDA cohort (3), and even when using hypothesis-free, cross-species, and cross-tissues omics analyses (4). Moreover, IL-6 is involved in the action of interferon alpha, until recently the most established model of inflammation-induced depression (5), and it could mediate the proapoptotic action of interferon alpha in the brain (6).

What is the lesson here? Never rely on a single immune marker in this kind of study. If Lamers *et al.* (1) had examined only CRP, they would have had a (false) negative finding, and a (false) lack of replication of many other studies before.

And, if you can, use more than one biological compartment—plasma proteins, blood messenger RNA, and peripheral blood mononuclear cells. We have also recently shown that the levels of two inflammatory biomarkers lead to better outcome prediction in depression than one single biomarker (7).

Incidentally, the large numerosity in the sample allow Lamers *et al.* (1) to clarify two other important points. First, increased IL-6 is present across both male and female sexes, something that previous studies have not always been able to address because of smaller sample sizes. Second, increased IL-6 is present even after adjusting for body mass index and thus is not due just to lifestyle and weight gain. We recently found the same results in a large study of patients with

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depression using body mass index–adjusted CRP in patients with more severe, treatment-resistant depression (8).

The second main finding from Lamers *et al.* (1) is that increased IL-6 at baseline predicts continuous depression at the 2- and 6-year follow-ups. In other words, Lamers *et al.* (1) confirm that increased inflammation longitudinally predicts a more chronic form of depression, which is also more likely to be resistant to antidepressant treatment, although this effect seems to be present in women only.

This is a particularly important finding in the overall theoretical framework of using inflammatory biomarkers to prospectively identify patients who are less likely to respond to antidepressants and who may have a higher likelihood of responding to anti-inflammatory interventions (7).

One interesting point that Lamers *et al.* (1) could not address, because of the study's naturalistic design, is whether inflammation does change because of antidepressant treatment or because of treatment response or because of an interaction between the two. A recent meta-analysis shows that plasma IL-6 levels decrease with antidepressant treatment in both responders and nonresponders, but tumor necrosis factor alpha decreases only in responders (and CRP is not influenced) (9).

Thus, we need to identify the correct immune biomarker for each specific question, to avoid findings that cannot be replicated or that drive us in the wrong direction—or worse, findings that drive us away from the right direction.

Lamers *et al.* (1) have one more important negative finding. They do not find an association between increased inflammation at baseline and increased risk of future depression in people who were not depressed at baseline.

So does inflammation truly come before depression, as the narrative on genetic loading and the role of childhood trauma suggests (10)? If so, why this signal was not detected in the NESDA cohort?

One possibility is that the age of the participants (an average of 42 years of age when they were included in the cohort) may have masked this. Perhaps everybody who had inflammation earlier in their lives because of immune gene loading or exposure to childhood trauma had developed depression by 42 years of age. So this is not truly a negative finding, but rather the wrong sample for the right question.

Yes, the NESDA cohort is one of the best samples to address clinically relevant questions in the immunopsychiatry of depression—but the NESDA cohort alone cannot answer them all.

Let's hope Spider-Man will soon start working with other researchers.

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