

## **Immunopsychiatry in 2021: premise to promise, and back again**

2021 was another busy year for the nascent field of immunopsychiatry. A key premise of the contemporary agenda lies in bottom-up pathways: immune mechanisms can affect brain function and contribute to psychiatric illness. An argument follows that irrespective of their origins, these signals can be targeted therapeutically. In turn, there is seemingly a promise of novel precision therapeutics for common and often otherwise treatment-resistant psychiatric disorders. This optimistic vision is not unfounded; there is a growing body of observational, mechanistic, and interventional findings spanning multiple psychopathologies and immune mechanisms (1). However, some recent treatment trials have yielded more sobering findings. We argue that while this should provoke pause for thought, it is far too early to despair.

More recent larger randomised controlled trials examining agents such as minocycline in schizophrenia have failed to separate anti-inflammatory treatment from placebo based on improvements in psychopathology (2).

A favoured explanation is that sub-groups in whom these mediators are abnormally raised have been lost amidst those without these features (3). Attempts have therefore been made to stratify clinical groups into putative biological entities, often using circulating biomarkers concentration thresholds for classification. However, stratified well-powered studies testing anti-cytokine monoclonal antibodies, such as infliximab for bipolar depression (4) and sirukumab (5) in unipolar depression, have also struggled to find a benefit, despite the clear disease-modifying actions of these treatments in prototypical inflammatory diseases.

Peripheral blood markers do not necessarily reflect what is happening in the brain, so it could simply be that better biomarker approaches are needed perhaps involving multi-modal panels that include cerebrospinal fluid, or it may be that something more fundamental is amiss. Even in brain diseases where neuroinflammation is undoubted such as multiple sclerosis, the road to effective immune therapies has been both long and winding. For primary psychiatric disorders where immunopathology, if present, is likely to be more subtle, the model might need adjustment. The use of biomarkers as a bold objective approach encapsulates a vision of immunopsychiatry as a modernising scientific force for therapeutic good. However, a starting point of categorical diagnoses, encompassing considerable underlying heterogeneity, might mean that relevant signals are obscured. An illustrative comparison comes from NMDAR-antibody encephalitis, a brain disease with a psychiatric onset where causative immune mechanisms are well-characterised. Here there is a clinical structure – it just does not map very well onto the classifications of diagnostic manuals (6).

2021 saw a return to emphasising the potential utility of psychiatric phenotype to enrich for therapeutically tractable neuroimmune mechanisms. For example, with findings reminiscent of the overlap between sickness behaviour and biological symptoms of depression, Frank and colleagues found in a large pooled analysis that higher concentrations of peripheral CRP were more strongly associated with sleep, appetite, and energy than an emotional feature such as hopelessness (7). Alongside these findings, the emerging concept of immunometabolic depression has phenotype at its core, emphasising a clinical picture of atypical depression (8). Perhaps in 2022 and beyond, this joint clinical-laboratory approach will inform experimental medicine approaches, potentially incorporating adaptive trial methodologies, to foster progress across psychiatric disorders.

Rubor, calor, tumor, dolor – neuroinflammation may conjure up images of red hot brains in need of cooling off, a useful metaphor for encephalitis perhaps, but the longer term promise of immunopsychiatry may also lie in the less inflammatory aspects of neuroimmunology. A thought-provoking take from emerging studies of brain and immunity is that of one functional system, with a blurring of boundaries between the two. Conceptually unified by homeostasis, understanding and applying this aptly named “seventh sense” (9) might prove to be more suitable for the complex aetiologies of psychiatric disorders. 2021 has also reminded us that psychotropic medication can also be potent immune modulators in their own right (10) – indicating that further understanding immune mechanisms of well-established treatments could yet be fruitful. It should no longer be a surprise that the immune system has something to do with psychiatry; the challenge now is to design studies that make sense of this relationship. The translation of neuroimmune

premises into clinical promise is not a foregone conclusion. Akin to the bumpy but nonetheless progressive integration of neuroscience and genomics into psychiatry, we will probably be trying to figure out how to best leverage neuroimmune breakthroughs for psychiatric illness for quite some time yet.

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#### Competing interests declaration

TP has participated in educational speaker meetings organised by Lundbeck, Otsuka, Sunovion, Schwabe Pharma and Recordati. AAD and BL report no competing interests.

#### References

1 – De Picker LJ. The future of immunopsychiatry: Three milestones to clinical innovation. *Brain Behav Immun Health*. 2021 Jul 30;16:100314. doi: 10.1016/j.bbih.2021.100314. PMID: 34589805; PMCID: PMC8474175.

2 – Deakin B, Suckling J, Barnes TRE, et al. The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial. *Lancet Psychiatry*. 2018 Nov;5(11):885-894.

3 – Miller AH, Pariante CM. Trial failures of anti-inflammatory drugs in depression. *Lancet Psychiatry*. 2020 Oct;7(10):837. doi: 10.1016/S2215-0366(20)30357-6. PMID: 32949510.

4 – McIntyre RS, Subramaniapillai M, Lee Y, et al. Efficacy of Adjunctive Infliximab vs Placebo in the Treatment of Adults With Bipolar I/II Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2019 Aug 1;76(8):783-790

5 – <https://clinicaltrials.gov/ct2/show/results/NCT02473289?view=results>

6 – Al-Diwani A, Handel A, Townsend L, et al. The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data. *Lancet Psychiatry*. 2019 Mar;6(3):235-246.

7 – Frank P, Jokela M, Batty GD, Cadar D, Steptoe A, Kivimäki M. Association Between Systemic Inflammation and Individual Symptoms of Depression: A Pooled Analysis of 15 Population-Based Cohort Studies. *Am J Psychiatry*. 2021 Oct 14 doi: 10.1176/appi.ajp.2021.20121776. Epub ahead of print.

8 – Milaneschi Y, Lamers F, Penninx BWJH. Dissecting Depression Biological and Clinical Heterogeneity-The Importance of Symptom Assessment Resolution. *JAMA Psychiatry*. 2021 Mar 1;78(3):341.

9 – Kipnis J. Immune system: The "seventh sense". *J Exp Med*. 2018 Feb 5;215(2):397-398.

10 – Reis G, Moreira-Silva E, Silva D, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2021 Oct 27; doi: 10.1016/S2214-109X(21)00448-4.