

Unravelling the origins of autoimmune psychosis

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Anti-NMDAR encephalitis is an autoimmune brain illness that is often mistaken as a psychiatric disorder since it causes psychoses and other behavior alterations. Despite having these similarities, the illness does

not respond to common antipsychotic treatments.

A new study by the University of Barcelona (UB) and the August Pi i Sunyer Biomedical Research Institute (IDIBAPS) shows these symptoms would be caused by alterations in the quantity of dopaminergic receptors D1R and D2R in the hippocampal area of the brain. These results, published in the journal *Annals of Neurology*, shed light on the biological base of psychotic symptoms in this and other autoimmune psychoses and they could ease the development of new drugs in the future.

The study results from the bachelor's degree final project of the former student of the Faculty of Medicine and Health Sciences of the UB Marc Carceles-Cordon and it is co-led by Josep Dalmau, ICREA professor, director of the Program on Clinical and Experimental Neuroimmunology at IDIBAPS-Hospital Clínic and UB, and lecturer of Neurology at the University of Pennsylvania (Philadelphia, United States) and Jesús Planagumà, researcher at IDIBAPS. Other participants in the study are the UB and IDIBAPS researchers Francesco Mannara, Esther Aguilar and Aida Castellanos.

Schizophrenia-like symptoms

The objective of the study was to improve the understanding of the molecular origins of the psychotic symptoms in anti-NMDAR encephalitis, the most representative example for autoimmune encephalitis. These are a series of inflammatory brain diseases caused due to the generation of antibodies that attack proteins found in the surface of the neurons of the affected patients. In this illness, found by Professor Dalmau in 2007, the antibodies affect the NMDA receptor, one of the most important ones in synaptic transmission, causing alterations in behavior and neuropsychiatric symptoms that are similar to those from schizophrenia.

Given these similarities, researchers considered the hypothesis that there could be a converging mechanism between autoimmune psychosis and this psychiatric disorder. "Since the dopaminergic system of schizophrenia is altered, we focused on the analysis of the levels of dopaminergic receptors in [cell cultures](#) and in one animal model of anti-NMDAR encephalitis," notes Marc Carceles-Cordon.

This model, carried out by the research group of the UB, administers mice the cerebrospinal fluid that contains pathological antibodies from patients with anti-NMDAR encephalitis. Then, mice develop similar symptoms to those seen in patients, which are molecularly correlated to what occurs in the brain of those affected. The new study adopted the pre-existing model, which has been used successfully in other projects, to study psychotic symptoms in depth.

A first step towards potential treatments

The results show that giving [cerebrospinal fluid](#) from patients with anti-NMDAR encephalitis produces several changes in the levels of D1r and D2R in neuron brain cultures and similar alterations in the animal model of the disease. These changes cause memory deficits and psychotic behavior in mice. Last, they observed that all of this reverts when stopping the administration of antibodies to patients.

According to the researchers, these results help understand the biological base of the psychiatric symptoms of anti-NMDAR encephalitis, and the autoimmune psychosis, with important implications in the design of new treatments. "In the future, these data can provide us with the development of antipsychotic drugs that consider the molecular base of this symptom and are more efficient than current antipsychotics -which have been used for decades-, which are not useful and can even be counter-productive when trying to control psychotic symptoms of anti-NMDAR [encephalitis](#)," notes Marc Carceles Cordon.

Moreover, the study can help understand other types of psychosis, a symptom that affects different mental disorders. "For a long time, we regarded this [symptom](#) as a part of schizophrenia, but psychosis is present in many mental illnesses (depression, dementia, etc.), and understanding its underlying mechanisms can, in the future, guide treatments aimed at reducing the pain of the patients," concludes the researcher.

More information: Marc Carceles-Cordon et al, NMDAR Antibodies Alter Dopamine Receptors and Cause Psychotic Behavior in Mice, *Annals of Neurology* (2020). [DOI: 10.1002/ana.25829](https://doi.org/10.1002/ana.25829)

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