Understanding psychosis, cognitive impairment and motor symptoms induced by NMDA receptor dysfunction: from mechanisms to prevention and therapy (NMDAR-PSY)

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Schizophrenia is one of the most severe psychiatric disorders with onset of symptoms mainly during young adulthood, followed in many cases by a lifelong chronic evolution that generates tremendous medical care and social problems. The origins of schizophrenia are so far unclear and most drugs used in the therapy of the disorders have been developed serendipitously. A core symptom of schizophrenia is altered cognition, which cannot be improved by current medications. Interestingly, severe cognitive deficits, associated with sharp shrinkage of the hippocampus (a brain structure playing a key role in learning and memory), were found in patients with anti-NMDA receptor (NMDAR) encephalitis. This represents a recently discovered, mainly paraneoplastic form of autoimmune encephalitis, in which autoantibodies against glutamate NMDAR induce psychotic and often also motor symptoms (like severe catatonia) that are indistinguishable from those seen in schizophrenia. Whereas psychosis in these patients is largely curable, the lost long-lasting cognitive deficits cannot be efficiently treated. In the present project, we aim to determine the possible beneficial effect of drugs enhancing NMDAR function to alleviate symptoms associated with NMDAR hypofunction both in genetically modified mice as well as in humans suffering from schizophrenia. Our approach is highly interdisciplinary including several morphological, electrophysiological, behavioral, as well as clinical and complex data analysis methods. By including two different cohorts of individuals with prodromal *versus* chronic, therapy-resistant schizophrenia, we aim to provide a differentiated view regarding the effect of NMDAR enhancers in specific phases of the disease. Additionally, we aim to determine if the therapeutic response is influenced by genetic factors in these patients. Our project aims to bring together pre-clinical and clinical research: since pathological changes at molecular and cellular level cannot be studied in humans, we will analyze two genetically modified mouse lines with alterations in NMDAR in selective neuronal populations, and will extensively compare these data with those resulting from the analysis of humans suffering from schizophrenia or humans at high risk of developing the disease. The final goal of our study is to better understand the mechanisms by which NMDAR dysfunction induces the numerous, partly difficult to treat abnormalities seen in schizophrenia and anti-NMDAR encephalitis and to contribute to the development of more selective and efficient antipsychotic drugs.