A Role for D-aspartate Oxidase in Schizophrenia and in Schizophrenia-related Symptoms Induced by Phencyclidine in Mice.

M. Squillace1, F. Errico1, V. D’Argenio2, F. Sforazzini3, F. Iasevoli4, G. Guerri2, F. Napolitano1, T. Angrisano5, A. Di Maio1, D. Vitucci1, A. Bifone3, L. Chiariotti6, A. Bertolino7, A. De Bartolomeis4, F. Salvatore2, A. Gozzi3, A. Usiello1

1Laboratory of Behavioural Neuroscience, Ceinge Biotecnologie Avanzate, Naples, Italy ; 2Laboratory of Next Generation Sequencing, Ceinge Biotecnologie Avanzate, Naples, Italy ; 3Center for Neuroscience and Cognitive Systems, Istituto Italiano di Tecnologia, Rovereto, Italy ; 4Laboratory of Molecular and Translational Psychiatry Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy ; 5Department of Biology, University of Naples "Federico II", Naples, Italy ; 6Department of Molecular Medicine and Medical Biotechnology, University of Naples "Federico II", Naples, Italy ; 7Group of Psychiatric Neuroscience Department of Neuroscience Basic Sciences and Sense Organs, University of Bari "Aldo Moro", Bari, Italy

Introduction: D-aspartate (D-Asp) is an atypical amino acid that binds to and activates NMDARs. D-Asp occurs abundantly in the embryonic brain of mammals and rapidly decreases after birth, due to the activity of the enzyme D-Aspartate Oxidase (DDO). The agonistic activity of D-Asp on NMDARs and its neurodevelopmental occurrence make this D-amino acid a potential mediator for NMDAR-related alterations observed in schizophrenia. Consistently, substantial reduction of D-Asp was observed in post-mortem schizophrenia brains.

Aims: We evaluated the potential contribution of D-Asp as neurodevelopmental modulator of brain circuits and behaviors relevant to schizophrenia.

Objectives: We analyzed DDO mRNA expression in the post-mortem prefrontal cortex of schizophrenic patients. Moreover, we treated knockout mice for Ddo gene (Ddo-/-) with the NMDAR antagonist phencyclidine to evaluate their schizophrenia-relevant behaviors and circuits. Finally, we assessed cortico-hippocampal connectivity of these mice.

Methods: DDO mRNA detection was performed by quantitative PCR. Phencyclidine-induced schizophrenia-like behaviours were assessed through motor activity and prepulse inhibition paradigms. Resting-state and pharmacological fMRI were used to evaluate functional circuits and connectivity.

Results: DDO mRNA expression is increased in frontal samples of schizophrenic patients. In mice, the absence of Ddo gene produces a significant reduction in phencyclidine-induced motor hyper-activity and prepulse inhibition deficit. Furthermore, increased levels of D-Asp in Ddo-/- animals significantly inhibit functional circuits activated by phencyclidine, and affect the development of cortico-hippocampal connectivity networks potentially involved in schizophrenia.

Conclusions: Our data suggest that D-Asp, through the regulation exerted by DDO, may have a role in the pathophysiology of schizophrenia.