The hippocampal prefrontal circuit: A key hub for potential therapeutic targets

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Despite considerable efforts, neuropsychiatric disorders continue to represent a huge personal and socio-economic burden. The approval of psychotropic drugs with novel mechanisms of action has been rare in recent years. The pathology-to-drug discovery approach inspired the creation of NEWMEDS (Novel Methods Leading to New Medications in Depression and Schizophrenia), a European project designed to identify specific brain circuits, particularly those involving the prefrontal cortex, that are involved in the pathophysiology and treatment of major depression and schizophrenia. We discovered and cross-validated, independently, the precise brain circuits at risk. Our research supports the idea that the projection of neurons extending from the hippocampus to the medial prefrontal cortex (H-PFC) is crucial for cognition and emotional regulation via the top-down modulation of neuronal activity in other cortical and subcortical areas. We demonstrated that the hippocampus, which itself has a unidirectional input to the PFC is highly stress dependent and crucially involved in the pathophysiology of several psychiatric diseases and recently, showed evidence for the idea that H-PFC neuroplasticity has face validity for modeling ketamine-clozapine interactions. The H-PFC pathway has a potentially crucial role in the pathophysiology of several psychiatric diseases, and it offers a specific target for therapeutic intervention consistent with reframing of psychiatric diseases in terms of brain circuits. All data from ours and other partners confirm the importance of a circuit-based approach to evaluate established and novel compounds.

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