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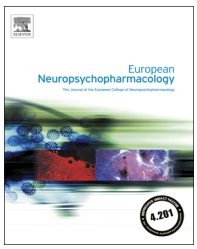

REVIEW

The hippocampal-prefrontal pathway: The weak link in psychiatric disorders?

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Abstract
While the hippocampal formation and the prefrontal cortex each have a well-established role in cognitive and mnemonic processes, the extent and manner in which these structures interact to achieve these functions has not been fully delineated. Recent research in rodents compellingly supports the idea that the projection of neurons extending from the CA1 region of the hippocampus and from the subiculum to the prefrontal cortex, referred to here as the H-PFC pathway, is critically involved in aspects of cognition related to executive function and to emotional regulation. Concurrently, it is becoming evident that persons suffering from schizophrenia, depression, and post-traumatic stress disorder display structural anomalies and aberrant functional coupling within the hippocampal-prefrontal circuit. Considering that these disorders involve varying degrees of cognitive impairment and emotional dysregulation, dysfunction in the H-PFC pathway might therefore be the common element of their pathophysiology. This overlap might also be intertwined with the pathway's evident susceptibility to stress and with its relationship to the amygdala. In consequence, the H-PFC pathway is a potentially crucial element of the pathophysiology of several psychiatric diseases, and it offers a specific target for therapeutic intervention, which is consistent with the recent emphasis on reframing psychiatric diseases in terms of brain circuits.

Contents

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1. Introduction

Rarely is a symptom exclusive to a specific psychiatric disorder. Indeed, seemingly distinct disorders can have overlapping symptoms, which typically vary over time and according to the disease severity. Cognitive impairment, for example, is a major cause of disability in schizophrenia, but also emerges in depression and in anxiety disorders (Elvevag and Goldberg, 2000; Mantella et al., 2007; Porter et al., 2003). Emotional dysregulation is central to depression and to anxiety disorders, yet it also emerges in schizophrenia (Braga et al., 2005). There is also substantial comorbidity between these disorders (Braga et al., 2005; Kaufman and Charney, 2000), and there is abundant evidence for a shared genetic basis, as well as shared risk factors that influence hippocampal–prefrontal interaction (Esslinger et al., 2009; Rasetti et al., 2011). Recently, the National Institute of Mental Health (NIMH) has made a push to classify mental disorders in relation to dysfunction in the relevant brain circuits (Insel et al., 2010). Thus, while mental disorders surely have complex pathophysiology, it is possible that the similarity in symptoms is the consequence of disruption in common brain circuits.

The hippocampus and subiculum are implicated in diverse functions, including spatial and contextual processing, memory, and emotional processing (Fanselow and Dong, 2010; O'Mara et al., 2009). The prefrontal cortex (PFC) participates in numerous cognitive functions that serve executive function, including working memory, temporal processing, decision making, flexibility and goal-oriented behavior (Kesner and Churchwell, 2011). Recent experimental findings in animals have begun to elucidate the manner in which the hippocampus influences the activation of ensembles of neurons in the PFC during such behaviors. These electrophysiological observations are consistent with a wider body of evidence that implicates hippocampal–prefrontal interaction in aspects of executive functioning. In parallel, the analysis of functional imaging data in people suffering from different psychiatric disorders has revealed marked aberrations in the structure, activation, and functional coupling in the hippocampal–PFC circuit.

A projection of neurons termed the hippocampal-to-PFC pathway (H-PFC pathway) comprises the major efferent anatomical connection from hippocampal formation (defined here as the hippocampus, prosubiculum, and subiculum) to the PFC. The activity of this pathway is highly sensitive to stress, which is a major precipitating factor for symptoms of depression, schizophrenia and anxiety disorders. The pathway also has important interactions with the amygdala, and there is strong evidence in rodents implicating the H-PFC pathway in aspects of executive function and in contextual processing that serves emotional regulation. This article reviews preclinical and clinical evidence to argue that the H-PFC pathway has an important role in functions that appear aberrant in several psychiatric disorders. Namely, we suggest that the pathway transmits information which serves working memory and aspects of learning, as well as contextual processing that lends to recognition memory and emotional regulation. Furthermore, genetic factors and stress can dysregulate these processes and thereby contribute to aberrant functional coupling between the hippocampal formation and PFC, which contributes to the deficits in cognition and emotional regulation that are common to an array of psychiatric disorders.

2. The H-PFC pathway

2.1. Anatomy

While there are many multi-synaptic routes that can transmit signals from the hippocampal formation to the PFC, the H-PFC pathway represents the significant monosynaptic unidirectional projection between the regions (Ongur and Price, 2000). A direct cortical input originating from the hippocampal formation has been well characterized in rats and monkeys. In rats, the H-PFC pathway originates from the CA1 region of the hippocampus and from the subiculum, with the strongest projections originating from the ventral hippocampus (VH) and subiculum, but