European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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Hippocampal-prefrontal connectivity as a translational phenotype for schizophrenia

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Received 9 February 2016; received in revised form 16 November 2016; accepted 19 December 2016

KEYWORDS
Hippocampus;
Prefrontal cortex;
Functional neuroimaging;
Schizophrenia;
Short-term memory

Abstract
Finding novel biological targets in psychiatry has been difficult, partly because current diagnostic categories are not defined by pathophysiology and difficult to model in animals. The study of species-conserved systems-level mechanisms implicated in psychiatric disease could be a promising strategy to address some of these difficulties. Altered hippocampal-prefrontal (HC-PFC) connectivity during working memory (WM) processing is a candidate for such a translational phenotype as it has been repeatedly associated with impaired cognition in schizophrenia patients and animal models for psychiatric risk factors. Specifically, persistent hippocampus-dorsolateral prefrontal cortex (HC-DLPFC) coupling during WM is an intermediate phenotype for schizophrenia that has been observed in patients, healthy relatives and carriers of two different risk polymorphisms identified in genome-wide association studies. Rodent studies report reduced coherence between HC and PFC during anesthesia, sleep and task performance in both genetic, environmental and neurodevelopmental models for schizophrenia. We discuss several challenges for translation including differences in anatomy, recording modalities and WM paradigms and suggest that a better understanding of HC-PFC coupling across species can be achieved if translational neuroimaging is used to control for task differences. The evidence for potential neurobiological substrates underlying HC-PFC dysconnectivity is evaluated and research strategies are proposed that aim to bridge the gap between findings from large-scale association studies and disease mechanisms.

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http://dx.doi.org/10.1016/j.euroneuro.2016.12.007
0924-977X/

Please cite this article as: Bähner, F., Meyer-Lindenberg, A., Hippocampal-prefrontal connectivity as a translational phenotype for schizophrenia. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2016.12.007

1. Introduction

More than 100 years ago, Carl Wernicke was the first to propose that schizophrenia may not be caused by focal brain abnormalities but result from disturbed interactions of brain regions and this idea has received increasing attention with the advent of human neuroimaging methods (Stephan et al., 2009). The hypothesis that disturbed HC-DLPFC interactions may be a core aspect of schizophrenia pathophysiology was motivated by findings that offered a mechanistic explanation for the suggested link between early neurodevelopmental disturbances and schizophrenia (Weinberger, 1987). The HC provides direct input to the DLPFC in primates (and to homologous regions in the rat) (Goldman-Rakic et al., 1984; Hoover and Vertes, 2007) and neonatal HC lesions in both rodents and primates lead to structural changes in prefrontal circuits that are accompanied by a set of schizophrenia-like cognitive impairments which emerge only after puberty (Bertolino, 1997; Heuer and Bachevalier, 2011; Tseng et al., 2009). This appeared to be a plausible pathophysiological mechanism as the HC is vulnerable in early brain development, for example to obstetrical complications which are a risk factor for schizophrenia (Weinberger, 1987). Early evidence for this hypothesis was provided in a study combining positron emission tomography (PET) and structural magnetic resonance imaging (MRI) in monozygotic twins discordant for schizophrenia (Weinberger et al., 1992): the more a symptomatic twin differed from the healthy twin with respect to left HC volume, the more they differed in DLPFC activation during a rule switching paradigm. Meyer-Lindenberg et al. used the n-back task together with PET measurements (Meyer-Lindenberg et al., 2005) to directly probe HC-DLPFC functional connectivity during high versus low WM load in both patients and controls. They found that in controls, activation of the DLPFC increased, the HC was deactivated and both structures functionally uncoupled during high as compared to low WM load. In contrast, schizophrenia patients showed attenuated DLPFC activation/HC deactivation and persistent HC-DLPFC coupling under high WM load (Figure 1A). It was proposed that uncoupling may be beneficial for human WM performance as it leads to an inhibition of interfering cognitive processes, such as parallel encoding of stimuli in episodic memory (Meyer-Lindenberg et al., 2005). Several other studies using different WM tasks and coupling measures found that HC-DLPFC connectivity patterns separate patient scans from scans of healthy controls (Meyer-Lindenberg et al., 2001) and that dysconnectivity within networks comprising HC and lateral PFC can not only be found in chronic patients but

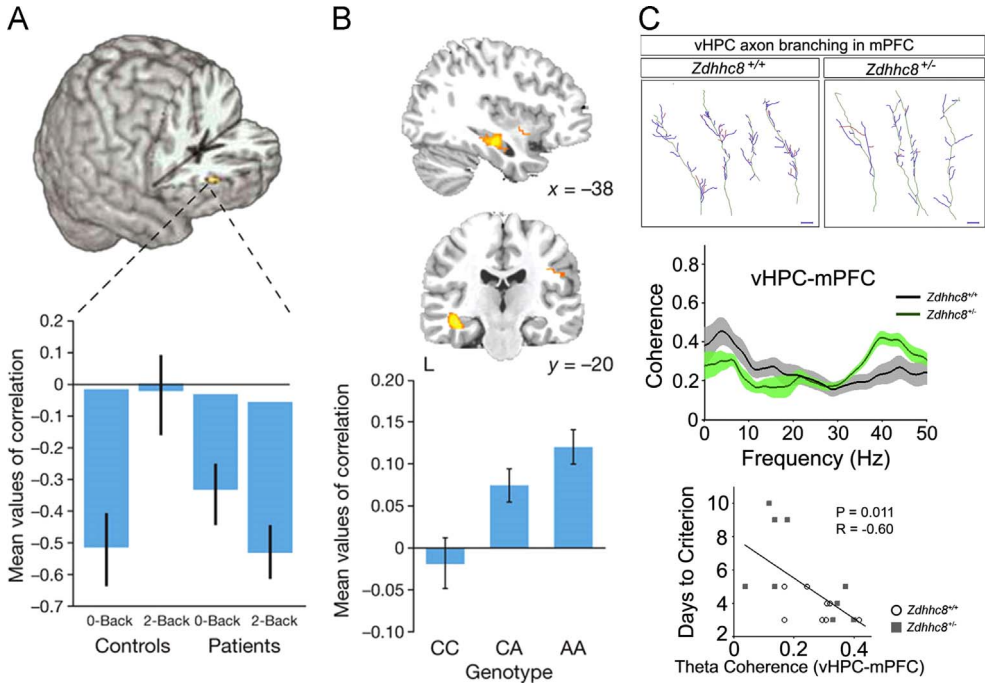

Figure 1 Hippocampal-prefrontal (HC-PFC) coupling is a systems-level phenotype that is related to genetic risk for schizophrenia. (A) Significant coupling (correlation of positron emission tomography/PET activity) of left hippocampus (HC) with right dorsolateral prefrontal cortex (DLPFC) during both the 2-back (high working memory/WM load) and 0-back (control condition) tasks in patients but only during the 0-back task in controls (Meyer-Lindenberg et al., 2005). (B) The same pattern of persistent HC-DLPFC coupling during high WM load in the n-back task can be observed in functional magnetic resonance imaging (fMRI) scans of healthy carriers of a genome-wide significant genetic risk variant (genotype AA in *ZNF804A*) (Esslinger et al., 2009). (C) Hippocampal axons of mice deficient for the gene *Zdhhc8* (*Zdhhc8*$^{+/-}$) make fewer branches in the medial PFC (mPFC) during development (upper trace), an effect that persists into adulthood. Mutant mice display decreased HC-mPFC theta coherence (middle trace) and theta coherence at baseline is correlated with days to reach the performance criterion in a spatial WM task (lower trace) (Mukai et al., 2015). Error bars indicate standard errors. Reprinted from Meyer-Lindenberg et al., 2005, Meyer-Lindenberg, 2010, Esslinger et al., 2009 and Mukai et al., 2015, with permission from American Medical Association, Nature Publishing Group, the American Association for the Advancement of Science and Elsevier.

Please cite this article as: Bähner, F., Meyer-Lindenberg, A., Hippocampal-prefrontal connectivity as a translational phenotype for schizophrenia. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2016.12.007