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Altered resting-state functional connectivity and anatomical connectivity of hippocampus in schizophrenia

Yuan Zhou [a,1], Ni Shu [a,1], Yong Liu [a], Ming Song [a], Yihui Hao [b], Haihong Liu [b], Chunshui Yu [c], Zhening Liu [b,*], Tianzi Jiang [a,*]

[a] National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, PR China
[b] Institute of Mental Health, Second Xiangya Hospital, Central South University, Changsha 410011, Hunan, PR China
[c] Department of Radiology, Xuanwu Hospital of Capital University of Medical Science, Beijing 100053, PR China

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Abstract

Hippocampus has been implicated in participating in the pathophysiology of schizophrenia. However, the functional and anatomical connectivities between hippocampus and other regions are rarely concurrently investigated in schizophrenia. In the present study, both functional magnetic resonance imaging (fMRI) during rest and diffusion tensor imaging (DTI) were performed on 17 patients with paranoid schizophrenia and 14 healthy subjects. Resting-state functional connectivities of the bilateral hippocampi were separately analyzed by selecting the anterior hippocampus as region of interest. The fornix body was reconstructed by diffusion tensor tractography, and the integrity of this tract was evaluated using fractional anisotropy (FA). In patients with schizophrenia, the bilateral hippocampi showed reduced functional connectivities to some regions which have been reported to be involved in episodic memory, such as posterior cingulate cortex, extrastriate cortex, medial prefrontal cortex, and parahippocampus gyrus. We speculated that these reduced connectivity may reflect the disconnectivity within a neural network related to the anterior hippocampus in schizophrenia. Meanwhile the mean FA of the fornix body was significantly reduced in patients, indicating the damage in the hippocampal anatomical connectivity in schizophrenia. The concurrence of the functional disconnectivity and damaged anatomical connectivity between the hippocampus and other regions in schizophrenia suggest that the functional–anatomical relationship need to be further investigated.

Keywords: Schizophrenia; Hippocampus; fMRI; Diffusion tensor tractography; Functional connectivity; Anatomical connectivity

Abbreviations: fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; BOLD, blood oxygen level-dependent; DT-t, diffusion tensor tractography; PCC, posterior cingulate cortex; MPFC, medial prefrontal cortex; STG, superior temporal gyrus.

* Corresponding authors. Jiang is to be contacted at National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, PR China. Tel.: +86 10 8261 4469; fax: +86 10 62551993. Liu, Institute of Mental Health, Second Xiangya Hospital, Central South University, Changsha 410011, PR China. Tel.: +86 0731 529 2470; fax: +86 0731 5554052.
E-mail addresses: zheningliu@yahoo.com.cn (Z. Liu), jiangtz@nlpr.ia.ac.cn (T. Jiang).
[1] These authors equally contribute to this work.

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1. Introduction

Convergent evidence from histological, molecular biology, structural, neuropsychological and functional imaging suggests that hippocampus involves in the pathophysiology of schizophrenia (Gothelf et al., 2000; Harrison, 2004). According to the opinion that the complex clinical presentations of schizophrenia are contributed to the abnormality in inter-regional interaction rather than the abnormality of single region (Friston, 1998), it is significant to investigate the interaction between the hippocampus and other brain regions from two different perspectives, i.e., functional and anatomical connectivity.

Recently, resting-state functional connectivity attracts more and more researchers' attention. Spontaneous low-frequency (<0.08 Hz) fluctuation (SLFF) of the signal in the blood oxygen level-dependent (BOLD) MR imaging is often used to measure the resting-state functional connectivity (Biswal et al., 1995; Greicius et al., 2003; Lowe et al., 1998). The low-frequency BOLD coherence may be related to neuronal activity (Leopold et al., 2003). And many researchers have observed that in functionally related brain regions, even located remotely, these fluctuations are synchronous (Biswal et al., 1995; Lowe et al., 1998). This implies the existence of neuronal connections that facilitate coordinated activity in the human brain. In different neuropsychiatric diseases, including schizophrenia, the abnormalities in resting-state functional connectivity have been reported (Liang et al., 2006; Tian et al., 2006; Wang et al., 2006; Zhou et al., 2007a; Zhou et al., 2007b). Liang et al found that the temporal regions including hippocampus showed reduced functional connectivities with distributed brain regions during rest in schizophrenia (Liang et al., 2006). Because this study focused on the inter-regional functional connectivities of 116 regions of the whole brain, this preliminary study cannot reveal detailed information on the hippocampal connectivity patterns of schizophrenia. In terms of the other two recent studies, one was interested in the functional connectivity pattern of the dorsolateral prefrontal cortex not that of the hippocampus (Zhou et al., 2007a), and the other focused on the inter-regional functional connectivities just within the default mode network and its anti-correlated network or between the networks (Zhou et al., 2007b). Thus exact information on functional connectivity of the hippocampus could not be obtained from the above studies. In order to obtain more precise and detailed information, it is necessary to analyze the resting-state functional connectivity patterns of the hippocampus in a voxel-wise matter.

On the other hand, a relative new neuroimaging technique, diffusion tensor imaging (DTI), affords the possibility to in vivo explore anatomical connectivity in the human brain. By measuring the degree of anisotropy in random motion of water molecules, DTI provides the information about cellular integrity and pathology (Eriksson et al., 2001; Le Bihan, 2003; Rugg-Gunn et al., 2002). A higher anisotropy of diffusion reflects a motion of water molecules favored in a specific direction, for example, parallel to highly structured white matter fibers. By tracking along the principal diffusion direction, the course of white matter fiber tracts may be visualized, which is known as diffusion tensor tractography (DT-t). Fornix is a major pathway linking the hippocampus with other brain regions (Chance et al., 1999; Kuroki et al., 2006). Although the fornix integrity in schizophrenia has been assessed by ROI-based (Kuroki et al., 2006) and voxel-based (Kanaan et al., 2005; Kubicki et al., 2007; Kubicki et al., 2005) analysis, the results are inconsistent. In the present study, we investigated the fornix integrity using DT-t, which has not been performed in schizophrenia although it has been used to visualize the fornix in healthy subjects (Catani et al., 2002; Wakana et al., 2004) or epilepsy patients (Concha et al., 2005).

We hypothesized that the resting-state functional connectivity of the hippocampus would be decreased; meanwhile, the integrity of the fornix measured by DT-t would be damaged in the same patients with schizophrenia. In order to test our hypothesis, we investigated the hippocampal functional connectivity by using region-of-interest (ROI)-based correlation analysis (Biswal et al., 1995; Wang et al., 2006). We selected the anterior hippocampus as ROI based on the following considerations. 1) The anterior hippocampus may be relevant to hypotheses regarding the pathophysiology of schizophrenia (Szeszko et al., 2003). 2) MRI studies suggest that the subtle hippocampal changes in schizophrenia may primarily involve the anterior division (Csernansky et al., 2002; Heckers and Konradi, 2002; Narr et al., 2004; Pegues et al., 2003; Szeszko et al., 2003). 3) Abnormalities in anterior hippocampal regions in patients with schizophrenia are linked to deficits on neuropsychological tests related to frontal lobe function (Bilder et al., 1995), impaired ability to identify new items (Weiss et al., 2004) and verbal forgetting (Rametti et al., 2007). In addition, given the existence of extensive afferent and efferent neocortical connections in the anterior hippocampus, which integrates neural activity from widespread neocortical inputs and outputs (Sperling et al., 2003; Wang et al., 2006), this region is an appropriate candidate to link functional connectivity and anatomical connectivity.

By combining of DTI and functional connectivity analyses, the current study provides a particular perspective to understand the abnormality of the connectivity associated with the hippocampus in schizophrenia. This