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Research Report

Long-and short-range functional connectivity density alteration in non-alcoholic cirrhotic patients one month after liver transplantation: A resting-state fMRI study

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ABSTRACT

Purpose: To longitudinally evaluate long- and short-range functional connectivity density (FCD) alteration in cirrhotic patients one month after liver transplantation (LT) and their correlation with cognitive changes by using resting-state functional magnetic resonance imaging (rs-fMRI).
Methods: Twenty seven candidates awaiting LT and 24 age-, gender-, and education-matched healthy controls (HCs) were studied. All 27 patients and HCs performed rs-fMRI examinations. Of 27 cirrhotic patients, 13 patients received LT underwent the repeated rs-fMRI examinations one month after LT. Laboratory and psychometric tests were carried out. The long- and short-range FCD maps derived from degree centrality calculation were compared. Correlations between FCD alteration and laboratory/psychometric changes were evaluated as well.
Results: In cirrhotic patients, most of the brain areas with altered long- and short-range FCD could reverse one month after LT, which was accompanied with cognitive and liver functional

Abbreviations: rs-fMRI, resting-state fMRI; DMN, default mode network; FCD, functional connectivity density; HE, hepatic encephalopathy; MHE, minimal HE; OHE, overt HE; LT, liver transplantation; HC, healthy controls; pre-LT, prior to LT; post-LT, after LT; MFG, middle frontal gyrus; MHE, minimal HE; MPFC, medial prefrontal cortex; DST, digital symbol test; NCT-A, number connection test type A; PCC, posterior cingulate cortex; PCu, precuneus; preCG, precentral gyrus; REC, right rectus gyrus; SMA, supplementary motor area

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improvement. The reduced long-range FCD in right posterior cingulate cortex (PCC) and Left middle frontal gyrus (MFG), and reduced short-range FCD in right precuneus (PCu) persisted in the early period after LT. In addition, one month after LT, the post-LT group showed reduced long-range FCD in right rectus gyrus (REC) and left medial prefrontal cortex (MPFC), and reduced short-range FCD in left middle temporal gyrus (MTG), when compared with the pre-LT group. We found Δdigital symbol test (ΔDST) score positively correlated with long-range ΔFCD in right precentral gyrus (preCG) ($r=0.72$, $P<0.01$) and right supplementary motor area (SMA) ($r=0.59$, $P<0.05$).

Conclusion: LT results in favorable effect on cognitive function in cirrhotic patient, which can be reflected by FCD alteration. However, persistence of PCC/PCu functional connectivity disturbance one month after LT indicates complete cognitive function restoration may need a longer time.

1. Introduction

Cognitive impairment is an important complication of cirrhosis (Brodersen et al., 2014; McPhail et al., 2013; Qi et al., 2014; Zhang et al., 2014b), with hepatic encephalopathy (HE) as the most prevalent etiology (Ferenci et al., 2002). The spectrum of cognitive impairment in cirrhosis is a continuum, ranging from minimal HE (MHE) to overt HE (OHE) and coma (Bajaj et al., 2009). HE is diagnosed by the presence of prominent neurological manifestations which can be explained by liver failure or portosystemic shunting. MHE is commonly diagnosed by psychometric tests (Ferenci et al., 2002). Patients with MHE are supposed to suffer from cognitive deficits (Zhang et al., 2013; Zhang et al., 2014a) in the domains of attention, executive functioning, working memory, psychomotor speed and so on, which could impair life quality and predict OHE (McPhail et al., 2013; Zhang et al., 2014c). Recently, Qi et al. (2014) found abnormal functional connectivity within the default mode network in cirrhotic patients without clinical manifestation and MHE, which indicated that even cirrhotic patients with normal psychometric tests suffered from brain functional disturbance.

Liver transplantation (LT), as the most effective therapy for the patients with advanced cirrhosis, can restore liver function completely. Low-grade brain edema and cognitive function can be improved by LT (Ishihara et al., 2013). Nevertheless, some studies indicated the restoration of neuropsychological disturbance is not complete or not generalized to all cognitive functions (Mattarozzi et al., 2012) with residual cognitive and psychomotor deficits (Mechtcheriakov et al., 2004). The underlying neurological mechanism is not well understood.

Neuroimaging is a useful tool for discovering the neurological mechanism of structural and functional brain changes following LT in cirrhotic patients, and may provide new biomarkers for evaluating the efficacy of LT (Ishihara et al., 2013). It is widely agreed that globus pallidus hyperintensity on T1-weighted images can be reversed slowly after the cessation of hepatic cell damage. However, complete reversibility of brain metabolite changes reflected in MR spectroscopy (7–8 months after LT) precedes this process (Naegele et al., 2000). Diffusion tensor imaging (DTI) is useful to assess white matter integrity following LT. Some DTI studies with voxel-based analysis (VBA) or tract-based spatial-statistic (TBSS) found the improved cognitive function after LT could be attributed to reduced brain edema (Ishihara et al., 2013; Lin et al., 2014a).

Apart from brain metabolic and structural MRI studies mentioned above, in recent years, blood oxygenation level-dependent (BOLD) resting state functional MRI (rs-fMRI), without requirement of specific experimental tasks, has attracted increasing attention for studying neural mechanism of cognition dysfunction in patients with cirrhosis (Zhang et al., 2013). A body of local neuronal activity alterations in cirrhotic patients has been found by using regional homogeneity (ReHo) (Lv et al., 2013) and amplitude of low frequency fluctuation (ALFF) (Qi et al., 2012). Moreover, whole-brain functional connectivity (intrinsic coherence of neural activity between anatomically separated regions) by using rs-MRI based on independent component analysis (ICA) (Chen et al., 2013; Zhang et al., 2012a), region of interest analysis (ROI) (Zhang et al., 2012b), and topological analysis based on graph theory (Hsu et al., 2012; Zhang et al., 2014b) have revealed the changes of brain functional connectivity or network topological properties (e.g. small-worldness) in patients with cirrhosis. These rs-fMRI studies indicated that, as a dynamic process, impairment and reorganization of brain network functional connectivity might exist during the evolution of HE from cirrhosis without HE, MHE to OHE. Regarding the dynamic feature of brain network (Buckner et al., 2013), we suppose that LT might exert influence on this process. Recently, Lin et al. (2014b) used graph theory to monitor the reestablishment of brain network in patients without OHE 6 to 12 months after LT. They found that dynamic disruptions and reorganization in intrinsic large-scale networks were associated with cognitive deficits and recovery under the interference of LT. However, their study focused on the long-term effect of LT on brain functional and cognitive recovery. To the best of our knowledge, the alteration of brain function connectivity in patients with cirrhosis during the early period after LT has not yet been documented.

In addition, as frequently used methods of brain functional connectivity analysis, neither ICA nor ROI can examine multiple networks and measure the joint strength between